University of Nebraska - Lincoln

DigitalCommons@University of Nebraska - Lincoln

Uniformed Services University of the Health Sciences

U.S. Department of Defense

2014

Cognitive Effects of Nicotine

Mehmet Sofouglu
Yale University School of Medine

Aryeh I. Herman
Yale University School of Medine

Cendrine Robinson
Uniformed Services University of the Health Science

Andrew J. Waters
Uniformed Services University of the Health Science

Follow this and additional works at: http://digitalcommons.unl.edu/usuhs

CHAPTER TWELVE

Cognitive Effects of Nicotine

Mehmet Sofuoglu[1], Aryeh I. Herman[1], Cendrine Robinson[2] and Andrew J. Waters[2]

[1]Department of Psychiatry and VA Connecticut Healthcare System, School of Medicine, Yale University, West Haven, CT, USA
[2]Department of Medical and Clinical Psychology, Uniformed Services University of the Health Science, Bethesda, MD, USA

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 rein force 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 α7 and α4β2 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 abstinent 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. How-ever, nicotine significantly impaired the performance of participants in the high atten-tion 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 smok-ing (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 func-tional 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 acti-vation 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 observa-tions 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. α4β2, α3β4) or homomeric channels that are formed by a group of α subunits (e.g. α6 or α7). The two most commonly expressed nAChRs in the brain are α4β2 and α7 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 α2, α3, α4, α5, α7, β2, and β4 (Changeux, 2010). As will be summarized below, most of the studies that have been conducted to date have focused on the α7 and β2 subunits (Kenney and Gould, 2008).

2.2.1. Nicotinic Acetylcholine Receptors

2.2.1.1. a7nAChR

α7 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, α7 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; Quik et al., 1997; Seguela et al., 1993). Relative to α4β2 nAChRs, a7nAChRs 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 a7nAChRs may be a mechanism that allows the release of several neurotransmitters, including DA, to be maintained after the α4β2 nAChRs have been desensitized (Giniatullin et al., 2005).

a7nAChR 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), a7nAChR 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 a7nAChR knock–out mice due to compensatory changes during development (Young et al., 2004).

In humans, a7nAChRs 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 a7nAChRs 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 a7nAChR 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 a7nAChR 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. α4β2 nAChR

Compared with a7nAChRs, α4β2 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 α4β2 receptor subtype has a high affinity for a number of agonists including nicotine, ACh, varenicline, and cytisine. The activation of α4β2 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 β2 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 β2 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 β2 knock-out mice, whereas associative memory performance was the expected response to nicotine administration in wild-type mice. In a more recent study, β2 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 α4β2 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 α4β2 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 α4β2 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 α4β2 and α7 subtypes, α2, α5, α3, and β4 subunits may also participate in cognitive-enhancing effect of nicotine (Changeux, 2010). For example, the a5 subunit is widely expressed both in the central and peripheral nervous systems as part of α4β2, α3β2, and α3β4 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 α5 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 a5 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 (Munafo 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, Loughead 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
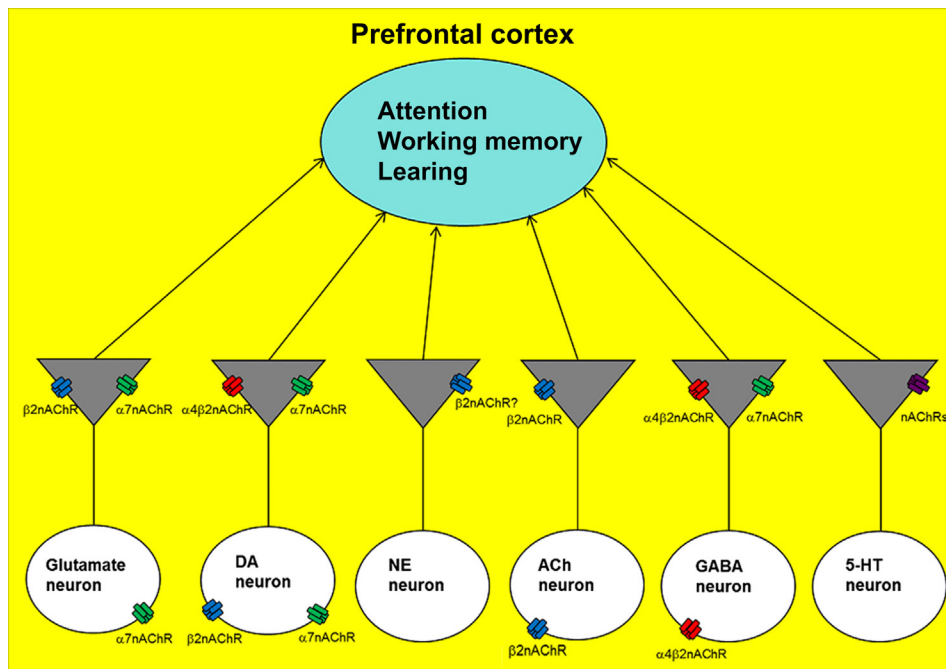
Figure 1 This illustrates the hypothesized effects of nicotinic acetylcholine receptors (nAChRs) on the regulation of dopamine (DA), glutamate, norepinephrine (NE), serotonin (5-HT), GABA, and acetylcholine (ACh) release in the prefrontal cortex. Activation of nAChRs enhances the release of neurotransmitters, 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 α4β2 and α7 nAChRs in the cognitive-enhancing effects of nicotine. The α7 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 β2 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 α7β2 and α7 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 α5 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 α7 nAChR agonists. A promising group of medications are those that are selective for the α7 receptors (Wallace and Porter, 2011). These medications are undergoing clinical trials as cognitive-enhancers for patients with schizophrenia, Alzheimer's disease, and ADHD.

