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Nicotinic receptor mechanisms and cognition in normal states and neuropsychiatric disorders

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Abstract

Cigarette smoking rates in the American population are approximately 23%, whereas rates of smoking in clinical and population studies of individuals with neuropsychiatric disorders are typically two- to four-fold higher. Studies conducted in a variety of neuropsychiatric populations [e.g. attention-deficit hyperactivity disorder (ADHD), Alzheimer's disease, schizophrenia] have collectively suggested that nicotine may be efficacious in remediating selected cognitive deficits associated with these disorders, thus providing a framework for understanding the specific vulnerability of these patients to smoking initiation and maintenance. However, the specific gain in cognitive performance produced by nicotine administration in healthy subjects with normal cognitive function is less clear. This article reviews our current understanding of central nicotinic acetylcholine receptor (nAChRs) systems in normal and neuropsychiatric disease states and, specifically, their role with respect to cognitive dysfunction and clinical symptoms in several specific neuropsychiatric populations, including ADHD, Alzheimer's disease, Parkinson's disease, Tourette's Disorder, schizophrenia and affective disorders. The potential benefits of nicotinic agents for therapeutic use in neuropsychiatric disorders is discussed, as well as directions for further research in this area.

Keywords

attention; cigarette smoking; cognitive function; executive function; nicotinic receptor; neuropsychiatric disorder; working memory

Introduction

It has been long-appreciated that cigarette smokers may derive some gains in memory and attention from smoking, and smokers often endorse psychomotor and cognitive impairment during tobacco abstinence. Nonetheless, experimental support for the procognitive effects of cigarette smoking has been scarce because it has been hard to separate direct gains in cognitive performance from nicotine administration *per se* from the reversal of nicotine withdrawal effects. This has lead to the proposal that nicotine may ultimately produce no benefits on mood, anxiety and cognition (Heishman, 1999), and may even contribute to their worsening (Parrott,

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2003). However, while this may be true in non-pathological states, there is increasing evidence that in a number of neuropsychiatric disorders [e.g. schizophrenia, attention-deficit hyperactivity disorder, Parkinson's disease, Alzhemier's disease, affective disorders], individuals typically smoke cigarettes at higher prevalence rates than in the general population (Lasser *et al*., 2000; George and O'Malley, 2004), and/or that neurocognitive deficits which are well-described clinical features of these disorders may be remediated by nicotine administration or smoking (Newhouse *et al*., 1997; Levin *et al*., 1998; Levin, 2002; Shytle *et al*., 2002). Accordingly, the use of nicotine and nicotinic agents has received considerable attention as a therapeutic strategy in these disorders, and the development of subtype-selective agonists and antagonists for the nicotinic acetylcholine receptor (nAChR) is of considerable academic and commercial interest. Furthermore, a better understanding of how nicotine may benefit neurocognitive dysfunction in particular disorders may have relevance for our understanding of why many of these individuals are vulnerable to tobacco addiction and dependence, and might suggest targeted strategies for smoking cessation in these populations. This review evaluates the evidence obtained from basic science and clinical studies which support the notion that nicotine and nicotinic agents may have beneficial effects on various aspects of neurocognitive and clinical function, particularly in individuals with well-defined cognitive compromise, such as in neuropsychiatric disease states, and makes recommendations for further animal and human research in this area.

Methods for study selection

We systematically surveyed the English-language literature using MEDLINE database searches for the period 1966 to January 2004 for the search terms 'neuropsychiatric disorder', 'psychiatric disorder', 'nicotine', 'smoking', 'cognition' and 'neuropsychology'. Proceedings of major conferences in the last 3 years were also surveyed. English-language human studies incorporating an adequate control group were included in the review. Bibliographies of relevant studies were also reviewed for completeness.

For the classification of studies shown in Tables 1 and 2, two authors (K.A.S. and K.L.B.) independently and blindly rated each original article for determination of the strength of evidence of the article. Articles were rated: '1' for 'strong evidence' if there was substantiation of results by at least one replication study; '2' for 'modest evidence' if there was a single well-controlled study with no replication data or several moderately well controlled studies with supporting findings; and '3' for 'little evidence' if the study design was not well controlled and there was no evidence of replication.

