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Cognitive Effects of Nicotine

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1. INTRODUCTION

Cigarette smoking is the primary cause of preventable death in developed countries. An estimated 435,000 premature deaths in the U.S. and 5.5 million deaths worldwide are caused by smoking each year (CDC, 2008). Approximately half of all cigarette smokers will die as a result of smoking-related diseases, including lung cancer, coronary heart disease, stroke, and chronic obstructive pulmonary disease. In the United States, it is estimated that 30% of the deaths caused by cancer each year result from cigarette smoking. Lung cancer results in approximately 1.2 million deaths worldwide, and over 90% of those cases are caused by cigarette smoking (Jemal et al., 2008). To put these figures in perspective, it is estimated that more individuals in the United States die from smoking-related causes than from alcohol-related causes, car accidents, suicide, AIDS, homicide, and illegal drug use combined. The estimated total economic and healthcare cost of cigarette smoking in the United States is \$193 billion per year (CDC, 2008).

Over the past 50 years, the rate of smoking in the United States has decreased from 40% to 20%, but there has been less of a decline in the smoking rate among people with low incomes, low educational levels, psychiatric disorders and/or other addictions (CDC, 2011). Quitting smoking is associated with immediate health benefits regardless of age or the presence of smoking-related diseases (Menzin et al., 2009; Godtfredsen and Prescott, 2011), but even when smokers utilize evidence-based cessation treatments, only 15–25% of those who quit succeed in avoiding tobacco use for at least one year (Fiore et al., 2008; Herman and Sofuoglu, 2010). Thus, it is necessary to develop more effective treatments for nicotine addiction. The development of new treatments requires a better understanding of the individual factors that contribute to the initiation and maintenance of nicotine addiction.

A large body of evidence from animal and human studies supports the notion that nicotine has cognitive-enhancing effects. Smokers report that smoking has beneficial effects on concentration and memory (Piper et al., 2004; Russell et al., 1974; Wesnes and Warburton, 1983), and abstinence from smoking is associated with decreases in cognitive function such as difficulty concentrating, impaired attention, and reductions in the

efficiency of working memory (Harrison et al., 2009; Hatsukami et al., 1984; Hughes and Hatsukami, 1986; Jacobsen et al., 2005; McClernon et al., 2008; Xu et al., 2005). However, nicotine use enhances performance in several domains of cognitive functioning, including attention, working memory, and complex task performance in satiated smokers and nonsmokers (Baschnagel and Hawk, 2008; Ernst et al., 2001; Foulds et al., 1996; Heishman, 1998; Lawrence et al., 2002; Meinke et al., 2006; Mumenthaler et al., 1998; Trimmel and Wittberger, 2004).

Over the past decade, there have been great advances in the understanding of the neurobiology of the nicotinic acetylcholine receptor (nAChR) as it relates to cognitive function and the reward (Changeux, 2010; Dos Santos Coura and Granon, 2012). Further more, functional neuroimaging studies provide essential information regarding the brain regions that mediate the rewarding and cognitive effects of nicotine (Newhouse et al., 2011; Sharma and Brody, 2009). As a result of these advances, the cognitive-enhancing effects of nicotine are increasingly recognized as important factors that contribute to the initiation and maintenance of smoking (Levin et al., 2006). Nicotine may positively reinforce smoking behaviors by enhancing cognitive function, especially among individuals in whom normal cognitive functioning is impaired. A high prevalence of smoking is observed among individuals with schizophrenia (de Leon and Diaz, 2005) and attention deficit hyperactivity disorder (ADHD) (Milberger et al., 1997). These psychiatric disorders are associated with cognitive impairments (Chamberlain et al., 2011). Medications that target the $\alpha 7$ and $\alpha 4\beta 2$ nAChRs have also emerged as cognitive-enhancers for the treatment of neuropsychiatric disorders (Wallace and Porter, 2011).

The goal of this chapter is to provide a brief overview of the cognitive effects of nicotine. The first section of this review focuses on the cognitive effects of nicotine in humans. We then review the neurobiological mechanisms of the cognitive effects of nicotine with a focus on the nicotinic acetylcholine (ACh) and dopamine (DA) receptors. Finally, we address the potential treatment implications of this area of research. The chapter will primarily focus on the acute effects that nicotine has on cognitive performance; the long-term (chronic) cognitive effects of smoking will not be covered (Swan and Lessov-Schlaggar, 2007). For more details, several recent reviews provide excellent overviews of behavioral pharmacology (Heishman et al., 2010), neuroimaging (Newhouse et al., 2011; Sharma and Brody, 2009), and preclinical studies (Dos Santos Coura and Granon, 2012; Mansvelder et al., 2006; Poorthuis et al., 2009) of this broad topic.