ACKNOWLEDGMENTS

REFERENCES

Adler, L.E., Hoffer, L.D., Wiser, A., Freedman, R., 1993. Normalization of auditory physiology by cigarette smoking in schizophrenic patients. Am. J. Psychiatry 150, 1856–1861.

Asghari, V., Sanyal, S., Buchwaldt, S., Paterson, A., Jovanovic, V., Van Tol, H.H., 1995. Modulation of intracellular cyclic AMP levels by different human dopamine D4 receptor variants. J. Neurochem. 65, 1157–1165.

Bailey, C.D., De Biasi, M., Fletcher, P.J., Lambe, E.K., 2010. The nicotinic acetylcholine receptor alpha5 subunit plays a key role in attention circuitry and accuracy. J. Neurosci. 30, 9241–9252.

Balfour, D.J., 2009. The neuronal pathways mediating the behavioral and addictive properties of nicotine. Handb. Exp. Pharmacol. 192, 209–233.

Baschnagel, J.S., Hawk Jr., L.W., 2008. The effects of nicotine on the attentional modification of the acoustic startle response in nonsmokers. Psychopharmacology (Berl) 198, 93–101.

Benowitz, N.L., 2009. Pharmacology of nicotine: addiction, smoking-induced disease, and therapeutics. Annu. Rev. Pharmacol. Toxicol. 49, 57–71.

Berrettini, W., Yuan, X., Tozzi, F., Song, K., Francks, C., Chilcoat, H., Waterworth, D., Muglia, P., Mooser, V., 2008. Alpha-5/alpha-3 nicotinic receptor subunit alleles increase risk for heavy smoking. Mol. Psychiatry 13, 368–373.

Besson, M., Suarez, S., Cormier, A., Changeux, J.P., Granon, S., 2008. Chronic nicotine exposure has dissociable behavioural effects on control and beta2-/- mice. Behav. Genet. 38, 503–514.

Bierut, L.J., Madden, P.A., Breslau, N., Johnson, E.O., Hatsukami, D., Pomerleau, O.F., Swan, G.E., Rutter, J., Bertelsen, S., Fox, L., Fugman, D., Goate, A.M., Hinrichs, A.L., Konvicka, K., Martin, N.G., Montgomery, G.W., Saccone, N.L., Saccone, S.F., Wang, J.C., Chase, G.A., Rice, J.P., Ballinger, D.G., 2007. Novel genes identified in a high-density genome wide association study for nicotine dependence. Hum. Mol. Genet. 16, 24–35.

Breese, C.R., Lee, M.J., Adams, C.E., Sullivan, B., Logel, J., Gillen, K.M., Marks, M.J., Collins, A.C., Leonard, S., 2000. Abnormal regulation of high affinity nicotinic receptors in subjects with schizophrenia. Neuropsychopharmacology 23, 351–364.

Center for Disease Control, 2008. Smoking-attributable mortality, years of potential life lost, and productivity losses–United States, 2000-2004. MMWR Morb. Mortal. Wkly. Rep. 57, 1226–1228.

Center for Disease Control, 2011. Current cigarette smoking prevalence among working adults–United States, 2004-2010. MMWR Morb. Mortal. Wkly. Rep. 60, 1305–1309.

Chamberlain, S.R., Robbins, T.W., Winder-Rhodes, S., Muller, U., Sahakian, B.J., Blackwell, A.D., Barnett, J.H., 2011. Translational approaches to frontostriatal dysfunction in attention-deficit/hyperactivity disorder using a computerized neuropsychological battery. Biol. Psychiatry 69, 1192–1203.

Changeux, J.P., 2010. Nicotine addiction and nicotinic receptors: lessons from genetically modified mice. Nat. Rev. Neurosci. 11, 389–401.

Chen, Y., Sharples, T.J., Phillips, K.G., Benedetti, G., Broad, L.M., Zwart, R., Sher, E., 2003. The nicotinic alpha 4 beta 2 receptor selective agonist, TC-2559, increases dopamine neuronal activity in the ventral tegmental area of rat midbrain slices. Neuropharmacology 45, 334–344.

Cheon, K.A., Ryu, Y.H., Kim, Y.K., Namkoong, K., Kim, C.H., Lee, J.D., 2003. Dopamine transporter density in the basal ganglia assessed with [^{123}I]IPT SPET in children with attention deficit hyperactivity disorder. Eur. J. Nucl. Med. Mol. Imaging 30, 306–311.

Clader, J.W., Wang, Y., 2005. Muscarinic receptor agonists and antagonists in the treatment of Alzheimer's disease. Curr. Pharm. Des. 11, 3353–3361.

Colzato, L.S., van den Wildenberg, W.P., van Wouwe, N.C., Pannebakker, M.M., Hommel, B., 2009. Dopamine and inhibitory action control: evidence from spontaneous eye blink rates. Exp. Brain Res. 196, 467–474.

