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Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

Invited review

Dual role of nicotine in addiction and cognition: A review of neuroimaging studies in humans

Agnes J. Jasinska^{a,*}, Todd Zorick^{b,c}, Arthur L. Brody^{b,c,***}, Elliot A. Stein^{a,**}^a National Institute on Drug Abuse, Intramural Research Program, 251 Bayview Blvd, Baltimore, MD 21224, United States^b University of California at Los Angeles, Department of Psychiatry, 300 UCLA Medical Plaza, Los Angeles, CA 90095, United States^c VA Greater Los Angeles Healthcare System, United States

ARTICLE INFO

Article history:

Received 21 November 2012

Received in revised form

28 December 2012

Accepted 19 February 2013

Keywords:

Nicotine
Tobacco
Smoking
Dopamine
PET
SPECT
fMRI
Addiction
Cognition

ABSTRACT

Substantial evidence demonstrates both nicotine's addiction liability and its cognition-enhancing effects. However, the neurobiological mechanisms underlying nicotine's impact on brain function and behavior remain incompletely understood. Elucidation of these mechanisms is of high clinical importance and may lead to improved therapeutics for smoking cessation as well as for a number of cognitive disorders such as schizophrenia. Neuroimaging techniques such as positron emission tomography (PET), single photon emission computed tomography (SPECT), and functional magnetic resonance imaging (fMRI), which make it possible to study the actions of nicotine in the human brain *in vivo*, play an increasingly important role in identifying these dual mechanisms of action. In this review, we summarize the current state of knowledge and discuss outstanding questions and future directions in human neuroimaging research on nicotine and tobacco. This research spans from receptor-level PET and SPECT studies demonstrating nicotine occupancy at nicotinic acetylcholine receptors (nAChRs) and upregulation of nAChRs induced by chronic smoking; through nicotine's interactions with the mesocorticolimbic dopamine system believed to mediate nicotine's reinforcing effects leading to dependence; to functional activity and connectivity fMRI studies documenting nicotine's complex behavioral and cognitive effects manifest by its actions on large-scale brain networks engaged both during task performance and at rest.

This article is part of a Special Issue entitled 'Neuroimaging'.

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1. Introduction

Nicotine's addiction liability is demonstrated by the high prevalence of cigarette smoking and low quit success rates, despite well-documented health risks (Bartal, 2001; Mokdad et al., 2004) and societal costs (Leistikow, 2000; Leistikow et al., 2000; Leistikow and Miller, 1998) of smoking. Approximately 20% of Americans still smoke (Brown, 2009; CDC, 2009), and although most smokers endorse a desire to quit (Fiore et al., 2000), very few (<5%) will actually do so in a given year without treatment, and only about 20–25% will achieve abstinence with 6 months or more of effective treatment (Cahill et al., 2011; Holmes et al., 2004; Hughes et al., 1999; Hurt et al., 1997; Jorenby et al., 1999; Killen

et al., 1999, 2000). Therefore, there continues to be a vital need to improve outcomes for cigarette smokers seeking treatment (Ray et al., 2009).

Nicotine, an alkaloid found in tobacco leaves, has been used by humans for its psychoactive properties for thousands of years. But it is only in the last several decades that the cellular and physiological mechanisms underlying nicotine's complex effects on brain function and behavior, including nicotine's abuse and dependence liability and its effects on cognitive function, have begun to be revealed. Most of this fundamental knowledge has been obtained from preclinical models and *in vitro* tissue preparations. More recently, neuroimaging techniques such as positron emission tomography (PET), single photon emission computed tomography (SPECT), and functional magnetic resonance imaging (fMRI) have made it possible to study the actions of nicotine and cigarette smoking on brain circuits and processes underlying addiction and cognition in the human brain *in vivo*.

In this review, we summarize the current state of knowledge and list some outstanding questions and possible future directions in human neuroimaging research on nicotine and tobacco. This

* Corresponding author. Tel.: +1 443 740 2621.

** Corresponding author. Tel.: +1 443 740 2650.

*** Corresponding author. University of California at Los Angeles, Department of Psychiatry, 300 UCLA Medical Plaza, Los Angeles, CA 90095, United States. Tel.: +1 310 268 4778.

E-mail addresses: jasinskaaj@mail.nih.gov (A.J. Jasinska), abrody@ucla.edu (A.L. Brody), EStein@intra.nida.nih.gov (E.A. Stein).

research has both clinical and basic-science importance. A better understanding of the effects of nicotine and tobacco smoking on the human brain is a critical step toward the development of more effective smoking cessation treatments, for which there is a pressing need (CDC, 2009). At the same time, experimenter administered nicotine can be used as a research tool to interrogate a range of brain processes in both healthy and patient populations, as well as to develop novel therapeutic drugs for such cognitive disorders as schizophrenia, Alzheimer's disease (AD), and attention-deficit hyperactivity disorder (ADHD).

2. Brain imaging of nicotinic acetylcholine receptors

Most psychoactive agents exert their effects by mimicking an endogenous neurotransmitter and binding to its neuronal receptors. In this case, nicotine serves as a ligand at nicotinic acetylcholine receptors (nAChRs). nAChRs are ligand-gated ion channels consisting of unique combinations from a family of at least seventeen ($\alpha 1$ – $\alpha 10$, $\beta 1$ – $\beta 4$, γ , δ , ϵ) similar, but distinct, subunits (Wu and Lukas, 2011). While many nAChR subtypes have been identified, the heteromeric $\alpha 4\beta 2^*$ receptor is one of the most common in the mammalian brain (Wu et al., 2006), and will be the focus of this section because the majority of brain imaging studies of smokers have focused on this receptor. Receptors containing the $\alpha 4$ subunit are reported to be central to the mediation of nicotine-induced reward, tolerance, and sensitization (Perry et al., 2002), while those containing the $\beta 2$ subunit have been shown to be functionally significant in nicotine self-administration (Epping-Jordan et al., 1999; Picciotto et al., 1998; Walters et al., 2006). Nicotinic acetylcholine receptors are located throughout the brain, with the highest density seen in the thalamus, followed by the basal ganglia, and frontal, cingulate, occipital, and insular cortices (Clarke et al., 1984; Ding et al., 1996; Mamede et al., 2004).

For examining the acute and chronic effects of cigarette smoking, PET and SPECT scanning have been performed in human smokers, with the most commonly used radiotracers being 2-[^{18}F]fluoro-3-(2(S)azetidinylmethoxy) pyridine (abbreviated as 2-FA) for PET scanning (Koren et al., 1998) and 123-labeled 5-iodo-A-85380 (abbreviated as 5-IA) for SPECT scanning (Horti et al., 1999). These radiotracers bind with high affinity and relative specificity to $\alpha 4\beta 2^*$ nAChRs (Koren et al., 1998), and the safety and reliability of these radiotracers have been verified (Bottlaender et al., 2003; Chefer et al., 2003; Fujita et al., 2002; Kimes et al., 2008; Valette et al., 1999).