2.1. COGNITIVE EFFECTS OF NICOTINE IN HUMANS

In their meta-analysis, Heishman et al. (2010) found that there was little consistency in the dose-response functions of nicotine both within and across domains. They concluded that nicotine improves performance on tasks requiring motor abilities,

attention, and memory functions even in the absence of the confounding effects of withdrawal relief (Heishman et al., 2010).

Given the availability of several excellent reviews of the cognitive effects of nicotine in humans, we have chosen to focus on a few studies that illustrate the methodology used in and the typical results obtained from human studies that examine the effects that nicotine administration has on cognitive performance.

Myers et al. (2008) conducted a placebo-controlled double-blind study that examined the dose-dependent effects of nicotine that was administered via a nasal spray (placebo, 1 or 2 mg) in 28 smokers. The participants in this study were tested twice: once after overnight abstinence and once under ad libitum smoking conditions. At each session, the smokers received nasal sprays that contained a placebo, 1 or 2 mg of nicotine in a random order at 90-min intervals. After each dose was administered, various tests of cognitive function, including the continuous performance test (CPT), an arithmetic test, and the N-back test, were administered. In the CPT, the participants were shown a series of letters in rapid succession, and they were asked to press a button when the target letter (X) appeared. In the arithmetic test, the participants were asked to determine whether the solutions to single-digit addition or subtraction problems were correct. In the N-back test, the participants were asked to remember a series of letters that were presented individually on a computer screen, and they were asked to identify whether a letter was repeated with one intervening letter. In the ad libitum smoking condition, nicotine enhanced performance on both the CPT and the arithmetic test in a dose-related manner, but it did not affect working memory performance, which had been assessed using the N-back test. Smokers showed more prominent cognitive impairment in the smoking abstinence condition, and nicotine administration improved cognitive function. This study was well designed, and it demonstrates that nicotine has cognitive-enhancing effects on attentional and computational task performance while controlling for both the nicotine dose and the abstinence interval (Myers et al., 2008).

Another study by Poltavski and Petros (2006) addressed the question of whether the cognitive-enhancing effects of nicotine were moderated by the baseline attention level of an individual. A total of 62 nonsmokers with low- and high-attention levels were recruited for their study. The participants were treated with either a placebo or 7 mg nicotine patch, and each of them completed the Wisconsin Card Sorting Test (WCST), the classic Stroop task, and the CPT. In the Stroop task, the participants were asked to press a button on the basis of the color of the word that appeared on a computer screen while ignoring its meaning. In the WCST, the participants were instructed to place cards sequentially below four key cards, but they were not informed of the rule by which the cards were to be sorted. Instead, the participants received positive verbal reinforcement if they arrived at the correct sorting strategy. After every 10 consecutive cards, the rule was changed, and the participant was tasked with finding the next correct strategy. Participants in the low attention group who were treated with nicotine performed better

on the CPT test compared with participants who were treated with the placebo. However, nicotine significantly impaired the performance of participants in the high attention group on the WCST. These results suggest that nicotine optimizes performance on cognitive tasks instead of improving it, and baseline cognitive function is important in modulating the effects of nicotine (Poltavski and Petros, 2006).

It is worth noting that the acute cognitive-enhancing effects of nicotine noted above may mediate some of the acute mood-enhancing or mood-stabilizing effects of nicotine (Waters and Sutton, 2000). For example, by improving attentional focus on a benign distracter stimulus, nicotine may alleviate the negative consequences of a stressor (Kassel and Shiffman, 1997).

Recently, implicit cognition researchers (Wiers and Stacy, 2006) have assessed the impact of smoking cues (vs. control cues) on cognition (Waters and Sayette, 2006). For example, the smoking Stroop task assesses attentional bias to smoking cues, and the Implicit Association Test assesses automatic (implicit) memory associations. Few studies have examined the acute effect of nicotine on task performance; however one study reported that memory associations to smoking cues became less positive after smoking (vs. not smoking) a cigarette (Waters et al., 2007). In addition, attentional bias was reduced by smoking (vs. not smoking) a cigarette (Waters et al., 2009). Acute smoking may reduce the distracting influence of cigarette cues on cognitive performance.