Corrigall, W.A., Franklin, K.B., Coen, K.M., Clarke, P.B., 1992. The mesolimbic dopaminergic system is implicated in the reinforcing effects of nicotine. Psychopharmacology (Berl) 107, 285–289.

Couey, J.J., Meredith, R.M., Spijker, S., Poorthuis, R.B., Smit, A.B., Brussaard, A.B., Mansvelder, H.D., 2007. Distributed network actions by nicotine increase the threshold for spike-timing-dependent plasticity in prefrontal cortex. Neuron 54, 73–87.

Croft, R.J., Lee, A., Bertolot, J., Gruzelier, J.H., 2001. Associations of P50 suppression and desensitization with perceptual and cognitive features of "unreality" in schizotypy. Biol. Psychiatry 50, 441–446.

Dani, J.A., Bertrand, D., 2007. Nicotinic acetylcholine receptors and nicotinic cholinergic mechanisms of the central nervous system. Annu. Rev. Pharmacol. Toxicol. 47, 699–729.

de Leon, J., Diaz, F.J., 2005. A meta-analysis of worldwide studies demonstrates an association between schizophrenia and tobacco smoking behaviors. Schizophr. Res. 76, 135–157.

Dos Santos Coura, R., Granon, S., 2012. Prefrontal neuromodulation by nicotinic receptors for cognitive processes. Psychopharmacology. http://dx.doi.org/10.1007/s00213-011-2596-6.

Dunbar, G., Boeijinga, P.H., Demazieres, A., Cisterni, C., Kuchibhatla, R., Wesnes, K., Luthringer, R., 2007. Effects of TC-1734 (AZD3480), a selective neuronal nicotinic receptor agonist, on cognitive performance and the EEG of young healthy male volunteers. Psychopharmacology (Berl) 191, 919–929.

Ernst, M., Heishman, S.J., Spurgeon, L., London, E.D., 2001. Smoking history and nicotine effects on cognitive performance. Neuropsychopharmacology 25, 313–319.

Evans, D.E., Park, J.Y., Maxfield, N., Drobes, D.J., 2009. Neurocognitive variation in smoking behavior and withdrawal: genetic and affective moderators. Genes Brain Behav. 8, 86–96.

Fernandes, C., Hoyle, E., Dempster, E., Schalkwyk, L.C., Collier, D.A., 2006. Performance deficit of alpha7 nicotinic receptor knockout mice in a delayed matching-to-place task suggests a mild impairment of working/episodic-like memory. Genes Brain Behav. 5, 433–440.

Fiore, M.C., Jaen, C.R., Baker, T.B., 2008. Treating Tobacco Use and Dependence: 2008 Update. Clinical Practice Guideline. U.S. Department of Health and Human Services, Rockville, MD.

Floresco, S.B., Magyar, O., Ghods-Sharifi, S., Vexelman, C., Tse, M.T., 2006. Multiple dopamine receptor subtypes in the medial prefrontal cortex of the rat regulate set-shifting. Neuropsychopharmacology 31, 297–309.

Foulds, J., Stapleton, J., Swettenham, J., Bell, N., McSorley, K., Russell, M.A., 1996. Cognitive performance effects of subcutaneous nicotine in smokers and never-smokers. Psychopharmacology (Berl) 127, 31–38.

Freedman, R., Hall, M., Adler, L.E., Leonard, S., 1995. Evidence in postmortem brain tissue for decreased numbers of hippocampal nicotinic receptors in schizophrenia. Biol. Psychiatry 38, 22–33.

Giessing, C., Thiel, C.M., Rosler, F., Fink, G.R., 2006. The modulatory effects of nicotine on parietal cortex activity in a cued target detection task depend on cue reliability. Neuroscience 137, 853–864.

Gilbert, D., McClernon, J., Rabinovich, N., Sugai, C., Plath, L., Asgaard, G., Zuo, Y., Huggenvik, J., Botros, N., 2004. Effects of quitting smoking on EEG activation and attention last for more than 31 days and are more severe with stress, dependence, DRD2 A1 allele, and depressive traits. Nicotine Tob. Res. 6, 249–267.

Giniatullin, R., Nistri, A., Yakel, J.L., 2005. Desensitization of nicotinic ACh receptors: shaping cholinergic signaling. Trends Neurosci. 28, 371–378.

Godtfredsen, N.S., Prescott, E., 2011. Benefits of smoking cessation with focus on cardiovascular and respiratory comorbidities. Clin. Respir. J. 5, 187–194.

Gotti, C., Fornasari, D., Clementi, F., 1997. Human neuronal nicotinic receptors. Prog. Neurobiol. 53, 199–237.

Gotti, C., Moretti, M., Gaimarri, A., Zanardi, A., Clementi, F., Zoli, M., 2007. Heterogeneity and complexity of native brain nicotinic receptors. Biochem. Pharmacol. 74, 1102–1111.

Granon, S., Changeux, J.P., 2006. Attention-deficit/hyperactivity disorder: a plausible mouse model? Acta Paediatr. 95, 645–649.

Granon, S., Faure, P., Changeux, J.P., 2003. Executive and social behaviors under nicotinic receptor regulation. Proc. Natl. Acad. Sci. U.S.A. 100, 9596–9601.