Definition of cognition

Cognition is broadly defined as the information-handling aspect of behaviour (Lezak, 1995). Several constructs in cognition are often studied as the major focus of neuropsychiatric disorders, and these typically include attention, memory and executive functioning. Attention is defined as the ability to focus behaviour, or the ability to avoid distractibility. An intact attentional system is thought to be fundamental for the successful execution of other higher-order functions (Gitelman, 2003), although impairments in attention are incorporated in the most common deficiencies among most types of brain pathology, including neuropsychiatric disease (Lezak, 1995). Memory is the complex process of registering, storing, retaining and retrieving previously encountered information, many stages of which are disrupted in individuals with brain impairment, and is related to attentional functioning because it requires the ability to attend to new information for adequate learning and recall (Lezak, 1995). Executive functions have been broadly defined as several abilities that incorporate organization and planning and cognitive flexibility, and that help to sustain the processes of attention and memory (Wecker *et al*., 2000); thus, it is often argued that many of these functions overlap

and require the operation of one for optimal performance of another. For example, in the literature concerning schizophrenia, spatial working memory function has been described as a 'master' cognitive process that contributes intrinsically to performance on other important domains, such as executive function and attention, which are also known to be abnormal in this disorder (Green, 1996; Green *et al*., 1997; Goldman-Rakic, 1999).

Nicotinic acetylcholine receptor

The neurotransmitter acetylcholine has been associated with the processes of arousal, learning and memory, and it is well-established that cholinergic agonists are known to improve memory while, in general, cholinergic antagonists impair memory (Bartus *et al*., 1985). Such a finding linked research of cholinergic neurones to studies of various forms of progressive dementia. There are two major cholinergic systems which contribute to cognition (i.e. muscarinic and nicotinic). Several reviews are available on muscarinic nAChR systems in cognitive function, in both normal and neuropsychiatric disease states (Avery *et al*., 1997; Terry and Buccafisco, 2003; Zhou *et al*., 2003). Here, we will focus on nAChR systems.

Pre-clinical studies have demonstrated that nicotine alters the function of several central neurotransmitter systems, including dopamine (DA), norepinephrine (NE), serotonin (5-HT), glutamate, γ-aminobutyric (GABA) and endogenous opioid peptides (Mansvelder and McGehee, 2002; Picciotto, 2003). Nicotine's receptors in the brain comprise nAChRs, which are diverse members of the neurotransmitter-gated ion channel superfamily, and which play critical neuromodulatory roles in the central nervous system (Picciotto *et al*., 2000; Picciotto, 2003). The endogenous neurotransmitter for nAChRs is acetylcholine. There are two general families of central nAChRs (Picciotto, 2000): (i) high-affinity (β_2 subunit-containing nAChRs, which exist in a heteropentameric configuration of α subunits combined with β subunits) receptors, which are sensitive to the nicotinic antagonists mecamylamine and dihydro-β-erythrodine and (ii) low-affinity (α_7 subunit-containing nAChR homopentameric complexes) receptors which are sensitive to the snake venom toxin α-bungarotoxin and the selective antagonist methyllycaconitine. Both high- and low-affinity nAChRs appear to be present on mesocorticolimbic DA neurones (Wooltorton *et al*., 2003), and α_7 nAChRs are enriched in the hippocampus and cortex and appear to facilitate information processing and sensory integration (Leonard and Bertrand, 2001). Stimulation of pre-synaptic nAChRs on these neurones by nicotine increases transmitter release and metabolism. Unlike most agonists which produce receptor downregulation with chronic exposure, chronic nicotine administration leads to desensitization and inactivation of nAChRs, and a 'paradoxical' upregulation of nAChR sites, a process that occurs within 7 days of repeated exposure to nicotine (Gentry and Lukas, 2002). Interestingly, it has been shown that normalization of nAChR upregulation with smoking cessation occurs after 4–8 weeks (Breese *et al*., 1997). Tolerance is another important aspect of the nicotine dependence syndrome but, interestingly, is not thought to be related to this phenomenon of nAChR desensitization and upregulation, which appears to be more closely related to the process of nicotine withdrawal (Littleton, 2001). Several human studies have suggested that although there is consistent evidence to suggest that tolerance to the effects of nicotine on mood and aversive effects occur, there is little or no evidence for the development of tolerance to the effects of nicotine on cardiovascular measures or psychomotor performance (Heishman and Henningfield, 2000; Perkins, 2002); however, lighter smokers who are not dependent (e.g. 'chippers') may have less nicotine tolerance (Shiffman *et al*., 1992). In general, non-smokers and non-dependent smokers appear to experience more positive and aversive effects and more cardiovascular reactivity compared to non-smokers and dependent smokers, respectively (Srivastava *et al*., 1991; Shiffman *et al*., 1992; Perkins *et al*., 1994; Perkins, 2002).