The brain regions that are activated by nicotine administration have been studied by functional neuroimaging studies in humans. In one of the earliest pharmacological functional magnetic resonance imaging (fMRI) studies, Stein et al. (1998) administered saline followed by three doses of nicotine (0.75, 1.50, and 2.25 mg/70 kg) intravenously. Their study found that nicotine activated several brain regions, including the nucleus accumbens, amygdala, cingulate, and frontal cortex, in a dose-dependent manner. These brain regions are known to be involved in the reward and cognitive functions. Another study (Rose et al., 2003) used positron emission tomography imaging to examine the changes in regional cerebral blood flow (rCBF). That study found that in cigarette smokers, nicotine increased or normalized the amount of rCBF in the left frontal region and decreased the amount of rCBF in the left amygdala, which concurs with the results of the Stein et al. study. In several other fMRI studies, the administration of nicotine via nicotine gum enhanced neuronal activity in prefrontal and parietal brain regions (Giessing et al., 2006; Thiel and Fink, 2008; Vossel et al., 2008). Together, these results support the notion that nicotine-induced activation of the prefrontal cortex plays a role in the cognitive-enhancing effects of nicotine. The results of the neuroimaging studies are consistent with the well-established observations that the prefrontal cortex plays a role in a number of cognitive functions including attention, working memory, response inhibition, affective processing, decision making, and goal-directed behavior (Miller and Cohen, 2001). As will be summarized below, nAChRs in the prefrontal cortex modulate the functions of many other neurotransmitters, including glutamate, DA, GABA, serotonin, norepinephrine, and ACh.



2.2. NEUROBIOLOGY OF THE COGNITIVE EFFECTS OF NICOTINE

Nicotine, which is the main addictive chemical in tobacco smoke, is essential in continued and compulsive tobacco use (Benowitz, 2009). Nicotine enters cerebral circulation within 10–60 s after a cigarette puff, and it binds to the nAChRs that are normally activated by ACh (Rose et al., 1999). nAChRs are ligand-gated ion channels that are permeable to sodium, potassium, and calcium ions. These receptors are excitatory and show relatively fast responses; their response times are of the order of milliseconds (Clader and Wang, 2005; Dani and Bertrand, 2007). It is important to note that ACh is hydrolyzed by the enzyme acetylcholinesterase within milliseconds of its release into the synaptic cleft; in contrast, no such rapid breakdown mechanism exists to remove nicotine from the synaptic cleft, so it activates the nAChR longer than ACh (Penton and Lester, 2009). This prolonged activation of the nAChR by nicotine results in the desensitization of the receptor and in its temporary inability to be activated by subsequent agonist activity. The desensitization and tolerance of the nAChR are thought to be crucial in the development of nicotine addiction (Picciotto et al., 2008; Quick and Lester, 2002).

Most nAChRs in the CNS are located presynaptically, and they modulate the release of several neurotransmitters, such as ACh, DA, serotonin, glutamate, GABA, and norepinephrine (Dani and Bertrand, 2007). Some nAChRs, such as those on the dopaminergic neurons in the ventral tegmental area, are also located postsynaptically. nAChRs can either be heteromeric channels that are formed by a combination of α and β subunits (e.g. $\alpha 4\beta 2$, $\alpha 3\beta 4$) or homomeric channels that are formed by a group of α subunits (e.g. $\alpha 6$ or $\alpha 7$). The two most commonly expressed nAChRs in the brain are $\alpha 4\beta 2$ and $\alpha 7$ nAChRs (Dani and Bertrand, 2007). Activation of nAChRs increases extracellular levels of DA in the nucleus accumbens and the prefrontal cortex; these brain areas are thought to be critical in mediating the rewarding and cognitive effects of nicotine, respectively (Balfour, 2009; Corrigall et al., 1992; Dos Santos Coura and Granon, 2012; Rahman et al., 2008).