Gray, R., Rajan, A.S., Radcliffe, K.A., Yakehiro, M., Dani, J.A., 1996. Hippocampal synaptic transmission enhanced by low concentrations of nicotine. Nature 383, 713–716.

Guan, Z.Z., Zhang, X., Blennow, K., Nordberg, A., 1999. Decreased protein level of nicotinic receptor alpha7 subunit in the frontal cortex from schizophrenic brain. Neuroreport 10, 1779–1782.

Guillem, K., Bloem, B., Poorthuis, R.B., Loos, M., Smit, A.B., Maskos, U., Spijker, S., Mansvelder, H.D., 2011. Nicotinic acetylcholine receptor beta2 subunits in the medial prefrontal cortex control attention. Science 333, 888–891.

Gulick, D., Gould, T.J., 2008. Varenicline ameliorates ethanol-induced deficits in learning in C57BL/6 mice. Neurobiol. Learn. Mem. 90, 230–236.

Guo, S., Chen da, F., Zhou, D.F., Sun, H.Q., Wu, G.Y., Haile, C.N., Kosten, T.A., Kosten, T.R., Zhang, X.Y., 2007. Association of functional catechol O-methyl transferase (COMT) Val108Met polymorphism with smoking severity and age of smoking initiation in Chinese male smokers. Psychopharmacology (Berl) 190, 449–456.

Harrison, E.L., Coppola, S., McKee, S.A., 2009. Nicotine deprivation and trait impulsivity affect smokers' performance on cognitive tasks of inhibition and attention. Exp. Clin. Psychopharmacol. 17, 91–98.

Hatsukami, D.K., Hughes, J.R., Pickens, R.W., Svikis, D., 1984. Tobacco withdrawal symptoms: an experimental analysis. Psychopharmacology (Berl) 84, 231–236.

Heishman, S.J., 1998. What aspects of human performance are truly enhanced by nicotine? Addiction 93, 317–320.

Heishman, S.J., Kleykamp, B.A., Singleton, E.G., 2010. Meta-analysis of the acute effects of nicotine and smoking on human performance. Psychopharmacology 210, 453–469.

Herman, A.I., Sofuoglu, M., 2010. Comparison of available treatments for tobacco addiction. Curr. Psychiatry Rep. 12, 433–440.

Herman, A.I., Jatlow, P.I., Gelernter, J., Listman, J.B., Sofuoglu, M., , 2013. COMT Val158Met modulates subjective responses to intravenous nicotine and cognitive performance in abstinent smokers. Pharmacogenomics J , http://dx.doi.org/10.1038/tpj.2013.1. [Epub ahead of print] PubMed PMID: 23459442; PubMed Central PMCID: PMC3675163.

Hirvonen, M., Laakso, A., Nagren, K., Rinne, J.O., Pohjalainen, T., Hietala, J., 2004. C957T polymorphism of the dopamine D2 receptor (DRD2) gene affects striatal DRD2 availability in vivo. Mol. Psychiatry 9, 1060–1061.

Hoyle, E., Genn, R.F., Fernandes, C., Stolerman, I.P., 2006. Impaired performance of alpha7 nicotinic receptor knockout mice in the five-choice serial reaction time task. Psychopharmacology (Berl) 189, 211–223.

Hughes, J.R., Hatsukami, D., 1986. Signs and symptoms of tobacco withdrawal. Arch. Gen. Psychiatry 43, 289–294.

Jackson, K.J., Marks, M.J., Vann, R.E., Chen, X., Gamage, T.F., Warner, J.A., Damaj, M.I., 2010. Role of alpha5 nicotinic acetylcholine receptors in pharmacological and behavioral effects of nicotine in mice. J. Pharmacol. Exp. Ther. 334, 137–146.

Jacobsen, L.K., Krystal, J.H., Mencl, W.E., Westerveld, M., Frost, S.J., Pugh, K.R., 2005. Effects of smoking and smoking abstinence on cognition in adolescent tobacco smokers. Biol. Psychiatry 57, 56–66.

Jacobsen, L.K., Pugh, K.R., Mencl, W.E., Gelernter, J., 2006. C957T polymorphism of the dopamine D2 receptor gene modulates the effect of nicotine on working memory performance and cortical processing efficiency. Psychopharmacology (Berl) 188, 530–540.

Janes, A.C., Pizzagalli, D.A., Richardt, S., deB Frederick, B., Chuzi, S., Pachas, G., Culhane, M.A., Holmes, A.J., Fava, M., Evins, A.E., Kaufman, M.J., 2010. Brain reactivity to smoking cues prior to smoking cessation predicts ability to maintain tobacco abstinence. Biol. Psychiatry 67, 722–729.

Jemal, A., Thun, M.J., Ries, L.A., Howe, H.L., Weir, H.K., Center, M.M., Ward, E., Wu, X.C., Eheman, C., Anderson, R., Ajani, U.A., Kohler, B., Edwards, B.K., 2008. Annual report to the nation on the status of cancer, 1975–2005, featuring trends in lung cancer, tobacco use, and tobacco control. J. Natl. Cancer Inst. 100, 1672–1694.