In examining the acute effects of smoking/nicotine administration, 2-FA PET and 5-IA SPECT studies have demonstrated the effect of cigarette smoking on $\alpha 4\beta 2^*$ nAChR occupancy. In one PET study, smoking varying amounts of a regular cigarette (none, 1 puff, 3 puffs, 1 full cigarette, or to satiety [2 ½–3 cigarettes]) resulted in 0, 33, 75, 88, and 95% receptor occupancy, respectively (Brody et al., 2006a) (Fig. 1A). This study also demonstrated that smoking only 13% (1–2 puffs) of a cigarette and having a venous plasma nicotine concentration of 0.87 ng/mL (roughly 1/25th of the level achieved in typical daily smokers) resulted in 50% occupancy of $\alpha 4\beta 2^*$ nAChRs for 3.1 h after smoking. Therefore, cigarette smoking in amounts used by typical daily smokers leads to nearly complete occupancy of $\alpha 4\beta 2^*$ nAChRs, such that tobacco-dependent smokers maintain $\alpha 4\beta 2^*$ nAChR saturation throughout the day. In a similar study using 5-IA SPECT (Esterlis et al., 2010), smoking to satiety (mean – 2.4 cigarettes) also resulted in a prolonged period of occupancy of the majority of $\beta 2^*$ -containing nAChRs (mean – 67% [range, 55–80%]). The actual percent occupancy from smoking to satiety for the second study was lower than the first, and these slightly discrepant results may have been due to differences in abstinence period before scanning, number of cigarettes smoked during scanning, imaging methodology/timing issues, brain regions studied,

and/or statistical calculation methods for determining percent occupancy.

In addition to studies examining regular cigarette smoking, other acute cigarette smoke exposures (namely denicotinized and low nicotine cigarettes, and secondhand smoke) have recently been examined for their effects on $\alpha 4\beta 2^*$ nAChR occupancy. In one study (Brody et al., 2009a) (Fig. 1B), denicotinized cigarettes containing only trace amounts of nicotine (0.05 mg) and low nicotine cigarettes (0.6 mg nicotine) were smoked during 2-FA PET scanning to determine if components of smoking other than nicotine (e.g., other constituents of tobacco smoke or the touch, feel, smell, and taste of a cigarette) result in $\alpha 4\beta 2^*$ nAChR occupancy. This study demonstrated that smoking a denicotinized and a low-nicotine cigarette resulted in 26% and 79% $\alpha 4\beta 2^*$ nAChR occupancies, respectively. Given the consistency of findings between this study and the one cited above with standard cigarettes (Brody et al., 2006a), the denicotinized/low nicotine cigarette study demonstrates that nicotine inhalation during smoking appears to be solely responsible for $\alpha 4\beta 2^*$ nAChR occupancy, with other factors (if present at all) having either short-lived or very minor effects. And in a second study, secondhand smoke exposure (Brody et al., 2011) was also found to occupy a substantial percentage of $\alpha 4\beta 2^*$ nAChRs (Fig. 1C). In this study, smokers and nonsmokers underwent two PET scanning sessions, during which they sat in the passenger's seat of a car for 1 h and either were or were not exposed to secondhand smoke from a smoker seated in the driver's seat. In this study, the secondhand smoke exposure resulted in 19% occupancy of $\alpha 4\beta 2^*$ nAChRs, with no significant differences between smokers and nonsmokers, again demonstrating substantial receptor occupancy from cigarette smoke exposure.

Medications for treating tobacco dependence have also been examined for their acute effects on $\alpha 4\beta 2^*$ nAChR occupancy. In one SPECT scanning study (Esterlis et al., 2011), use of a nicotine inhaler produced an average 55.9% occupancy of $\beta 2^*$ -nAChRs 2–5 h post-challenge, which was less than the occupancy produced by smoking a standard cigarette (67.6%). Use of the nicotine inhaler was associated with diminished cigarette withdrawal, but not craving, possibly indicating that higher nAChR occupancy than is achieved with the nicotine inhaler is needed to reduce craving (or perhaps other conditional stimuli such as the taste and feel of the smoke in the throat, etc. may be required to diminish craving). In a similar study comparing varenicline (Chantix[®]) to placebo administration during PET scanning sessions (Lotfipour et al., 2012), low dose varenicline administration (0.5 mg) was associated with complete saturation of available $\alpha 4\beta 2^*$ nAChRs. Smoking to satiety, but not low-dose varenicline, significantly reduced withdrawal symptoms, indicating that factors other than varenicline binding to $\alpha 4\beta 2^*$ nAChRs lead to reduced withdrawal.

As for chronic effects of smoking/nicotine administration, several lines of research demonstrate that smoking leads to up-regulation of nAChRs in the human brain, including the common $\alpha 4\beta 2^*$ nAChR (Gentry and Lukas, 2002). Human postmortem tissue studies show that chronic smokers have increased numbers of $\alpha 4\beta 2^*$ nAChRs compared to non-smokers (Benwell et al., 1988; Breese et al., 1997), and that former smokers (>1 year abstinent) have nAChR densities similar to non-smokers (Breese et al., 1997). Many laboratory animal studies also demonstrate up-regulation of nAChRs in response to chronic nicotine administration (Marks et al., 2011; Pauly et al., 1989, 1996; Shoaib et al., 1997; Yates et al., 1995; Zhang et al., 2002). Taken together, these studies indicate that nAChRs up-regulate with smoking or nicotine administration, but that this up-regulation is reversible with an extended period of abstinence from smoking.

PET and SPECT brain imaging studies of human smokers, using 2-FA and 5-IA, have demonstrated up-regulation of available $\alpha 4\beta 2^*$