The cellular mechanisms of nicotine-induced cognitive enhancement are not well characterized, but both the prefrontal cortex and hippocampal brain regions have been implicated in this effect (Leiser et al., 2009; Sarter et al., 2009). Electrophysiological data suggest that nicotine results in cognitive enhancement by improving the signal-to-noise ratio in the prefrontal cortex, and other evidence suggests that nicotine facilitates synaptic plasticity in the prefrontal cortex (Couey et al., 2007). The nAChR subunits that mediate the cognitive effects of nicotine may include $\alpha 2$, $\alpha 3$, $\alpha 4$, $\alpha 5$, $\alpha 7$, $\beta 2$, and $\beta 4$ (Changeux, 2010). As will be summarized below, most of the studies that have been conducted to date have focused on the $\alpha 7$ and $\beta 2$ subunits (Kenney and Gould, 2008).

2.2.1. Nicotinic Acetylcholine Receptors

2.2.1.1. $\alpha 7$ nAChR

$\alpha 7$ nAChRs are abundant in many brain regions that are associated with cognitive functions, including the hippocampus and prefrontal cortex (Gotti et al., 2007; Leiser et al., 2009). Like the NMDA type of glutamate receptor, $\alpha 7$ nAChRs are highly permeable to calcium, which allows them to enhance the release of neurotransmitters (e.g. glutamate) and to modulate synaptic plasticity (Gray et al., 1996; Quirk et al., 1997; Seguela et al., 1993). Relative to $\alpha 4\beta 2$ nAChRs, $\alpha 7$ nAChRs have a low affinity for nicotine and do not become desensitized at low nicotine concentrations (Quick and Lester, 2002; Wooltorton et al., 2003). This delayed desensitization of the $\alpha 7$ nAChRs may be a mechanism that allows the release of several neurotransmitters, including DA, to be maintained after the $\alpha 4\beta 2$ nAChRs have been desensitized (Giniatullin et al., 2005).

$\alpha 7$ nAChR knock-out mice show impairment in attention and working memory tasks (Fernandes et al., 2006; Hoyle et al., 2006). In a study by Young et al. (2004), $\alpha 7$ nAChR knock-out mice showed more errors of commission in a sustained attention task than the wild-type. It is also possible that both the distribution and density of various nAChR subtypes differ significantly between wild-type and $\alpha 7$ nAChR knock-out mice due to compensatory changes during development (Young et al., 2004).

In humans, $\alpha 7$ nAChRs may play a key role in the relationship between smoking and sensory gating sensitivity in individuals with schizophrenia (Adler et al., 1993; Nomikos et al., 2000; Taiminen et al., 1998). Between 75% and 85% of individuals with schizophrenia smoke cigarettes (de Leon and Diaz, 2005), and as many as 90% of them have cognitive deficits in at least one domain (e.g. attention, memory, or executive functioning) (Palmer et al., 1997; Leonard et al., 2001; Medalia et al., 2008; Poirier et al., 2002; Reichenberg et al., 2006). Postmortem examinations of the brains of schizophrenic patients revealed reductions in the density of $\alpha 7$ nAChRs in the hippocampus (Breese et al., 2000; Freedman et al., 1995; Guan et al., 1999; Martin-Ruiz et al., 2003), which has been linked to the sensory gating dysfunction that occurs in schizophrenia (Potter et al., 2006). Sensory gating is a process by which irrelevant stimuli are separated from meaningful ones, and it may underlie both sensory overload and the cognitive deficits that are observed in schizophrenic patients. Sensory gating dysfunction is measured as a reduced response to the middle latency (50 ms) component of an auditory event-related potential (Croft et al., 2001). Both nicotine and GTS-21 (DMXB-A), which is a partial $\alpha 7$ nAChR agonist, have been shown to reverse auditory gating deficits in a number of animal models and in schizophrenic patients (Martin and Freedman, 2007), and several $\alpha 7$ nAChR agonists are under investigation to reduce the cognitive deficits in individuals with schizophrenia, ADHD, and/or Alzheimer's disease (Wallace and Porter, 2011).

2.2.1.2. $\alpha 4\beta 2$ nAChR

Compared with $\alpha 7$ nAChRs, $\alpha 4\beta 2$ nAChRs have a high affinity for nicotine and become desensitized at low concentrations of nicotine that are within the range of nicotine

concentrations that is generally found in the blood of smokers (Gotti et al., 1997). The $\alpha 4\beta 2$ receptor subtype has a high affinity for a number of agonists including nicotine, ACh, varenicline, and cytisine. The activation of $\alpha 4\beta 2$ nAChRs that are located in DAergic cell bodies and presynaptic terminals increases DA release in both the nucleus accumbens and the prefrontal cortex (Chen et al., 2003), which, in turn, may contribute to the rewarding and cognitive-enhancing effects of nicotine, respectively.