After a period of overnight abstinence, nAChRs become resensitized, and then these nAChRs are thought to be fully responsive to nicotine as an exogenous agonist, which might explain why most smokers report that the most satisfying cigarette of the day is the first one in the morning. Mesolimbic DA (reward pathway) neurones are of particular importance because these neurones project from the ventral tegmental area (VTA) in the midbrain to anterior limbic forebrain structures such as the nucleus accumbens and cingulate cortex, and mediate the rewarding effects of nicotine. These neurones express high affinity nAChRs both on their cell bodies and terminals (Zoli *et al*., 2002), and receive inputs from glutamatergic and GABAergic neurones that have low and high affinity nAChRs on their terminals, respectively (Mansvelder *et al*., 2002). Similarly, there are nAChRs present pre-synaptically on midbrain DA neurones that project from the VTA to the prefrontal cortex (PFC) and that evoke DA release and metabolism when pre-synaptic nAChRs are activated by nicotine (Marshall, 1997). Such nAChR regulation may mediate the effects of nicotine and smoking on PFC-dependent cognitive function, including spatial working memory and executive function (Goldman-Rakic, 1999; George *et al*., 2000d; George *et al*., 2002; Sacco *et al*., 2004).

There is evidence that, similar to nicotine, competitive nAChR agonists are more likely to induce receptor desensitization (and upregulation) compared to allosteric modulators of nAChRs (e.g. galanthamine), which appear to be less prone to producing such nAChR desensitization (Maelicke *et al*., 2001), thereby maximizing nAChR stimulation effects with repeated drug dosing. A summary of the binding affinities of nicotine and various nicotinic agonists and antagonists, including allosteric modulators, is presented in Table 1 (Bertrand *et al*., 1992; Harvey *et al*., 1996; Donnelly Roberts *et al*., 1998; Parker *et al*., 1998; Fryer and Lukas, 1999a, 1999b; Maelicke *et al*., 2001; Shytle *et al*., 2002; Eaton *et al*., 2003; Samochocki *et al*., 2003; Zhao *et al*., 2003).

In addition to nicotine, there are approximately 4000 chemical constituents in tobacco, and some of these have psychopharmacological effects and thus contribute to the nicotine dependence state in humans. For example, an unidentified component of tobacco smoke (not nicotine, but likely to comprise harman and norharman alkaloids, which are known benzodiazepine inverse agonists) (Rommelspacher *et al*., 2002) inhibits both monoamine oxidase (MAO) A and B subtypes which are responsible for the metabolism of monoamine neurotransmitters such as NE and 5-HT (MAO-A) and DA (MAO-B) (Fowler *et al*., 1996a,b), and may contribute to the reinforcing properties of tobacco and to smoking-related cognitive enhancement. In addition, carbon monoxide (CO) is a combustion product of tobacco which, being a gaseous second messenger like nitric oxide (NO), known to be involved in neurotransmission (Baranano *et al*., 2001), could also contribute to the process of tobacco dependence.

Non-human studies of nAChRs and cognition

Several animal models of cognitive performance have been developed in the past 15 years which are considered to be analogues of cognitive processing in human subjects, and which have been used in cross-species validation of the effects of a number of psycho-active drugs, including nicotine (Levin, 1992, Levin and Simon, 1998; Levin, 2002). For example, there is strong evidence that acute and chronic nicotine (or selective nicotinic agonist) administration can enhance working memory (e.g. radial arm maze) (Levin, 1996; Levin, 1998; Levin *et al*., 1999; Levin, 2002) and attentional function in rodents (Stolerman *et al*., 2000; Hahn *et al*., 2003) and, in non-human primates (Schneider *et al*., 2003), cognitive processes that are known to depend, at least in part, on central DA and NE function. In rats, nicotine administration increases catecholamine (e.g. DA and NE) release and turnover in nigrostriatal, mesolimbic and mesocortical circuits, while acute nicotine abstinence (< 24 h) has been shown to result in decreases in central catecholamine function in both rodents (Vezina *et al*., 1992; Fung *et al*.,

1996; George *et al*., 1998; Hildebrand *et al*., 1998) and humans (West *et al*., 1984; Ward *et al*., 1991). Further support of the effects of nicotine on DA-mediated behaviour comes from studies suggesting that nicotine administration enhances long-lasting, reward-related learning in the rat (Olausson *et al*., 2003), as well as the observation that nicotine improves response accuracy, reduces omission rates and shortens response latency in the 5-choice serial reaction time task (5-CSRTT), a rodent model of attention (Stolerman *et al*., 2000; Hahn *et al*., 2003) However, there is accumulating evidence that other neurotransmitters, such as acetylcholine, glutamate and 5-HT (Arnsten, 2000; Robbins, 2000), also contribute to cognitive performance in these animal models.