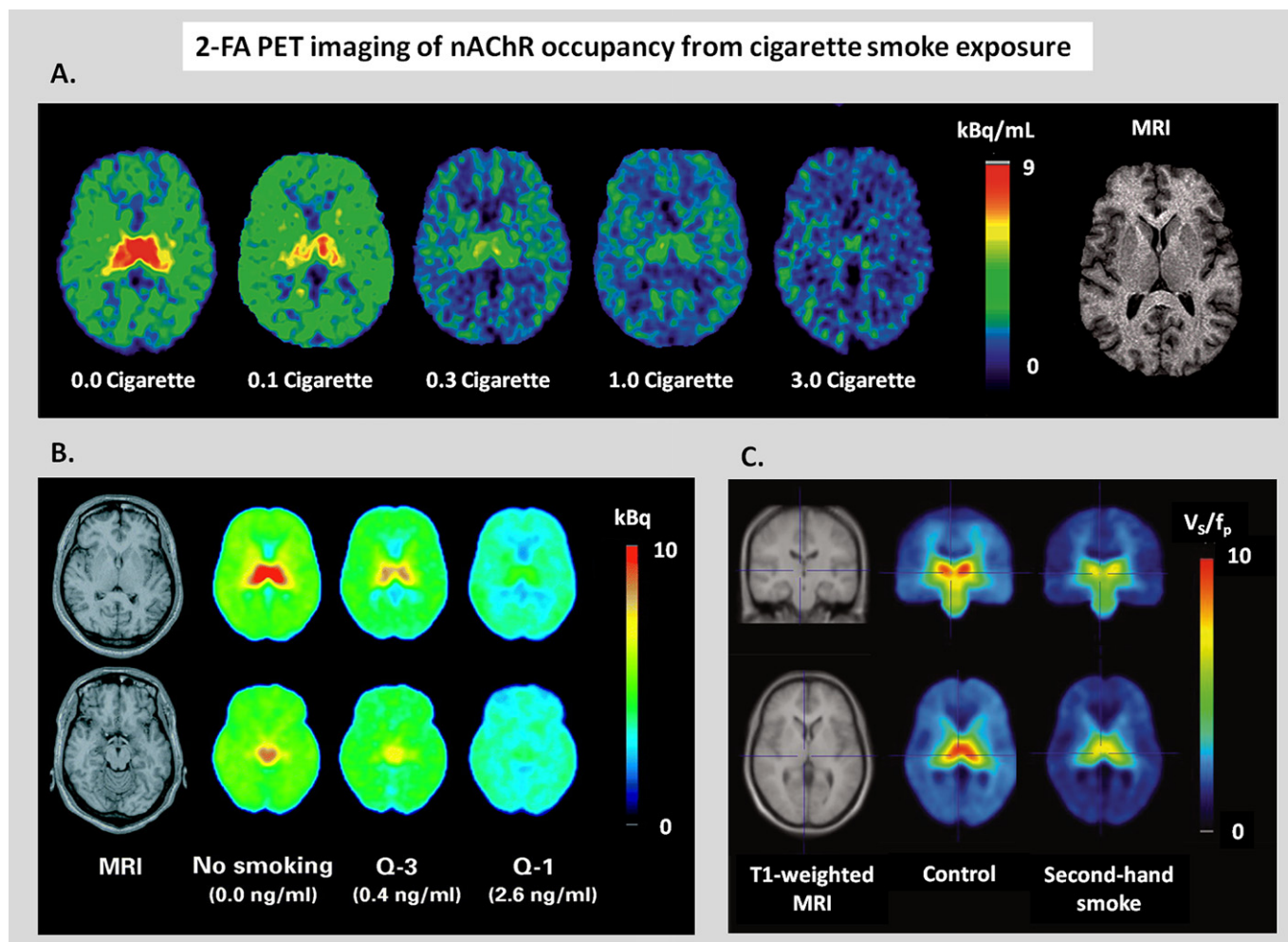


Fig. 1. Positron emission tomography (PET) studies using 2-[^{18}F]fluoro-3-(2(S)-azetidinylmethoxy) pyridine (abbreviated as 2-FA) to image $\alpha 4\beta 2^*$ nicotinic acetylcholine receptor (nAChR) occupancy from cigarette smoke exposure in humans *in vivo*. (A) Nicotine intake obtained from cigarette smoking in amounts used by typical daily smokers leads to nearly complete occupancy of $\alpha 4\beta 2^*$ nAChRs, indicating that tobacco-dependent smokers maintain $\alpha 4\beta 2^*$ nAChR saturation throughout the day. Horizontal slices at the level of the thalamus are shown. Modified from Brody et al. (2006a). (B) Relatively small amounts of nicotine in a denicotinized cigarette (Q-3, 0.05 mg nicotine) and a low-nicotine cigarette (Q-1, 0.6 mg nicotine) result in 26% and 79% $\alpha 4\beta 2^*$ nAChR occupancies, respectively, across thalamus (top panel), brainstem (bottom panel), and cerebellum (not shown). Modified from Brody et al. (2009a). (C) Similarly, nicotine from moderate second-hand smoke exposure results in 19% occupancy of $\alpha 4\beta 2^*$ nAChRs in both smokers (shown) and non-smokers. Modified from Brody et al. (2011).

nAChRs in smokers compared to non-smoking participants in brain regions other than the thalamus (Brody et al., 2012; Cosgrove et al., 2009, 2012; Mamede et al., 2007; Mukhin et al., 2008; Staley et al., 2006; Wullner et al., 2008). In follow-up scanning of smokers in two of these studies, nAChR up-regulation was found to normalize to levels of non-smokers when participants were given contingency management to maintain abstinence for roughly three (Mamede et al., 2007) to twelve (Cosgrove et al., 2009) weeks. Furthermore, these studies indicate that $\alpha 4\beta 2^*$ nAChR up-regulation in smokers is more pronounced in men (Cosgrove et al., 2012), menthol cigarette smokers (Brody et al., 2012), and smokers who have higher levels of urge to smoke to relieve withdrawal symptoms (Staley et al., 2006).

3. Ventral striatal dopamine signaling and tobacco dependence

Both pre-clinical and clinical studies have demonstrated the reinforcing effects of nicotine and its potential for abuse and dependence, although other aspects of cigarette smoking may also contribute to these effects, including reinforcing effects of non-

nicotinic components in tobacco smoke (for review, see (Rose, 2006)) and cognition-enhancing effects of nicotine (discussed in the section below). As with other drugs of abuse, the development of nicotine dependence in cigarette smokers occurs in several stages, starting with initial experimentation and recreational use, most often in adolescence, followed by a transition to chronic use, and ultimately escalating to abuse and dependence in susceptible individuals.

Similar to other drug use, cigarette smoking facilitates dopamine (DA) release in the ventral striatum (VST), thereby resulting in a “hijacking” of the brain’s reward circuitry (Baler and Volkow, 2011; Volkow et al., 2012; reviewed in De Biasi and Dani, 2011). In addition, the phenomenon of maladaptive behaviors resulting from DA signaling in the VST has also been proposed to contribute to non-substance related behavioral addictions, including obesity (Volkow et al., 2011) and pathological gambling (Leeman and Potenza, 2012). DA release in the VST/nucleus accumbens (NAc), among other regions, in response to nicotine is thought to be due to the activation of nAChRs on upstream DA neurons in the ventral tegmental area (VTA), the area of the midbrain containing cell bodies of DA neurons that project to the VST (Nisell et al., 1994). A

large body of literature spanning decades in many different types of addictive behaviors has clearly demonstrated the primacy of VST DA release in the development of addictive behaviors, including tobacco dependence.

Evidence for facilitation of DA release in the VST/nucleus accumbens (NAc) as underlying the reinforcing properties of nicotine has been most extensively demonstrated in rodent laboratory models (De Biasi and Dani, 2011). Data from non-human primates have also contributed to the understanding of VST DA release in tobacco dependence, showing that intravenous (IV) nicotine administration causes DA release (Dewey et al., 1999; Domino and Tsukada, 2009; Marengo et al., 2004; Tsukada et al., 2002), increased DA synthesis (Tsukada et al., 2005, 2002), and increased total catecholamine synthesis (Domino et al., 2009). Laboratory results from non-human primates and rodent models have thus provided convincing evidence that the mammalian dopaminergic VST reward pathway has both the appropriate neurochemical circuitry and experimental response to pharmacological manipulation to implicate this circuit as being important for tobacco dependence.