The $\beta 2$ subunit, which is found in over 90% of nAChR pentamers, is highly expressed in the basal ganglia, the thalamus, and the hippocampus (Perry et al., 1992, 1995; Spurden et al., 1997). Mice that lack the $\beta 2$ subunit of the nAChR demonstrate deficits in attention, working memory, and behavioral flexibility (Granon and Changeux, 2006; Granon et al., 2003; Guillem et al., 2011). It was reported that nicotine did not enhance associative memory performance in $\beta 2$ knock-out mice, whereas associative memory performance was the expected response to nicotine administration in wild-type mice. In a more recent study, $\beta 2$ knock-out mice displayed deficits in exploratory behavior that could be partially alleviated by nicotine treatment (Besson et al., 2008).

Pharmacological studies that used partial agonists of the $\alpha 4\beta 2$ nAChR to study its role in cognitive functioning support their role in cognitive functions in a manner that is consistent with the aforementioned findings. One of these partial agonists, AZD3480 enhanced both attention and episodic memory function in healthy volunteers (Dunbar et al., 2007). Similarly, varenicline, which is another partial agonist for the $\alpha 4\beta 2$ nAChR and which is marketed as a treatment for smoking cessation (Rollema et al., 2007), alleviated learning deficits in mice that had been induced by either alcohol administration (Gulick and Gould, 2008) or nicotine withdrawal (Raybuck et al., 2008). In a recent study of cigarette smokers, 10 days of varenicline treatment improved working memory and attention deficits that were induced by nicotine withdrawal (Patterson et al., 2009b). The partial agonists of the $\alpha 4\beta 2$ nAChR may potentially be used as cognitive-enhancing agents for the treatment neuropsychiatric disorders with cognitive deficits as cognitive-enhancing agents.

2.2.1.3. Other nAChR

In addition to $\alpha 4\beta 2$ and $\alpha 7$ subtypes, $\alpha 2$, $\alpha 5$, $\alpha 3$, and $\beta 4$ subunits may also participate in cognitive-enhancing effect of nicotine (Changeux, 2010). For example, the $\alpha 5$ subunit is widely expressed both in the central and peripheral nervous systems as part of $\alpha 4\beta 2$, $\alpha 3\beta 2$, and $\alpha 3\beta 4$ nAChRs. Although this subunit lacks key residues that could be involved in the binding of either nicotine or ACh, its inclusion changes the function of the nAChR in which it is included. Mice that lack the $\alpha 5$ subunit demonstrate increased nicotine reward responses and reduced aversion to high doses of nicotine (Jackson et al., 2010). Further, these mice have reduced cognitive performance in attention tasks relative to the performance of wild-type mice (Bailey et al., 2010).

In a recent study, Winterer et al. (2010) found a significant association between a functional variant, rs16969968, of the gene that encodes the $\alpha 5$ subunit of nAChRs

(CHRNA5) and performance on the N-back working memory task that is consistent with the results of the aforementioned preclinical studies. The rs16969968 SNP has been associated with the age at which an individual initiates cigarette smoking, the severity of the nicotine dependence as measured by the Fagerström Test for Nicotine Dependence score, and the number of cigarettes that an individual smokes each day (Berrettini et al., 2008; Bierut et al., 2007; Saccone et al., 2007; Winterer et al., 2010). These findings suggest that the vulnerability to nicotine dependence that is associated with this particular SNP may be mediated by a reduction in the cognitive performance of the individual. Thus, individuals with baseline cognitive impairments may be more vulnerable to nicotine dependence for the cognitive-enhancing effects of nicotine (Winterer et al., 2010).

2.2.2. Dopamine

DA is implicated in a number of cognitive functions, including working memory, attention, and response inhibition (Colzato et al., 2009; Nieoullon, 2002; Tanila et al., 1998). DA dysfunction has also been implicated in psychiatric disorders that are associated with poor attention and working memory function such as ADHD and schizophrenia (Cheon et al., 2003; Seeman and Kapur, 2000). As will be summarized below, studies are beginning to shed light on the role of DA in nicotine-induced cognitive enhancement.