Non-psychiatric human populations (Table 2)

There is some evidence for nicotinic receptor-mediated cognitive enhancement in non-psychiatric healthy controls. Recent studies have suggested that nicotine itself can alter the function of brain regions thought to contribute to neurocognitive function in humans. In functional magnetic resonance imaging (fMRI) studies, intravenous (i.v.) nicotine has been shown to dose-dependently increase subjective feelings of reward, and this is accompanied by activation of limbic and paralimbic brain areas such as the nucleus accumbens, amygdala, anterior cingulate cortex and prefrontal cortex (Stein *et al*., 1998). Similarly, the same group most recently demonstrated that transdermal nicotine administration improved task-related activation of the parietal cortex, thalamus and caudate during performance of the rapid visual information processing (RVIP) test, as well as generalized occipital cortical activity in an fMRI study of the effects of nicotine on cognitive mechanisms, indicating that areas that typically mediate visual attention, arousal and motor activation are activated with administration of nicotine (Lawrence and Ross, 2002). In both smokers and non-smokers, nicotine administration decreases regional cerebral blood flow (rCBF) in the anterior cingulate cortex and the cerebellum, and increases rCBF to the occipital cortex, which further illustrates the positive cognitive effects of nicotine on cortical areas mediating mood and attention, and also on the visual cortex (Ghatan *et al*., 1998). Other recent functional imaging studies have suggested that differences in cognitive activation of neural substrates in smokers and non-smokers using a working memory task (the ‘N-back’ test) may be related to trait factors rather than the direct effects of nicotine or smoking (Ernst, 2001a), and that previous exposure to smoking can alter brain responsiveness to nicotine administration (Ernst, 2001b). Accordingly, these neuroimaging studies illustrate the complexities of determining the effects of nicotine and smoking effects on brain function and complex behaviours such as cognitive performance, and suggest that their may be functional pathology that determines vulnerability to nicotine addiction.

Several studies have suggested that nicotine administration and smoking may improve sustained attentional function on a variety of classical neuropsychological tests of attention, vigilance and accuracy such as the Continuous Perfromance Test (CPT) and RVIP (Petrie and Deary, 1989; Parrott and Craig, 1992; Foulds *et al*., 1996; Levin *et al*., 1998; Murphy and Klein, 1998; Lawrence and Ross, 2002), and that smoking abstinence can impair attentional function (Hatsukami *et al*., 1989; Eisenberg *et al*., 1996) (Table 2). Similar effects of acute smoking and smoking abstinence (Pineda *et al*., 1998) and of transdermal nicotine (Knott *et al*., 1999) have been obtained using non-neuropsychological measures of attention, namely event-related potentials such as the P300 response. Interestingly, acute smoking or nicotine administration have been shown to improve, and abstinence to impair, selective attention as assessed by the classical Stroop Colour Word Test (Wesnes and Revell, 1984; Provost and Woodward, 1991; Pomerleau *et al*., 1994; Mancuso *et al*., 1999), but this effect on Stroop performance was not found in all studies (Suter *et al*., 1983; Parrott and Craig, 1992; George *et al*., 2002), and differences may be due to different drug administration and testing methodologies involved. Furthermore, in a modified version of the Stroop Test which involves

selective attention for smoking-related words, acute smoking improves, whereas abstinence impairs, smoking word-related reaction time responses (e.g. Stroop interference) (Gross *et al*., 1993; Rusted *et al*., 2000; Powell *et al*., 2002).

A classic measure of pre-attention is pre-pulse inhibition (PPI) of the startle response, an operational measure of sensorimotor gating (Swerdlow *et al*., 1992), and PPI is known to be deficient in a number of neuropsychiatric disorders (Swerdlow *et al*., 1992). There is strong evidence from pre-clinical studies that PPI is negatively modulated by dopamine (Swerdlow *et al*., 1992; Ralph-Williams *et al*., 2002). Nicotine and cigarette smoking effects have been evaluated in smokers and non-smokers without neuropsychiatric illness and, in some cases, smoking abstinence may impair PPI (Della Casa *et al*., 1999; Duncan *et al*., 2001), and acute smoking may improve sensorimotor gating (Kumari *et al*., 1996; Della Casa *et al*., 1999; Kumari and Gray, 1999; Duncan *et al*., 2001), while nicotine administration in non-smokers may modestly improve PPI (Kumari *et al*., 1997). Other studies have shown that acute cigarette smoking inhibits PPI (Hutchison *et al*., 2000), which is consistent with animal studies suggesting that augmentation of DA function inhibits PPI (Swerdlow *et al*., 1992). Methodological differences between these studies, such as the degree of nicotine dependence and length of smoking deprivation, may contribute to these discrepant findings.