Molecular brain imaging studies of the human (and non-human primate) VST DA system also strongly support the importance of this pathway in the pathophysiology of human tobacco dependence. Many studies have demonstrated that inhaled tobacco smoke can displace ^{11}C -raclopride from VST DA $\text{D}_{2/3}$ receptors in human smokers (Barrett et al., 2004; Brody et al., 2004b, 2006b, 2010, in press; Domino et al., 2012a,b; Scott et al., 2007), showing that smoking behavior produces *in vivo* VST DA release. Although insufflated nicotine did not produce a group difference in VST DA release, the degree of change among smokers was correlated with positive feeling states; this lack of effect of nicotine nasal spray was attributed to the fact that "cigarette smoking is more likely to have activated reward circuitry than intranasal nicotine" (Montgomery et al., 2007). Smokers using nicotine gum were also found to have decreased VST ^{11}C -raclopride binding compared to matched placebo, with no effect of gum on a non-smoking control group (Takahashi et al., 2008).

Smoking-induced VST DA release has also been linked to associated behavioral and neurochemical changes in human smokers, including increased hedonic response (Barrett et al., 2004), increased striatal opioid receptor activation (Scott et al., 2007), and improved self-reported mood (Brody et al., 2009b), demonstrating that smoking-related VST DA release correlates with other markers of smoking behavior in humans. The relationship between mood disorders and smoking was further explored in a study that showed that smokers with vs. without a history of major depression had a greater mean decrease in ^{11}C -raclopride binding potential before to after smoking a cigarette during PET scanning (Brody et al., 2009c). Additional evidence of VST DA signaling abnormalities in smokers was demonstrated in a study of response to challenge with 30 mg of d-amphetamine, where smokers showed blunted VST DA release compared to non-smokers (Busto et al., 2009). The genetic control of smoking-induced VST DA release has been demonstrated both for DA transporter alleles (Brody et al., 2006b) and mu opioid receptor alleles (Domino et al., 2012a). Therefore, multiple lines of evidence from studies of molecular imaging of smoking behavior, combined with concomitant pharmacological, psychological, and genetic evidence conclusively demonstrate that human smoking behavior is associated with VST DA release.

Given the established association between substance use disorders, related behavior addictions (such as obesity) and decreased VST $\text{D}_{2/3}\text{R}$ availability, baseline striatal DA tone has been increasingly recognized as a risk factor for addiction (Volkow et al., 2012). Therefore, many studies in human smokers have also attempted to assess whether the same holds true for human smokers; however,

the evidence is mixed. Several studies utilizing SPECT with DA receptor ligands ^{123}I -beta-CIT (Staley et al., 2001) and ^{123}I -BZM (Yang et al., 2006, 2008) found that smokers and non-smokers did not differ in terms of baseline VST DA receptor binding, despite one of these studies showing (in accordance with earlier findings (Salokangas et al., 2000)) that smokers had decreased VST DA transporter density (Yang et al., 2008). A limitation of these studies, admittedly, was small sample sizes, which may have limited their power to detect subtle differences in baseline VST DA receptor availability (Yang et al., 2008). Conversely, several studies with larger sample sizes using the PET radiotracer ^{18}F -fallypride did report baseline lower striatal DA receptor availability in smokers compared to non-smoking controls; one study found that smokers had less putamen DA $\text{D}_{2/3}\text{R}$ availability than non-smokers (Fehr et al., 2008), and a second found decreased striatal DA availability in smokers vs. non-smokers only in male, but not female, subjects (Brown et al., 2012). Additional studies with larger sample sizes are needed to conclusively determine whether human smokers have lower baseline striatal $\text{D}_{2/3}\text{R}$ availability.

Investigation into the relative role of D_1 vs. $\text{D}_{2/3}$ receptors in human tobacco-related VST DA signaling has also followed from work in animal models. In a group of smokers seeking treatment, increased left VST metabolism was seen with craving, and there was an inverse correlation of VST D_1 receptor availability and both VST metabolism and craving (Yasuno et al., 2007). Supporting the results of earlier work (Dagher et al., 2001), smokers also showed an overall decrease in VST D_1R availability compared to controls; however, there was no recovery in VST D_1R availability in smokers, even after 6 months of abstinence (Yasuno et al., 2007).

To summarize these results of DA signaling in tobacco dependence, ample evidence from both animal models and human smokers supports the hypothesis that both smoking behavior and nicotine administration result in activation of the VST reward pathway, via increased DA release and metabolism in the VST. This phenomenon may provide a common link between tobacco dependence and other human substance and non-substance behavioral addictions (Baler and Volkow, 2011; Volkow et al., 2011, 2012). Indeed, recent studies suggest that both acute (Rose et al., 2012b) and chronic (Rose et al., 2012a) exposure to nicotine is associated with altered reward-related striatal activity.

4. Acute and chronic nicotine actions on brain function and structure

A number of human neuroimaging studies have examined the effects of acute nicotine administration or cigarette smoking on brain activity in smokers in the absence of any explicit cognitive task. In an early fMRI study using cumulative intravenous nicotine administration (0.75, 1.50, and 2.25mg/70 kg of weight) in non-deprived smokers, Stein and colleagues (Stein et al., 1998) demonstrated that nicotine increased the Blood oxygenation level dependent (BOLD) fMRI signal in a number of cortical and subcortical regions, including the insula, the cingulate cortex, the dorsolateral, orbital, and medial prefrontal cortices, and portions of the temporal and occipital cortices, as well as the nucleus accumbens (NAc), amygdala, hypothalamus, and several nuclei of the thalamus. Early PET studies (Domino et al., 2000, 2004; Zubieta et al., 2001, 2005) using either nasal nicotine spray (vs. pepper solution spray) or nicotine cigarettes (vs. de-nicotinized cigarettes) in smokers after overnight abstinence showed that nicotine increased regional cerebral blood flow (rCBF) in the thalamus, occipital cortex, and cerebellum, but variably decreased rCBF in the amygdala, NAc, hippocampus, temporal cortex, and cingulate cortex.

Several neuroimaging studies have recently examined the impact of nicotine and tobacco on large-scale brain networks. These

intrinsic networks can be detected at rest by assessing correlations in temporal fluctuations in BOLD signal across brain regions (Beckmann et al., 2005; Fox et al., 2005; Greicius et al., 2003). Such identified networks are also engaged during a variety of cognitive tasks, and are believed to reflect the underlying structural and functional architecture of the human brain (Greicius et al., 2009; Smith et al., 2009; van den Heuvel et al., 2009). Therefore, an important goal for neuroimaging pharmacological research is to evaluate the impact of nicotine and tobacco on the coherence and dynamic interactions of these networks (for a recent review, see Sutherland et al., 2012).