Kang, N., Robinson, C., Wetter, D.W., Cinciripini, P., Yisheng Li, Y., Waters, A.J., 2012. Abstinence-induced decrements in sustained attention predict relapse in smoking cessation. Presentation at the Forthcoming American Psychological Association Conference, Orlando, FL.

Kassel, J.D., Shiffman, S., 1997. Attentional mediation of cigarette smoking's effect on anxiety. Health Psychol. 16, 359–368.

Kenney, J.W., Gould, T.J., 2008. Modulation of hippocampus-dependent learning and synaptic plasticity by nicotine. Mol. Neurobiol. 38, 101–121.

Lawrence, N.S., Ross, T.J., Stein, E.A., 2002. Cognitive mechanisms of nicotine on visual attention. Neuron 36, 539–548.

Leiser, S.C., Bowlby, M.R., Comery, T.A., Dunlop, J., 2009. A cog in cognition: how the alpha7 nicotinic acetylcholine receptor is geared towards improving cognitive deficits. Pharmacol. Ther. 122, 302–311.

Leonard, S., Adler, L.E., Benhammou, K., Berger, R., Breese, C.R., Drebing, C., Gault, J., Lee, M.J., Logel, J., Olincy, A., Ross, R.G., Stevens, K., Sullivan, B., Vianzon, R., Virnich, D.E., Waldo, M., Walton, K., Freedman, R., 2001. Smoking and mental illness. Pharmacol. Biochem. Behav. 70, 561–570.

Levin, E.D., McClernon, F.J., Rezvani, A.H., 2006. Nicotinic effects on cognitive function: behavioral characterization, pharmacological specification, and anatomic localization. Psychopharmacology (Berl) 184, 523–539.

Loughead, J., Wileyto, E.P., Valdez, J.N., Sanborn, P., Tang, K., Strasser, A.A., Ruparel, K., Ray, R., Gur, R.C., Lerman, C., 2008. Effect of abstinence challenge on brain function and cognition in smokers differs by COMT genotype. Mol. Psychiatry 14, 820–826.

Mansvelder, H.D., van Aerde, K.I., Couey, J.J., Brussaard, A.B., 2006. Nicotinic modulation of neuronal networks: from receptors to cognition. Psychopharmacology (Berl) 184, 292–305.

Martin-Ruiz, C.M., Haroutunian, V.H., Long, P., Young, A.H., Davis, K.L., Perry, E.K., Court, J.A., 2003. Dementia rating and nicotinic receptor expression in the prefrontal cortex in schizophrenia. Biol. Psychiatry 54, 1222–1233.

Martin, L.F., Freedman, R., 2007. Schizophrenia and the alpha7 nicotinic acetylcholine receptor. Int. Rev. Neurobiol. 78, 225–246.

McClernon, F.J., Kollins, S.H., Lutz, A.M., Fitzgerald, D.P., Murray, D.W., Redman, C., Rose, J.E., 2008. Effects of smoking abstinence on adult smokers with and without attention deficit hyperactivity disorder: results of a preliminary study. Psychopharmacology (Berl) 197, 95–105.

Medalia, A., Thysen, J., Freilich, B., 2008. Do people with schizophrenia who have objective cognitive impairment identify cognitive deficits on a self report measure? Schizophr. Res. 105, 156–164.

Meinke, A., Thiel, C.M., Fink, G.R., 2006. Effects of nicotine on visuo-spatial selective attention as indexed by event-related potentials. Neuroscience 141, 201–212.

Menzin, J., Lines, L.M., Marton, J., 2009. Estimating the short-term clinical and economic benefits of smoking cessation: do we have it right? Expert Rev. Pharmacoecon. Outcomes Res. 9, 257–264.

Milberger, S., Biederman, J., Faraone, S.V., Chen, L., Jones, J., 1997. Further evidence of an association between attention–deficit/hyperactivity disorder and cigarette smoking. Findings from a high–risk sample of siblings. Am. J. Addict. 6, 205–217.

Miller, E.K., Cohen, J.D., 2001. An integrative theory of prefrontal cortex function. Annu. Rev. Neurosci. 24, 167–202.

Missale, C., Nash, S.R., Robinson, S.W., Jaber, M., Caron, M.G., 1998. Dopamine receptors: from structure to function. Physiol. Rev. 78, 189–225.

Mumenthaler, M.S., Taylor, J.L., O'Hara, R., Yesavage, J.A., 1998. Influence of nicotine on simulator flight performance in non-smokers. Psychopharmacology (Berl) 140, 38–41.

Munafo, M.R., Johnstone, E.C., 2008. Smoking status moderates the association of the dopamine D4 receptor (DRD4) gene VNTR polymorphism with selective processing of smoking-related cues. Addict. Biol. 13, 435–439.

Myers, C.S., Taylor, R.C., Moolchan, E.T., Heishman, S.J., 2008. Dose–related enhancement of mood and cognition in smokers administered nicotine nasal spray. Neuropsychopharmacology 33, 588–598.

Newhouse, P.A., Potter, A.S., Dumas, J.A., Thiel, C.M., 2011. Functional brain imaging of nicotinic effects on higher cognitive processes. Biochem. Pharmacol. 82 (8), 943–951.

Nieoullon, A., 2002. Dopamine and the regulation of cognition and attention. Prog. Neurobiol. 67, 53–83.