DA acts via five receptor subtypes (D1–D5) (D1–D5) (Sealfon and Olanow, 2000; Sokoloff and Schwartz, 1995; Zhu et al., 2008). The DA receptors are also classified into two main receptor families: the D1-like family (which includes the D1 and D5 receptors) and the D2-like family (which includes the D2, D3 and D4 receptors). The D2 receptor family also functions as an autoreceptor that acts to reduce the release of DA (Missale et al., 1998). Among the DA receptors, D2 and D4 are the primary receptors that have been examined in relation to the cognitive effects of nicotine. The D2 receptor family is of particular interest, and it has been implicated in set shifting and cognitive flexibility (van Holstein et al., 2011). Blocking the D2 receptors in the prefrontal cortices of rats has been shown to impair their set shifting abilities without changing their abilities to perform working memory tasks (Floresco et al., 2006).

2.2.2.1. D2 Receptor

Several studies have shown that genetic variation in the human D2 receptor gene modulates abstinence-induced changes in cognitive measures (Evans et al., 2009; Gilbert et al., 2004) and nicotine's effects on cognitive performance.

Jacobsen et al. (2006) reported that following the administration of a nicotine patch, smokers who carried the 957T allele of the gene for the D2 receptor experienced some impairment in their working memory abilities during a task that involved a high verbal working memory load. This particular 957T allele increases the binding availability of the D2 receptor (Hirvonen et al., 2004), which suggests that the reduced working memory function may be due to excess baseline levels of DA in carriers of the 957T

allele. Alternatively, the working memory performance of individuals who were homozygous for the 957C allele was not appreciably different between placebo and nicotine patch conditions. Thus, the authors suggested that individuals who carry two copies of the 957C allele may not be able to further increase DA activity during the performance of tasks that involve a high working memory load (Jacobsen et al., 2006). This study illustrates the way in which genetic variation that controls D2 receptor levels may influence the cognitive responses to nicotine.

2.2.2.2. D4 Receptor

Both the structure and pharmacology of the D4 receptor are similar to those of the D2 receptor (Van Tol et al., 1991). One study found evidence that the D4 receptor gene may modulate the attentional bias for smoking-related words that was observed in ex-smokers using a modified Stroop task (Munafò and Johnstone, 2008). Ex-smokers who carried at least one allele with 7 (long) or more repeats had significantly increased levels of color naming interference (Stroop effect) when tested using smoking-related words compared with ex-smokers who carried six or fewer repeats on both alleles, but this difference was not observed among current smokers. The DRD4 7-repeat (long) allele is associated with reduced DA activity in comparison with the 2- or 4-repeat variants (short) (Asghari et al., 1995). These findings suggest that the long allele of the DRD4 gene predicts that abstinent smokers will experience greater attentional bias for smoking cues in abstinent smokers possibly through reduced DA activity (Asghari et al., 1995).

2.2.2.3. Catechol-O-methyltransferase

Catechol-O-methyltransferase (COMT) is an enzyme that inactivates DA, and it is associated with DA regulation, cognitive processes, and the cognitive effects of nicotine. COMT contains a well-studied single nucleotide polymorphism that results in the presence of either a methionine (Met) or valine (Val) (val158met) in the enzyme (Sengupta et al., 2008). The COMT enzyme that contains Met is one-fourth as active as the COMT enzyme that contains Val. Therefore, because the Val allele results in a form of COMT that has increased enzymatic efficiency compared with the Met allele, lower levels of DA occur in the prefrontal cortex (Guo et al., 2007). In a pioneering study, Loughhead et al. (2008) studied the influence of variations in COMT on cognitive deficits and brain function during abstinence from smoking. Smokers were tested under two conditions: normal smoking and overnight abstinence (the total duration of which was 14 h). In each condition, the working memory performance of the smokers was tested using the visual N-back task. During abstinence, the smokers who carried two copies of the Val allele exhibited decreased fMRI BOLD signals in both the bilateral dorsal lateral prefrontal cortex and the dorsal cingulate/medial PFC. They also exhibited slower reaction times in the N-back task compared with their