Hong and colleagues examined the effects of acute nicotine patch administration on the resting-state functional connectivity (rsFC) in brain circuits centered on the cingulate cortex in smokers. Acute nicotine enhanced connectivity between several subdivisions of the cingulate cortex and a number of frontal and parietal cortex regions. In contrast, the severity of nicotine dependence was specifically and negatively associated with a dorsal anterior cingulate (dACC)–VST circuit, suggesting a dissociation of acute (state-like) and chronic (addiction trait) nicotine effects on intrinsic brain function (Hong et al., 2009). Negative correlations between smoking severity and rsFC strength between the dACC, striatum, and insula were also found in smokers with schizophrenia, with an additive effect of schizophrenia diagnosis and smoking on the reduction in the dACC–insula connectivity (Moran et al., 2012). Furthermore, similar results were reported in a smoking-cue reactivity paradigm, with smokers who subsequently slipped during their quit attempt displaying reduced dACC–insula connectivity strength when viewing smoking cues compared to smokers who remained abstinent (Janes et al., 2010). Thus, the altered functional connectivity of the dACC and related regions observed at rest may be associated with altered reactivity to smoking cues, among other task-related consequences.

Cole et al. (2010) investigated the effects of nicotine replacement on the interactions between the default mode network (DMN) and executive control network (ECN) in abstinent smokers (Fig. 2A). These two brain networks show anti-correlated patterns of activity: the ECN is thought to be engaged during attention-demanding cognitive tasks, whereas the DMN is activated during rest and often deactivated during cognitive task performance (Raichle et al., 2001), with a larger degree of DMN deactivation associated with better task performance (Kelly et al., 2008; Weissman et al., 2006). Using a double-blind, placebo-controlled design, Cole et al. (2010) found that the therapeutic effect of nicotine replacement on cognitive withdrawal symptoms was associated with enhanced inverse coupling between the ECN and DMN, whereas non-responders showed no effect of nicotine replacement on ECN–DMN coupling. Similarly, Tanabe et al. (2011) investigated the effects of a 7 mg nicotine patch on resting-state activity in the DMN and visual attention network in non-smoking subjects (Fig. 2B). This study showed that acute nicotine suppressed activity within the DMN and increased activity in extra-striate regions within the visual attention network, even in the absence of explicit task and effortful processing, suggesting that nicotine's cognition-enhancing effects may involve shifting network activity from internally-directed to externally-directed processes. A reanalysis of these data with network topology techniques (Wylie et al., 2012) also revealed that acute nicotine increased local efficiency of the network, as well as regional efficiency for limbic and paralimbic brain regions, in healthy non-smokers. Consistently, Hahn et al. (2007) also observed nicotine-induced DMN deactivation during performance of a selective attention task. Overall, these recent neuroimaging studies of nicotine's effects on network dynamics fit well with the view that the endogenous cholinergic system modulates both local and global aspects of information processing in the

brain, and are consistent with neuroanatomical evidence of global cholinergic projections from the nucleus basalis and widely distributed acetylcholine-responsive interneurons (Mesulam and Geula, 1988; Xiang et al., 1998).

While investigations of the impact of chronic experimental nicotine administration on the human brain still present a challenge, several neuroimaging studies examined the effects of chronic cigarette smoking on structural brain measures. Using high-resolution structural MRI, Brody et al. (2004a) demonstrated smaller gray matter volume and lower gray matter densities in bilateral prefrontal cortex (PFC), along with smaller volume in the left dACC, in smokers compared to matched non-smoking controls. Furthermore, the gray matter densities in the PFC negatively correlated with the magnitude of lifetime smoking exposure as indexed by pack-years smoked. Similarly, Gallinat et al. (2006) showed that, compared to never-smokers, smokers presented with smaller gray matter volume and lower gray matter density in the frontal lobe (ACC, PFC, and orbitofrontal cortex, or OFC), occipital lobe, and temporal lobe (including parahippocampal gyrus), as well as volume or density deficits in the thalamus and cerebellum. Again, the gray matter volume in frontal, temporal, and cerebellar cortices was inversely correlated with lifetime smoking exposure in smokers (Gallinat et al., 2006). Cortical thinning of the medial OFC in smokers compared to never-smokers was also replicated (Kühn et al., 2010), including a negative association between the cortical thickness of the OFC and both daily and lifetime exposure to tobacco smoke.

Using diffusion tensor imaging (DTI) and fractional anisotropy (FA) as a measure of white matter integrity, Zhang et al. (2011) demonstrated that the most dependent smokers had lower prefrontal FA, which was negatively correlated with addiction severity as measured by FTND. In addition, smokers showed higher gray matter density in left insular cortex (Zhang et al., 2011), consistent with previous evidence of the role of the insula in supporting tobacco dependence (Naqvi and Bechara, 2009; Naqvi et al., 2007). Finally, chronic smoking and a diagnosis of schizophrenia have been shown to independently and additively reduce the FA of the white-matter fibers connecting the PFC with the striatum and thalamus (Zhang et al., 2010), suggesting that these two highly comorbid conditions have both common and distinct effects on brain structure, consistent with their additive, detrimental effects on functional-connectivity networks (Moran et al., 2012).

5. Acute nicotine modulation of cognitive brain function

In addition to its well-documented addiction liability, nicotine is also known to enhance aspects of cognitive function, including attention and memory (for a recent meta-analysis, see Heishman et al., 2010). This nicotine-induced enhancement of cognitive function has been observed both in nicotine-deprived smokers (in whom it may be due, at least in part, to relief of withdrawal), in non-deprived smokers, and in non-smokers (in whom it may reflect a true enhancement of cognitive function and/or an attenuation of pre-existing cognitive deficits) (Heishman et al., 2010). Indeed, nicotine and other nAChR ligands are being investigated as potential therapeutics for the treatment of cognitive deficits in schizophrenia, attention-deficit hyperactivity disorder, and Alzheimer's disease (D'Souza and Markou, 2012; Levin et al., 2006). On the other hand, chronic cigarette smoking has been associated with decreased cognitive performance in middle age (Kalmijn et al., 2002; Richards et al., 2003) and increased risk of cognitive decline and dementia later in life (for a meta-analysis, see Anstey et al., 2007). Human neuroimaging research has begun to elucidate the brain circuits and processes mediating the effects of acute nicotine and chronic cigarette smoking on cognitive function and