Nomikos, G.G., Schilstrom, B., Hildebrand, B.E., Panagis, G., Grenhoff, J., Svensson, T.H., 2000. Role of alpha7 nicotinic receptors in nicotine dependence and implications for psychiatric illness. Behav. Brain Res. 113, 97–103.

Palmer, B.W., Heaton, R.K., Paulsen, J.S., Kuck, J., Braff, D., Harris, M.J., Zisook, S., Jeste, D.V., 1997. Is it possible to be schizophrenic yet neuropsychologically normal? Neuropsychology 11, 437–446.

Parikh, V., Man, K., Decker, M.W., Sarter, M., 2008. Glutamatergic contributions to nicotinic acetylcholine receptor agonist–evoked cholinergic transients in the prefrontal cortex. J. Neurosci. 28, 3769–3780.

Patterson, F., Jepson, C., Loughead, J., Perkins, K., Strasser, A.A., Siegel, S., Frey, J., Gur, R., Lerman, C., 2009a. Working memory deficits predict short-term smoking resumption following brief abstinence. Drug Alcohol Depend. 106, 61–64.

Patterson, F., Jepson, C., Strasser, A.A., Loughead, J., Perkins, K.A., Gur, R.C., Frey, J.M., Siegel, S., Lerman, C., 2009b. Varenicline improves mood and cognition during smoking abstinence. Biol. Psychiatry 65, 144–149.

Penton, R.E., Lester, R.A., 2009. Cellular events in nicotine addiction. Semin. Cell Dev. Biol. 20, 418–431.

Perry, E.K., Court, J.A., Johnson, M., Piggott, M.A., Perry, R.H., 1992. Autoradiographic distribution of [^{3}H]nicotine binding in human cortex: relative abundance in subicular complex. J. Chem. Neuroanat. 5, 399–405.

Perry, E.K., Morris, C.M., Court, J.A., Cheng, A., Fairbairn, A.F., McKeith, I.G., Irving, D., Brown, A., Perry, R.H., 1995. Alteration in nicotine binding sites in Parkinson's disease, Lewy body dementia and Alzheimer's disease: possible index of early neuropathology. Neuroscience 64, 385–395.

Picciotto, M.R., Addy, N.A., Mineur, Y.S., Brunzell, D.H., 2008. It is not "either/or": activation and desensitization of nicotinic acetylcholine receptors both contribute to behaviors related to nicotine addiction and mood. Prog. Neurobiol. 84, 329–342.

Piper, M.E., Piasecki, T.M., Federman, E.B., Bolt, D.M., Smith, S.S., Fiore, M.C., Baker, T.B., 2004. A multiple motives approach to tobacco dependence: the Wisconsin Inventory of Smoking Dependence Motives (WISDM-68). J. Consult. Clin. Psychol. 72, 139–154.

Poirier, M.F., Canceil, O., Bayle, F., Millet, B., Bourdel, M.C., Moatti, C., Olie, J.P., Attar-Levy, D., 2002. Prevalence of smoking in psychiatric patients. Prog. Neuropsychopharmacol. Biol. Psychiatry 26, 529–537.

Poltavski, D.V., Petros, T., 2006. Effects of transdermal nicotine on attention in adult non-smokers with and without attentional deficits. Physiol. Behav. 87, 614–624.

Poorthuis, R.B., Goriounova, N.A., Couey, J.J., Mansvelder, H.D., 2009. Nicotinic actions on neuronal networks for cognition: general principles and long-term consequences. Biochem. Pharmacol. 78, 668–676.

Potter, D., Summerfelt, A., Gold, J., Buchanan, R.W., 2006. Review of clinical correlates of P50 sensory gating abnormalities in patients with schizophrenia. Schizophr. Bull. 32, 692–700.

Powell, J., Dawkins, L., West, R., Pickering, A., 2010. Relapse to smoking during unaided cessation: clinical, cognitive and motivational predictors. Psychopharmacology 212, 537–549.

Quick, M.W., Lester, R.A., 2002. Desensitization of neuronal nicotinic receptors. J. Neurobiol. 53, 457–478.

Quik, M., Philie, J., Choremis, J., 1997. Modulation of alpha7 nicotinic receptor-mediated calcium influx by nicotinic agonists. Mol. Pharmacol. 51, 499–506.

Rahman, S., Zhang, Z., Papke, R.L., Crooks, P.A., Dwoskin, L.P., Bardo, M.T., 2008. Region-specific effects of N, N'-dodecane-1,12-diyl-bis-3-picolinium dibromide on nicotine-induced increase in extracellular dopamine in vivo. Br. J. Pharmacol. 153, 792–804.

Raybuck, J.D., Portugal, G.S., Lerman, C., Gould, T.J., 2008. Varenicline ameliorates nicotine withdrawal-induced learning deficits in C57BL/6 mice. Behav. Neurosci. 122, 1166–1171.

Reichenberg, A., Weiser, M., Caspi, A., Knobler, H.Y., Lubin, G., Harvey, P.D., Rabinowitz, J., Davidson, M., 2006. Premorbid intellectual functioning and risk of schizophrenia and spectrum disorders. J. Clin. Exp. Neuropsychol. 28, 193–207.