With respect to the effect of nicotine on psychomotor performance, early studies suggested that smoking abstinence (up to 24 h) can reduce psychomotor performance as assessed by slowing of reaction times (Snyder *et al*., 1989). Subsequently, studies involving administration of nicotine gum (Ernst *et al*., 2001a) and a transdermal patch (Davranche and Audiffren, 2002) have shown that these routes of administration can improve reaction times probably via non-specific effects on arousal in both smokers and non-smokers. Furthermore, Le Houzec *et al*. (1994) demonstrated that subcutaneous nicotine can improve reaction times in non-smokers, without improvements in accuracy or vigilance.

There is little evidence that nicotine administration and smoking *per se* can improve verbal and non-verbal learning in smokers (independent of deprivation-induced deficits) and non-smokers (Bell *et al*., 1999; Sakurai and Kanazawa, 2002) and, interestingly, it has been shown that the nAChR antagonist mecamylamine (5–20 mg) dose-dependently worsens verbal learning and recall in non-smokers (Newhouse *et al*., 1992). However, a study by Min *et al*. (2001) demonstrated significantly improved learning in both smoking and non-smoking elderly non-demented adults over several trials on a verbal learning and memory task, and significantly improved verbal learning, visual object learning, as well as delayed recall and word retrieval performances, suggesting that these beneficial effects can be seen in otherwise healthy, or perhaps, marginally at-risk, elderly adults. Furthermore, there is some evidence that acute smoking (Park *et al*., 2000) or a history of smoking (Ernst *et al*., 2001a) is associated with impairment of working memory; smoking abstinence for up to 8 weeks was associated with improvement of spatial working memory in non-psychiatric smokers (George *et al*., 2002). Finally, Newhouse *et al*. (1994) administered single doses of the non-selective high-affinity nAChR antagonist mecamylamine at doses of 0, 5, 10 and 20 mg/day in healthy young controls and elderly subjects in a double-blind, placebo-controlled manner. Their findings suggested that, although at the highest dose (20 mg/day), there was a significant impairment in both groups in the learning condition of the Repeated Acquisition Task, elderly subjects appeared to be more sensitive to mecamylamine effects because there was a significant impairment with the 10 mg/day dose that was not observed in younger subjects. There was a similar enhanced sensitivity to mecamylamine on recognition memory, which was preferentially observed in elderly versus younger subjects. These results suggest an increased sensitivity to nAChR blockade, possibly due to an age-related dysfunction in nAChRs.

With respect to executive functioning, there is some evidence that acute smoking abstinence (up to 24 h) can impair performance on Trails B (Hatsukami *et al.*, 1989), but these effects are probably non-specific and related to decrements in psychomotor performance. Furthermore, performance on a logical reasoning task was unchanged by smoking abstinence, but modest performance improvements were observed after acute smoking (Bell *et al*., 1999).

There has been much discussion in the literature about whether non-psychiatric cigarette smokers derive any beneficial effects on cognitive performance, or whether any cognitive enhancement that is reported is simply due to reversal of tobacco withdrawal induced cognitive decrements (Spilich, 1994; Parrott, 2003). The preponderance of the evidence suggests that, in nicotine dependent smokers, cigarette smoking may simply reverse abstinence-related impairment in cognitive function (Hatsukami, 1989), and nicotine abstinence is known to impair attention and reaction time performance within 24 h after smoking abstinence (Hatsukami *et al*., 1989; Eissenberg *et al*., 1996). Interestingly, oral administration of cotinine (the proximal metabolite of nicotine) impaired performance on a verbal recall task and of N100 event-related potential latencies (Herzig *et al*., 1998), suggesting that tobacco abstinence-related cognitive impairment may be due in part to accumulation of this long-acting metabolite. Further studies of the direct effects of nicotine (and its metabolite cotinine) on cognitive performance in non-smoking (never smoking), healthy human subjects will be required to address these questions, independent of the effects of nicotine withdrawal.

Involvement of nAChR systems in clinical and cognitive function in neuropsychiatric disorders (Table 3)

Attention-deficit hyperactivity disorder (ADHD)

ADHD is characterized by a persistent pattern of inattention and distractibility and/or hyperactivity/impulsivity to the degree that it impairs academic or occupational functioning (First, 1994). Individuals with ADHD typically have demonstrated evidence of this disorder in their childhood years and, of these individuals, conservative estimates suggest that 50% continue to demonstrate clinically significant symptoms into adulthood (Barkley *et al*., 2002), putting the prevalence rates among adults at approximately 2% of the population (Weiss and Murray, 2003).