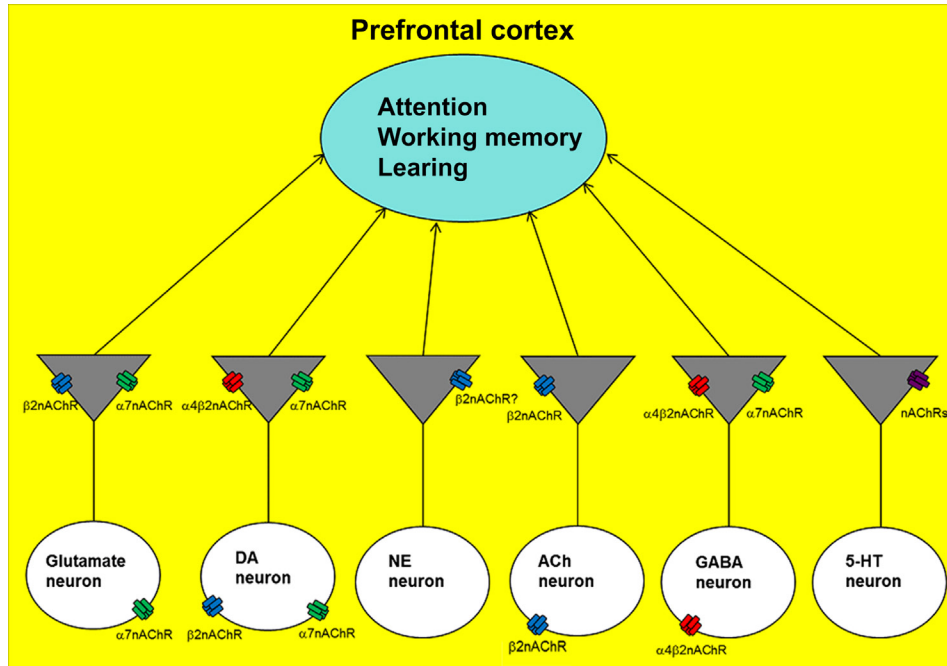


Figure 1 This illustrates the hypothesized effects of nicotinic acetylcholine receptors (nAChRs) on the regulation of dopamine (DA), glutamate, norepinephrine (NE), serotonin (5-HT), GABA, and acetylcholine (ACh) release in the prefrontal cortex. Activation of nAChRs enhances the release of neurotransmitters, but the exact types and locations of these nAChRs must still be determined. See [Dos Santos Coura and Granon \(2012\)](#) for details.

performances under normal smoking conditions ([Loughead et al., 2008](#)). These differences were not observed in smokers who carried at least one copy of the Met allele ([Loughead et al., 2008](#)).

In a recent study, we investigated the role of the COMT (val158met) polymorphism in acute responses to nicotine that was administered intravenously in a sample of African-American ($n = 56$) and European-American smokers ([Herman et al., 2013](#)). The study included a single laboratory session in which smokers were challenged with saline that was followed by the administration of 0.5 and 1.0 mg/70 kg doses of nicotine that were given at 30-min intervals following overnight abstinence from smoking. The cognitive measures that we investigated included the Mathematical Processing, CPT, and the Stroop Test, all of which were administered twice: once at the beginning of the session and once after the last nicotine administration. In African-Americans, the Val/Val genotype was associated with poorer performance on the CPT and the Stroop Test, but this was not the case for European-American smokers. The reduced transmission of DA during abstinence from smoking might have enhanced the way in which the COMT polymorphism affected cognitive performance such that a tighter control of

synaptic DA levels in smokers with the Val/Val genotype resulted in poorer performance on the Stroop Test and the CPT (Zhang et al., 2012).

2.3.3. Other Neurotransmitters

In addition to ACh and DA, other neurotransmitters participate in mediating the cognitive-enhancing effects of nicotine in both the hippocampus and the prefrontal cortex (Dos Santos Coura and Granon, 2012; Parikh et al., 2008; Sarter et al., 2009). The connections between the prefrontal cortex and many other cortical and subcortical areas, including the limbic system and the hippocampus, create a functional circuit that serves many cognitive functions, including attention, working memory, response inhibition, and decision making.

In the prefrontal cortex, the key neurotransmitters that are involved in cognitive functions include glutamate, DA, norepinephrine, serotonin, GABA, and ACh. The precise mechanisms for the cognitive-enhancing effects of nicotine have not yet been determined, but a working hypothesis for the interaction between nAChRs and neurotransmitter release in the prefrontal cortex is shown in Figure 1.