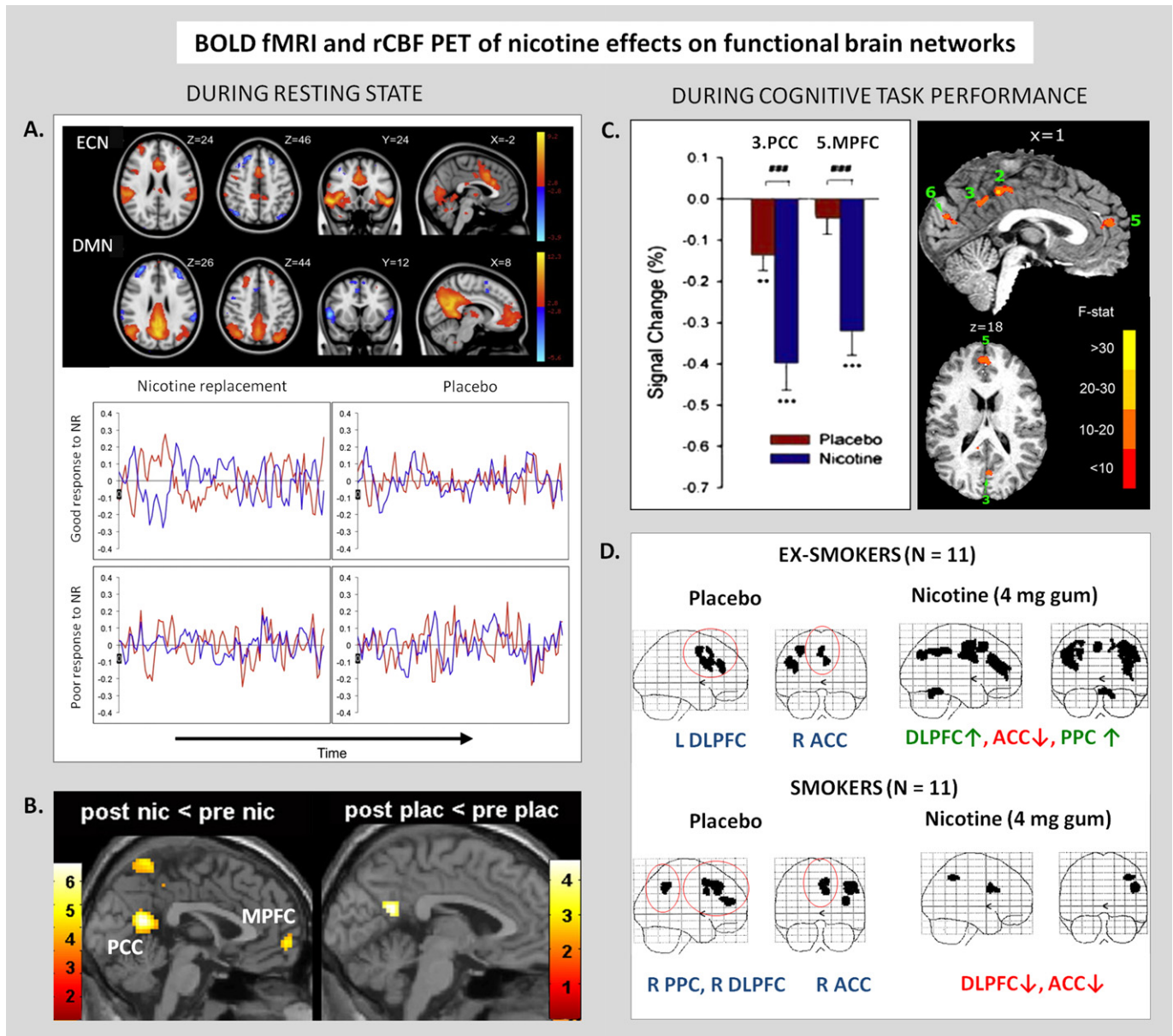


Fig. 2. Blood oxygenation level dependent (BOLD) functional magnetic resonance imaging (fMRI) and regional cerebral blood flow (rCBF) PET studies of nicotine effects on functional brain networks during (A, B) task-free resting state and (C, D) cognitive task performance. (A) Activation in the executive control network (ECN), encompassing ACC, DLPFC, and PPC, is anti-correlated with the default mode network (DMN), containing MPFC and PCC, during task-free resting state (top panel). Relative to placebo, nicotine enhanced the ECN–DMN anti-correlation in abstinent smokers who demonstrated a reduction in withdrawal symptoms following nicotine replacement (top time-course), but not in those who did not show such response (bottom time-course). Modified from Cole et al. (2010). (B) Nicotine decreased DMN activity (including MPFC and PCC) relative to pre-nicotine baseline during resting state in non-smokers. Modified from Tanabe et al. (2011). (C) Nicotine enhanced deactivation in the DMN (including MPFC and PCC) during a spatial attention task in minimally deprived smokers relative to placebo. Modified from Hahn et al. (2007). (D) Using rCBF PET, nicotine enhanced DLPFC response (within the ECN) during 2-back working memory task in ex-smokers but reduced it in ex-smokers, relative to placebo. Modified from Ernst et al. (2001). Abbreviations: ACC, anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; DMN, default mode network; ECN, executive control network; MPFC, medial prefrontal cortex; PCC, posterior cingulate cortex; PPC, posterior parietal cortex.

cognitive performance (for recent reviews, see also Bentley et al., 2011; Newhouse et al., 2011). A brief and selective review of acute nicotine and cigarette smoking on cognitive processes is presented below.

5.1. Sustained attention

Lawrence et al. (2002) used fMRI to assess acute effects of a 21 mg transdermal nicotine patch on the neural correlates of sustained attention in mildly abstinent smokers. Using the rapid visual

information-processing (RVIP) task, behavioral performance was associated with increased activity in the middle and inferior frontal cortices, anterior insula, parietal and occipital cortex, thalamus, caudate, and cerebellum, as well as with signal decreases in the medial frontal cortex, anterior and posterior cingulate, mid-insula, parahippocampus, and amygdala. In the placebo condition, smokers showed less task-induced activation in parietal cortex and caudate compared to non-smokers, whereas smokers on nicotine patch showed increased task-related activation in parietal cortex, caudate, and thalamus, as well as a general increase in activation in

the occipital cortex. Furthermore, smokers showed a trend toward a worse performance than non-smokers, but an improvement in performance in the nicotine condition compared to the placebo condition. Using the same task in participants with schizophrenia (Hong et al., 2011), nicotine produced generalized increases in activation in the frontal, insular, cingulate, parietal, and occipital cortices, and in the basal ganglia, midbrain, and cerebellum, and enhanced task performance, relative to the placebo conditions, with similar effects in patients and controls (i.e., no drug \times diagnosis interactions). Patients showed reduced task-related activations and impaired task performance compared to healthy controls in the placebo condition as well as on nicotine patch, suggesting that acute nicotine cannot—or the dose of nicotine used was not sufficient to—normalize the neural and behavioral deficits in the patient group (Hong et al., 2011).