Rates of cigarette smoking in individuals with ADHD have been found to be higher (approximately 40%) compared to the general population of normal adults (Pomerleau *et al*., 1995). The mechanisms behind these higher rates are hypothesized to be related to self-medication with nicotine of the putative cognitive (attentional and inhibitory) dysfunction associated with ADHD. Several lines of evidence that support this theory include the finding that those ADHD patients who were smokers retrospectively self-reported a higher level of symptoms associated with this disorder in childhood than did never smokers with ADHD, suggesting that the presence of greater symptomatology in childhood may be associated with a greater risk to smoke (Pomerleau *et al*., 1995). The mechanism for the effect of nicotine on reducing attentional deficits in ADHD may be similar to psychostimulants used to treat this disorder, and probably involves enhancement of central DA and NE function. Methylphenidate and dextroamphetamine are two psychostimulants used to treat ADHD by promoting DA and NE release; nicotine acts an indirect dopamine agonist and, similar to psychostimulants, exerts its effects by improving attention, the trademark deficit in this disorder (Levin, 1992). The most recent drug to be approved for the treatment of ADHD, the NE-specific reuptake inhibitor, atomoxetine, as well as the known efficacy in ADHD of the combined DA/NE reuptake inhibitor, bupropion, further supports the involvement of NE mechanisms in this disorder (Spencer and Beiderman, 2002).

Administration of transdermal nicotine to smokers was shown to improve reaction time in adults with ADHD in multiple studies (Conners *et al*., 1996; Levin *et al*., 1996a) on the CPT, a computerized test of attention validated in its use for diagnosing and assessing the severity and course of ADHD (Conners, 1995). A more recent study by the Duke group in adults with ADHD has shown that both the acute and chronic transdermal nicotine patch (TNP) can reduce hit rate reaction time variability on the CPT with a comparable effect size to the psychostimulant methylphenidate, and was also associated with reduced Clinical Global Impression–Severity (CGI–S) and depressed mood (Levin *et al*., 2001). In clinical treatment research in ADHD subjects, TNP in both smokers and nonsmokers was found to reduce symptoms adults diagnosed with ADHD on the CGI as well as improve self-reported vigor on a measure of measure of current mood states (Conners *et al*., 1996; Levin *et al*., 1996a), and reduce symptoms on several key domains related to ADHD on the Conners' Parent Rating Scale in children and adolescents with ADHD (Shytle, 2002). Recently, Wilens *et al*. (1999) reported that the novel nicotinic cholinergic agent ABT-418, a nicotinic agonist with selectivity for the $\alpha_4\beta_2$ nAChR, may reduce impulsivity, hyperactivity and attentional deficits in adults with ADHD. Taken together, these collective data strongly suggest the positive effects of (high-affinity) nAChR stimulation on attentional dysfunction and clinical symptomatology in patients with ADHD.

Alzheimer's disease

Alzheimer's Disease (AD), the most common form of dementia, is a progressive neuropsychiatric disease in which individuals demonstrate ongoing deterioration of cognitive abilities over time. Rates of AD in the general population range from 2% to 6% of individuals over the age of 65 years, with estimates that this rate will rise given the greater number of elderly adults predicted in the population in the coming years (Rocca *et al*., 1986). Changes in individuals with AD typically begin with apparently benign symptoms, often observed as a loss of interest in usual activities, or neglect of daily routines, and these eventually lead to more apparent forgetfulness, such as failing to keep appointments, neglecting chores and errands, or recalling names of acquaintances. The more obvious degeneration associated with AD in the middle stages include declines in planning, organization, cognitive adaptability, attention and concentration, and visuospatial deficits, thought to be the result of primary deficits in memory (Hyman *et al*., 1989), probably due to cholinergic neurone degeneration (Zhou *et al*., 2003), as well as dysnomia, and memory for recently learned information. Individuals with AD often present as being unaware of their cognitive declines, which is a characteristic feature of this disease. Remote memories remain intact much longer over the course of this disease; however, as the disease progresses into its later stages, memories for the distant past and recognition of close relatives and friends deteriorate, and apraxias and agnosias are likely to develop, leading to a loss of ability to dress or feed oneself (Victor, 2001).

Early detection of dementia symptoms is typically performed using validated dementia screening measures such as the Mattis Dementia Rating Scale (DRS) which taps characteristic areas of early decline in patients with AD, including attention, initiation, perseveration, construction, conceptualization and verbal and non-verbal memory. Sensitivity and specificity of these measures in the ability to differentiate AD from normal controls has been shown to be extremely high (Salmon *et al*., 2002). Deficits measured through comprehensive neuropsychological evaluation can help detect signs of this disorder years before the clinical diagnosis (Pasquier, 1999).