3. CONCLUSIONS

To summarize, human studies have demonstrated that nicotine has cognitive-enhancing effects in both nonsmokers and minimally deprived smokers. Cognitive functions in humans that are particularly improved by nicotine administration include fine motor functions, attentional functions, working memory, and episodic memory. These findings are consistent with human neuroimaging studies that have demonstrated activation in the prefrontal and parietal cortices following nicotine administration. Preclinical studies have implicated both $\alpha 4\beta 2$ and $\alpha 7$ nAChRs in the cognitive-enhancing effects of nicotine. The $\alpha 7$ subunit appears to modulate a sensory filtering function, and it may play an important role in the cognitive deficits that are associated with schizophrenia. Further, the $\beta 2$ subunit appears to be essential in mediating the cognitive functions that are associated with attention, working memory, and behavioral flexibility. The mechanisms of the cognitive-enhancing effects of nicotine may be mediated via the modulation of the release of various neurotransmitters by $\alpha 4\beta 2$ and $\alpha 7$ nAChRs in the prefrontal cortex. These neurotransmitters include DA, glutamate, serotonin, norepinephrine, GABA, and ACh, all of which contribute to the cognitive functions that take place in the prefrontal cortex (See Figure 12.1).

3.1. Treatment Implications

3.1.1. Targeting Cognitive Function as a Treatment for Smoking Cessation

Mounting evidence suggests that individuals with cognitive deficits may be more vulnerable to nicotine addiction (Yakir et al., 2007). In population-based studies, smokers were

found to have deficits in the cognitive functions that are related to attention, working memory, and impulse control (Wagner et al., 2012). These deficits were not correlated with lifetime nicotine use, and even smokers with low amounts of nicotine exposure display these deficits. These findings suggest that these deficits existed in some individuals before they began smoking. Further, Winterer et al. (2010) found that a genetic variation in the $\alpha 5$ nAChR may increase the degree to which an individual is vulnerable to nicotine dependence and may be associated with reduced performance on a working memory task. Presumably, individuals with genetic vulnerability may derive particular benefit from the cognitive-enhancing effects of nicotine (Winterer et al., 2010). Cognitive deficits are also common among patients with psychiatric disorders; for example, 75–90% of schizophrenia patients show evidence of cognitive deficits. Similarly, individuals with ADHD have impairment in their attention function, and ADHD is associated with elevated rates of smoking. Among smokers who were trying to quit smoking, it was found that poorer performance on the N-back test (a working memory task) predicted relapses (Patterson et al., 2009a).

We have also found that abstinence-induced deterioration in the performance of an individual on the Rapid Visual Information Processing Task, which assesses sustained attention and working memory, predicted whether smokers would relapse to smoking at the end of the study (Kang et al., 2012). Still more studies have reported that attentional biases to smoking cues predict relapses in smokers who are attempting to stop smoking (Janes et al., 2010; Powell et al., 2010; Waters et al., 2003). These findings suggest that cognitive-enhancement or cognitive-retraining may be an effective strategy for enabling people with nicotine addictions to quit smoking, especially smokers with cognitive deficits. Several behavioral and pharmacological cognitive-enhancement approaches have been under investigation, including approaches that use nAChR agonists (see below).

3.1.2. Subtype-Selective nAChR Agonists as Cognitive-Enhancers

Agonists that are selective for nAChRs may provide more effective cognitive enhancement than nicotine. Although nicotine produces cognitive enhancement, its therapeutic effects are limited due to rapid desensitization that temporarily renders the receptor inactive. As a result, nicotine also acts as an nAChR antagonist. It is important to note that desensitization of the nAChR is specific to both the agonist and the nicotinic receptor subtype. Conceivably, agonists that are selective for the various nAChR subtypes may be more effective cognitive-enhancers than nicotine. One such subtype-specific group of agonists that is under development as a cognitive enhancer is a group of $\alpha 7$ nAChR agonists. A promising group of medications are those that are selective for the $\alpha 7$ receptors (Wallace and Porter, 2011). These medications are undergoing clinical trials as cognitive-enhancers for patients with schizophrenia, Alzheimer's disease, and ADHD.

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