Rollema, H., Chambers, L.K., Coe, J.W., Glowa, J., Hurst, R.S., Lebel, L.A., Lu, Y., Mansbach, R.S., Mather, R.J., Rovetti, C.C., Sands, S.B., Schaeffer, E., Schulz, D.W., Tingley 3rd, F.D., Williams, K.E., 2007. Pharmacological profile of the alpha4beta2 nicotinic acetylcholine receptor partial agonist varenicline, an effective smoking cessation aid. Neuropharmacology 52, 985–994.

Rose, J.E., Behm, F.M., Westman, E.C., Coleman, R.E., 1999. Arterial nicotine kinetics during cigarette smoking and intravenous nicotine administration: implications for addiction. Drug Alcohol Depend. 56, 99–107.

Rose, J.E., Behm, F.M., Westman, E.C., Mathew, R.J., London, E.D., Hawk, T.C., Turkington, T.G., Coleman, R.E., 2003. PET studies of the influences of nicotine on neural systems in cigarette smokers. Am. J. Psychiatry 160, 323–333.

Russell, M.A.H., Peto, J., Patel, U.A., 1974. Classification of smoking by factorial structure of motives. J. R. Stat. Soc. 137, 313–346.

Saccone, S.F., Hinrichs, A.L., Saccone, N.L., Chase, G.A., Konvicka, K., Madden, P.A., Breslau, N., Johnson, E.O., Hatsukami, D., Pomerleau, O., Swan, G.E., Goate, A.M., Rutter, J., Bertelsen, S., Fox, L., Fugman,

D., Martin, N.G., Montgomery, G.W., Wang, J.C., Ballinger, D.G., Rice, J.P., Bierut, L.J., 2007. Cholinergic nicotinic receptor genes implicated in a nicotine dependence association study targeting 348 candidate genes with 3713 SNPs. Hum. Mol. Genet. 16, 36–49.

Sarter, M., Parikh, V., Howe, W.M., 2009. nAChR agonist–induced cognition enhancement: integration of cognitive and neuronal mechanisms. Biochem. Pharmacol. 78, 658–667.

Sealfon, S.C., Olanow, C.W., 2000. Dopamine receptors: from structure to behavior. Trends Neurosci. 23, S34–S40.

Seeman, P., Kapur, S., 2000. Schizophrenia: more dopamine, more D2 receptors. Proc. Natl. Acad. Sci. U.S.A. 97, 7673–7675.

Seguela, P., Wadiche, J., Dineley-Miller, K., Dani, J.A., Patrick, J.W., 1993. Molecular cloning, functional properties, and distribution of rat brain alpha 7: a nicotinic cation channel highly permeable to calcium. J. Neurosci. 13, 596–604.

Sengupta, S., Grizenko, N., Schmitz, N., Schwartz, G., Bellingham, J., Polotskaia, A., Stepanian, M.T., Goto, Y., Grace, A.A., Joober, R., 2008. COMT Val108/158Met polymorphism and the modulation of task-oriented behavior in children with ADHD. Neuropsychopharmacology 33, 3069–3077.

Sharma, A., Brody, A.L., 2009. In vivo brain imaging of human exposure to nicotine and tobacco. Handb. Exp. Pharmacol. 192, 145–171.

Sokoloff, P., Schwartz, J.C., 1995. Novel dopamine receptors half a decade later. Trends Pharmacol. Sci. 16, 270–275.

Spurden, D.P., Court, J.A., Lloyd, S., Oakley, A., Perry, R., Pearson, C., Pullen, R.G., Perry, E.K., 1997. Nicotinic receptor distribution in the human thalamus: autoradiographical localization of [^{3}H]nicotine and [^{125}I] alpha–bungarotoxin binding. J. Chem. Neuroanat. 13, 105–113.

Stein, E.A., Pankiewicz, J., Harsch, H.H., Cho, J.K., Fuller, S.A., Hoffmann, R.G., Hawkins, M., Rao, S.M., Bandettini, P.A., Bloom, A.S., 1998. Nicotine-induced limbic cortical activation in the human brain: a functional MRI study. Am. J. Psychiatry 155, 1009–1015.

Swan, G.E., Lessov-Schlaggar, C.N., 2007. The effects of tobacco smoke and nicotine on cognition and the brain. Neuropsychol. Rev. 17, 259–273.

Taiminen, T.J., Salokangas, R.K., Saarijarvi, S., Niemi, H., Lehto, H., Ahola, V., Syvalahti, E., 1998. Smoking and cognitive deficits in schizophrenia: a pilot study. Addict. Behav. 23, 263–266.

Tanila, H., Bjorklund, M., Riekkinen Jr., P., 1998. Cognitive changes in mice following moderate MPTP exposure. Brain Res. Bull. 45, 577–582.

Thiel, C.M., Fink, G.R., 2008. Effects of the cholinergic agonist nicotine on reorienting of visual spatial attention and top-down attentional control. Neuroscience 152, 381–390.

Trimmel, M., Wittberger, S., 2004. Effects of transdermally administered nicotine on aspects of attention, task load, and mood in women and men. Pharmacol. Biochem. Behav. 78, 639–645.

van Holstein, M., Aarts, E., van der Schaaf, M.E., Geurts, D.E., Verkes, R.J., Franke, B., van Schouwenburg, M.R., Cools, R., 2011. Human cognitive flexibility depends on dopamine D2 receptor signaling. Psychopharmacology 218, 567–578.