AD is biologically characterized by a deficit in acetylcholine, and specifically basal forebrain cholinergic neurones in the nucleus basalis of Meynert, with attendant reduction of nAChRs (Terry and Buccafusco, 2003). Changes in nAChRs studied in normally ageing controls have been determined to represent distinctly different changes from those receptors in patients with

AD (Court *et al*., 2001). Currently, the Food and Drug Authority approved treatments include cholinesterase inhibitors (ChEIs) such as physostigmine (Eserine®), donezepil (Aricept®) and rivastigmine (Exelon®), from which patients experience typically modest cognitive improvements (Delagarza, 2003) and, most recently, the combined ChEI and nAChR positive allosteric modulator galanthamine (Reminyl®) (Coyle and Kershaw, 2001; Maelicke *et al*., 2001) (Table 1).

Brenner *et al*. (1993) suggested that smoking is associated with a lower likelihood of developing AD. In a case–control study, Wang *et al*. (1997) showed that light smoking may decrease the risk for developing AD whereas heavier daily smoking may actually increase this risk. However, in a review of the literature on the potential neuroprotective effects of smoking in AD, Fratiglioni and Wang (2000) concluded that there is no clear evidence that smoking has a protective effect on the development of AD. Nonetheless, because of the clear involvement of nAChRs in the progression of AD, including the loss of nAChR binding sites in the brains of AD patients, nAChRs are likely to be pharmacological targets for medications development for the treatment of this disease.

In studies of the effects of nicotine on cognitive function in AD, the literature is rapidly expanding (Newhouse *et al*., 1997). In the domain of learning and memory, which represents an area of substantial cognitive deficit in patients with AD, results of the effects of nicotine have been mixed. Newhouse *et al*. (1988) demonstrated that i.v. nicotine (0.125, 0.25 and 0.50 μg/kg/min.) produced dose-dependent improvement in intrusion errors on a word recall task in non-smokers with AD, and that maximum effects occurred at 0.25 μg/kg/min, suggesting an ‘inverted-U’ dose–response pattern (Newhouse *et al*., 1988). By contrast, Jones *et al*. (1992) found that subcutaneous nicotine injections did not improve verbal or nonverbal short-term memory deficits in patients with AD (Jones *et al*., 1992). Administration of transdermal nicotine improved performance on a repeated acquisition task in patients with probable AD (Wilson *et al*., 1995); however, the study by White and Levin (1999) did not support this finding because they found that performance on a letter memory test did not improve with nicotine patch administration, and no difference between placebo and TNP conditions was detected on measures of short-term memory in AD patients (Snaedal *et al*., 1996). Furthermore, TNP did not improve performance on the Mattis DRS in patients with probable AD (Wilson *et al*., 1995). Finally, using a within-subjects, placebo-controlled study of three doses of the nAChR channel activator ABT-418 in subjects with moderate AD, Potter *et al*. (1999) demonstrated that this agent could dose-dependently improve deficits in total recall in a verbal learning task, a seven-item selective reminding task, and in non-verbal tasks such as spatial learning and memory and repeated acquisition. Methodological differences amongst these studies, including dose and route of nicotine administration, may explain these disparate effects of nicotine on learning and memory in AD.

In the domain of attentional processing, patients with mild-to-moderate AD demonstrated a reduced variability of response speed, as well as a reduction of errors of omission on a task of attentional function, after 1 day of exposure to TNP, and this improvement was sustained with chronic exposure to nicotine (White and Levin, 1999). However, Howe and Price (2001) found no effect of TNP on attentional performance in a sample of healthy older subjects at risk for developing dementia. Another study found that i.v. nicotine improved detection performance on the critical flicker fusion test in patients with AD, and improved their ability to discriminate stimuli and their reaction times, suggesting effects of nicotine on visual perceptual and attentional cortical mechanisms (Sahakian *et al*., 1989). Similarly, work by Jones *et al*. (1992) further supports this finding, and demonstrated improved perception on the flicker fusion task in patients with AD in response to subcutaneous nicotine administration. Administration of nicotine orally (nicotine polacrilex, 2 mg gum) was shown to shorten mismatch negativity (MMN) latencies in AD patients and, interestingly, these latencies were

improved with physostigmine pre-treatment (Engeland *et al*., 2002), although this same dose of nicotine gum did not alter auditory P300 (Oddball task) event-related potentials in either physostigmine-treated or non-treated AD patients (Knott *et al*., 2002). Thus, nicotine administration appears to improve some forms of attentional function in AD, but more controlled studies are needed.