Warbrick et al. (2012) used simultaneous fMRI and EEG to examine the effects of 1 mg nasal nicotine spray on the neural response to a visual oddball task in smokers. Compared to the placebo condition, nicotine decreased reaction times, which was associated with reduced BOLD response in the superior parietal and lateral occipital cortices and precuneus. Interestingly, they also analyzed their data informed by single-trial P3 component amplitude and found increased BOLD response in the precentral and postcentral gyri and ACC, highlighting the fact that different temporal resolutions of measurement (here: high temporal resolution of EEG coupled with more sluggish fMRI BOLD time-course) may provide complementary information about the underlying brain processes.

5.2. Selective attention

A series of fMRI studies (Giessing et al., 2006; Thiel and Fink, 2008; Thiel et al., 2005; Vossel et al., 2008) examined the effects of 2 mg nicotine gum on the neural correlates of selective visuo-spatial attention as assessed with a cued target detection task in non-smoking subjects. In these studies, re-orienting of attention was isolated by contrasting invalid-cue trials with valid-cue trials, and was associated with activation in the parietal, temporal, and middle frontal cortices. Acute nicotine reduced the BOLD response to invalidly cued trials in the parietal cortex as well as in the temporal, middle frontal, and cingulate cortices, which was in some cases accompanied by behavioral enhancement (i.e., speeded reaction times). Two studies by Stein and colleagues (Hahn et al., 2007, 2009) also examined the effects nicotine patch on the neural correlates of cued selective attention in mildly deprived smokers (Fig. 2C). These studies showed that nicotine reduced the activation (or induced deactivation) to all cued trials in the parietal cortex (angular gyrus), middle frontal cortex, and anterior and posterior cingulate cortices. These regions overlap with the DMN (Raichle et al., 2001). Consistent with the known predictive relationship between task performance and DMN deactivation (Kelly et al., 2008; Weissman et al., 2006), nicotine-induced deactivation in angular gyrus and posterior cingulate was positively correlated with performance improvements in smokers, controlling for nicotine plasma levels (Hahn et al., 2007). Furthermore, Rose et al. (2010) showed that the modulatory effects of acute nicotine on task-related brain response in smokers were not limited to attentional processes but extended to intentional and motor preparation processes. Compared to the placebo condition, nicotine increased the response to the intentional prime (signaling whether left or right hand response would be required) in the left inferior parietal lobule and supramarginal gyrus, as well as in the left postcentral gyrus; in contrast, nicotine decreased the response in the left postcentral gyrus to attentional primes (signaling whether the target will appear on the left or right side of the screen).

5.3. Working memory

In an early study of nicotine effects on working memory (WM), Ernst et al. (2001) used PET to measure changes in rCBF and examined the impact of 4 mg nicotine gum on brain activity during an n-back task in heavy smokers after overnight abstinence and in light ex-smokers (Fig. 2D). Consistent with numerous WM studies (Wager and Smith, 2003), in the placebo condition, the n-back task increased rCBF in the ACC, dorsolateral prefrontal (DLPFC), and inferior parietal cortices, with better task performance associated with stronger prefrontal activation in both smokers and ex-smokers (Ernst et al., 2001). In both smokers and ex-smokers, nicotine reduced rCBF in cingulate cortex relative to the placebo condition. In addition, nicotine enhanced activation in the prefrontal and parietal regions in ex-smokers, whereas it decreased prefrontal and parietal activation in current smokers.

Taking a different approach, Xu et al. (2005) used fMRI to compare brain activity during the n-back WM task in the same group of nicotine-dependent smokers during satiety (≤ 1.5 h abstinence) and following abstinence (≥ 14 h abstinence), in an attempt to explain the abstinence-related deficits in WM in smokers. This study showed an interaction of test condition (satiety, abstinence) and task load (1-back, 2-back, and 3-back) on DLPFC activity: whereas in a satiated state, the DLPFC activity was low during the easy 1-back condition and increased in the more difficult 2- and 3-back condition, in the abstinent state, the DLPFC was relatively high in the 1-back condition but failed to increase with increased working memory load. A follow-up study (Xu et al., 2006) compared the effects of smoking a cigarette following ad libitum smoking or overnight abstinence on DLPFC activity, and reported a 3-way interaction between acute smoking (pre- or post-cigarette), test session (smoking or abstinence), and n-back task load. Specifically, post-cigarette DLPFC activity was higher than pre-cigarette at low task load and lower at high task load after ad libitum smoking; in contrast, post-cigarette DLPFC activity was lower than pre-cigarette at low task load and higher at high task load following overnight abstinence. This pattern of activity suggests that the impact of acute smoking on WM processes in smokers depends on their recent smoking history and cognitive load: acute smoking after abstinence improves WM processes (presumably by alleviating withdrawal), whereas the effects of acute smoking in the satiated state varies with the WM difficulty (Xu et al., 2006).

The above interactions may explain the absence of acute (but not chronic) nicotine effects in a study by Sutherland et al. (2011), which examined the neural correlates of a WM task with an additional attentional-switch requirement in minimally deprived smokers. In another study, Kumari et al. (2003) used fMRI to examine the impact of acute nicotine administration on neural correlates of WM in a parametric n-back task in healthy non-smoking males. Compared to placebo, nicotine improved task performance as well as increased the BOLD response in the ACC, superior frontal, and superior parietal cortices that were activated by the n-back task. With respect to clinical groups, Jacobsen et al. (2004) examined the impact of nicotine patch (vs. placebo patch) on brain activity during an auditory WM task in schizophrenia subjects and healthy smokers. During the most difficult dichotic 2-back task condition, nicotine enhanced activation in the ACC and thalamus, as well as thalamo-cortical functional connectivity, to a greater degree in schizophrenic patients than in control subjects; nicotine also improved task performance of patients, whereas it decreased task performance in control subjects in this condition.

In sum, neuroimaging studies of acute nicotine modulation of cognitive function are in agreement with behavioral studies and paint an equally complex picture. Nicotine-induced enhancement

of cognitive task performance is associated with increases in activity in subcortical regions such as basal ganglia and thalamus, as well as with both increases and decreases in activity in frontal and parietal cortices. In addition, the impact of acute nicotine on task-related brain responses may be further modulated by the dose and route of administration, length of abstinence in smokers, and pre-existing cognitive deficits such as those associated with schizophrenia or ADHD diagnosis, as well as by the type and difficulty of the task itself. Thus, overall, nicotine seems to enhance executive function *not* via a single neuroanatomical site or mechanism, but via its modulation of multiple brain networks and transmitter systems, requiring a more specific characterization of nicotine effects on diverse task-induced tonic and phasic neuronal states. In particular, and consistent with nicotine-induced (or enhanced) down-regulation of the 'default mode' function observed across a range of different task paradigms (for review, see Bentley et al., 2011), nicotine may modulate the 'toggle' between the DMN and ECN—a key role attributed to a proposed dACC–insula network (Menon and Uddin, 2010; Seeley et al., 2007).