Van Tol, H.H., Bunzow, J.R., Guan, H.C., Sunahara, R.K., Seeman, P., Niznik, H.B., Civelli, O., 1991. Cloning of the gene for a human dopamine D4 receptor with high affinity for the antipsychotic clozapine. Nature 350, 610–614.

Vossel, S., Thiel, C.M., Fink, G.R., 2008. Behavioral and neural effects of nicotine on visuospatial attentional reorienting in non-smoking subjects. Neuropsychopharmacology 33, 731–738.

Wagner, M., Schulze-Rauschenbach, S., Petrovsky, N., Brinkmeyer, J., von der Goltz, C., Grunder, G., Spreckelmeyer, K.N., Wienker, T., Diaz-Lacava, A., Mobascher, A., Dahmen, N., Clepce, M., Thuerauf, N., Kiefer, F., de Millas, J.W., Gallinat, J., Winterer, G., 2012. Neurocognitive impairments in non-deprived smokers-results from a population-based multi-center study on smoking-related behavior. Addict. Biol. http://dx.doi.org/10.1111/j.1369–1600.2011.00429.x/.

Wallace, T.L., Porter, R.H., 2011. Targeting the nicotinic alpha7 acetylcholine receptor to enhance cognition in disease. Biochem. Pharmacol. 82, 891–903.

Waters, A.J., Carter, B.L., Robinson, J.D., Wetter, D.W., Lam, C.Y., Cinciripini, P.M., 2007. Implicit attitudes to smoking are associated with craving and dependence. Drug Alcohol Depend. 91, 178–186.

Waters, A.J., Carter, B.L., Robinson, J.D., Wetter, D.W., Lam, C.Y., Kerst, W., Cinciripini, P.M., 2009. Attentional bias is associated with incentive-related physiological and subjective measures. Exp. Clin. Psychopharmacol. 17, 247–257.

Waters, A.J., Sayette, M.A., 2006. Implicit cognition and tobacco addiction. In: Wiers, R.W., Stacy, A.W. (Eds.), Handbook on Implicit Cognition and Addiction. Sage, Thousand Oaks, CA, pp. 309–338.

Waters, A.J., Shiffman, S., Sayette, M.A., Paty, J.A., Gwaltney, C.J., Balabanis, M.H., 2003. Attentional bias predicts outcome in smoking cessation. Health Psychol. 22, 378–387.

Waters, A.J., Sutton, S.R., 2000. Direct and indirect effects of nicotine/smoking on cognition in humans. Addict. Behav. 25, 29–43.

Wesnes, K., Warburton, D.M., 1983. Effects of smoking on rapid information-processing performance. Neuropsychobiology 9, 223–229.

Wiers, R.W.H.J., Stacy, A.W., 2006. Handbook of Implicit Cognition and Addiction. Sage Publications, Thousand Oaks.

Winterer, G., Mittelstrass, K., Giegling, I., Lamina, C., Fehr, C., Brenner, H., Breitling, L.P., Nitz, B., Raum, E., Muller, H., Gallinat, J., Gal, A., Heim, K., Prokisch, H., Meitinger, T., Hartmann, A.M., Moller, H.J., Gieger, C., Wichmann, H.E., Illig, T., Dahmen, N., Rujescu, D., 2010. Risk gene variants for nicotine dependence in the CHRNA5-CHRNA3-CHRNB4 cluster are associated with cognitive performance. Am. J. Med. Genet. B Neuropsychiatr. Genet. 153B, 1448–1458.

Wooltorton, J.R., Pidoplichko, V.I., Broide, R.S., Dani, J.A., 2003. Differential desensitization and distribution of nicotinic acetylcholine receptor subtypes in midbrain dopamine areas. J. Neurosci. 23, 3176–3185.

Xu, J., Mendrek, A., Cohen, M.S., Monterosso, J., Rodriguez, P., Simon, S.L., Brody, A., Jarvik, M., Domier, C.P., Olmstead, R., Ernst, M., London, E.D., 2005. Brain activity in cigarette smokers performing a working memory task: effect of smoking abstinence. Biol. Psychiatry 58, 143–150.

Yakir, A., Rigbi, A., Kanyas, K., Pollak, Y., Kahana, G., Karni, O., Eitan, R., Kertzman, S., Lerer, B., 2007. Why do young women smoke? III. Attention and impulsivity as neurocognitive predisposing factors. Eur. Neuropsychopharmacol. 7 (5), 339–351.

Young, J.W., Finlayson, K., Spratt, C., Marston, H.M., Crawford, N., Kelly, J.S., Sharkey, J., 2004. Nicotine improves sustained attention in mice: evidence for involvement of the alpha7 nicotinic acetylcholine receptor. Neuropsychopharmacology 29, 891–900.

Zhang, L., Dong, Y., Doyon, W.M., Dani, J.A., 2012. Withdrawal from chronic nicotine exposure alters dopamine signaling dynamics in the nucleus accumbens. Biol. Psychiatry 71, 184–191.

Zhu, H., Clemens, S., Sawchuk, M., Hochman, S., 2008. Unaltered D1, D2, D4, and D5 dopamine receptor mRNA expression and distribution in the spinal cord of the D3 receptor knockout mouse. J. Comp. Physiol. A Neuroethol. Sens. Neural Behav. Physiol. 194, 957–962.