6. Linking nicotine's roles in addiction and cognition

As reviewed in the sections above, nicotine has a dual action in the brain: it promotes addiction (Tuesta et al., 2011) and it modulates cognition (Bentley et al., 2011). Although typically investigated separately, both clinical evidence and theoretical accounts suggest that nicotine's addictive and cognitive properties are closely linked and interact in important ways. Individuals may self-medicate with nicotine to enhance cognitive and attentional processes (Evans and Drobos, 2009), which may partially account for the high prevalence of cigarette smoking among individuals with cognitive disorders such as schizophrenia, ADHD, or AD. Similarly, nicotine withdrawal symptoms include both cognitive deficits and deficits in reward processing and motivation. Thus, nicotine's reinforcing and cognition-enhancing effects are likely to involve at least partially overlapping brain processes, networks, and transmitter systems.

In particular, nicotine may exert its reinforcing and cognition-enhancing effects at least in part by enhancing DA signaling in mesolimbic and mesocortical DA pathways, respectively (Fig. 3). In addition to its well-established role in addiction, DA is also a critical modulator of a range of cognitive processes (for a recent review, see Cools and D'Esposito, 2011). Although some overlap exists, DA's role in addiction has been associated primarily with mesolimbic DA pathways connecting the VTA with VST and amygdala, whereas DA's effects on cognition may be mediated by the mesocortical DA pathways connecting the VTA with the cortical regions, including the PFC. nAChRs are present on VTA DA projection neurons (Clarke and Pert, 1985; Deutch et al., 1987) and are known to enhance the activity of these neurons and DA release (Calabresi et al., 1989; Imperato et al., 1986). Therefore, it is likely that by binding to nAChRs in the VTA, nicotine enhances DA signaling in both mesolimbic and mesocortical DA pathways, and therefore also enhance the processes mediated by their target brain regions and networks, leading to nicotine addiction and nicotine-induced cognitive enhancement, respectively.

Further indirect evidence linking nicotine and DA stems from the observation that nicotine and DA agonists present similar inverted-U dose–effect curves with respect to both intensity of drug self-administration and cognitive task performance. Thus, in self-administration studies of nicotine and stimulants such as cocaine, the ascending limb of the dose–response curve is thought to represent the increasingly rewarding or reinforcing properties of increasing dosage of the drug, whereas the descending limb of the dose–response curve reflects the aversive properties of high drug

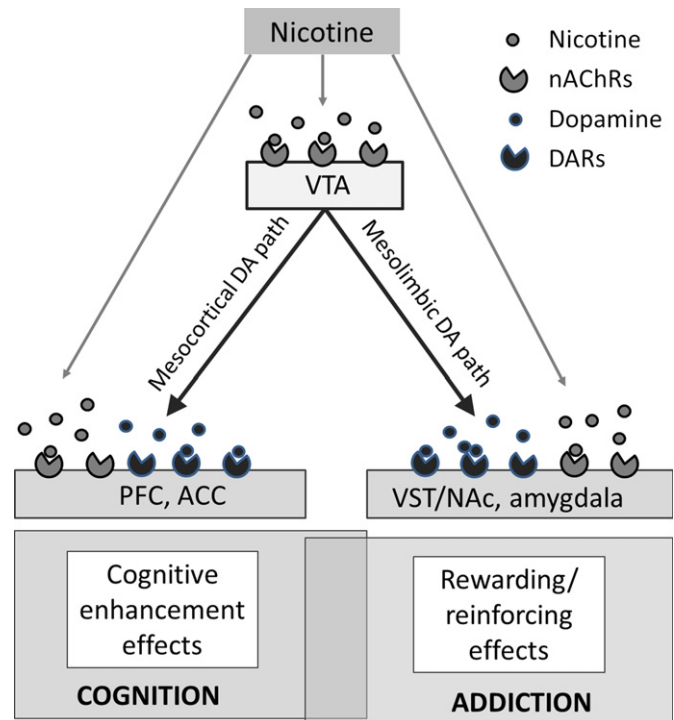


Fig. 3. A simplified diagram of nicotine's dual action in the brain. Nicotine's reinforcing and cognition-enhancing properties may be linked at least in part by nicotine-induced enhancement of DA signaling in the mesolimbic and mesocortical DA pathways, respectively. ACC, anterior cingulate cortex; DARs, dopamine receptors; NAc, nucleus accumbens; nAChRs, nicotinic acetylcholine receptors; PFC, prefrontal cortex; VST, ventral striatum; VTA, ventral tegmental area.

doses as well as receptor satiation (for review, see Lynch and Carroll, 2001). In studies of nicotine's effects on cognition, absence of nicotine in heavy smokers produces cognitive deficits characteristic of withdrawal (similar deficits are seen with nAChR antagonists in non-smokers), moderate doses of nicotine typically produce cognitive enhancement (and/or alleviation of withdrawal-related cognitive deficits in smokers), whereas very high doses of nicotine typically impair cognitive performance (for review, see Bentley et al., 2011). And analogously, in studies of DA's role in cognition, DA depletion impairs cognitive processing, moderate levels of DA produce optimal cognitive performance, whereas very high levels of dopamine impair cognition (for review, see Cools and D'Esposito, 2011).

Thus, nicotine's addictive and cognition-enhancing properties appear to be linked at least in part through nicotine-induced enhancement of DA signaling in the mesolimbic and mesocortical DA pathways, respectively. Although it should be acknowledged that the interactions and mutual modulation between DA and nicotine (as well as endogenous acetylcholine) in both addictive behavior and cognitive function are certainly more complex than summarized above.

7. Outstanding questions and future directions

Despite recent progress in nicotine- and tobacco-related neuroimaging research, several outstanding questions remain. A major goal of future research will be to elucidate the relationship and degree of overlap between the nAChR subtypes and those brain circuits mediating nicotine's addiction liability vs. its cognition-enhancing effects. We envision several lines of investigation, using complementary and increasingly integrative approaches,

contributing toward that goal. One important goal will be to map receptor-level actions to circuit-level effects of acute nicotine administration by combining PET with pharmacological fMRI in the same participants. Another gap to be filled will be to dissociate and compare the acute and chronic effects of nicotine using prospective placebo-controlled, double-blind designs with precise nicotine doses (as opposed to ad libitum smoking). Critical knowledge will also be gained by elucidating the impact of genetic variation in cholinergic signaling and metabolism on all levels of brain function, from receptor-level to circuit-level, in response to acute and chronic nicotine, using imaging genetics and imaging pharmacogenetics approaches (Hong et al., 2010). Ultimately, well-powered and well-controlled studies combining neuroimaging, genetics, and pharmacological manipulations in well-characterized samples are most likely to produce new breakthroughs and accelerate translation to clinical treatments.

Acknowledgments

Supported by the Intramural Research Program of NIDA (E.A.S., A.J.J.) and grants R01 DA20872 from the National Institute on Drug Abuse (A.L.B.), 19XT-0135 from the Tobacco-Related Disease Research Program (A.L.B.), and a Merit Review Award from the Department of Veterans Affairs, Office of Research and Development (A.L.B.).

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