Parkinson's disease

Parkinson's disease (PD) is a degenerative disease that typically begins between the fourth and seventh decades, and affects 1% of the population over the age of 65 years. This disease is marked by tremor, poverty of voluntary movement, rigidity, and shuffling gait (Victor, 2001). Generally speaking, patients with PD have been found to smoke at lower rates than controls (Baumann *et al*., 1980) both during the illness and before its diagnosis. It has been observed that there is a significant loss of nicotinic binding sites and dopaminergic neuronal degeneration in the substantia nigra (from which DA cell bodies project to caudate putamen, and is part of the extrapyramidal motor system) in patients with PD (Bosboom *et al*., 2003). The potential role of nAChRs as targets for treatment of neurochemical changes related to this disease has been raised (Burghaus *et al*., 2003), including the specific treatment of cognitive dysfunction associated with PD (Newhouse *et al*., 1997). Initial pre-clinical and epidemiological studies presented competing evidence about the potential neuroprotective effects of nicotine and cigarette smoking in PD (Rajput, 1984; Rajput *et al*., 1987; Grandinetti *et al*., 1994). Subsequent well-controlled studies (Gorell *et al*., 1999) and an extensive review of the literature (Fratiglioni, 2000) have more fully supported the notion that, although the mechanisms are not entirely understood, cigarette smoking provides a neuroprotective effect, albeit undefined, against the development of PD, and this effect cannot be accounted for by sample or study design bias as has been suggested.

There has only been one published study in the literature on the effects of nicotine on cognition in PD (Kelton *et al*., 2000). In this study, multiple doses of i.v. nicotine (up to 1.25 mg/kg/min.) were infused in $n = 15$ non-demented patients with early-to-moderate PD (average Hoehn–Yahr stage = 1.77, Mini-Mental State Examination score = 28.6/30), which was followed by transdermal nicotine at doses up to 14 mg/day for up to 2 weeks. These investigators found that acute i.v. nicotine improved several areas of cognitive performance in PD patients, including reaction time, speed of processing and tracking errors, but not in other areas, such as selective attention and semantic retrieval. Transdermal nicotine improved extrapyramidal functions, and this effect was sustained for up to 30 days after patch discontinuation. Consistent with these positive effects on extrapyramidal function, Fagerstrom *et al*. (1994) presented a case study of two elderly patients diagnosed with PD who, after administration of nicotine gum, demonstrated a reduction in tremor, disorganized thinking, bradykinesia, and increased energy. By contrast, other studies with nicotine administration have shown that neither nicotine gum nor patch significantly altered symptoms of PD (Clemens *et al*., 1995; Vieregge *et al*., 2001), and after 12 h of exposure to nicotine via the patch, PD patients showed a worsening of motor performance compared to the placebo condition (Ebersbach *et al*., 1999). Clearly, further controlled studies of nicotine's effects on cognitive and motor function in PD are warranted.

Tourette's disorder

Gilles de la Tourette's syndrome, commonly known as Tourette's Disorder (TD), is a typically lifelong neurological disorder characterized by motor and verbal tics of unknown cause. To be classified as TD, motor symptoms must have appeared before the age of 21 years, and the prevalence rates are approximately 0.05% (Simon, 2002). Several lines of evidence suggest the role of nAChRs in mediating Tourette's-related symptoms. McConville *et al*. (1991 (1992) studied the effect of TNP in TD patients currently treated with haloperidol, and the

combination of TNP and haloperidol significantly reduced tics compared to haloperidol treatment alone. Silver *et al*. (2001a) extended this finding and confirmed that nicotine gum augments haloperidol treatment more effectively than placebo gum in reducing the symptoms of TD as measured by the Clinical and Parent Global Improvement Scales. Nicotine administered by patch has also been shown to reduce the number of tics in non-smoking patients with TD, as measured by the Yale Global Tic Severity Scale (Dursun and Reveley, 1997). Long-term administration of nicotine leads to nAChR desensitization and upregulation, and thus the use of nicotinic antagonist treatment for motor symptoms of TD has been proposed; however, an 8-week placebo-controlled trial of mecamylamine (up to 7.5 mg/day) was not superior to placebo as a monotherapy for children and adolescents with TD in an 8-week trial (Silver *et al*., 2001). Nicotinic mechanisms have been studied in an animal pharmacological model of TD, which demonstrated that both acute and chronic nicotine administration reduced a drug-induced head twitch response in mice (Tizabi *et al*., 2001).

Affective and anxiety disorders

Increasing attention has been paid to the role of nicotine dependence and smoking in affective disorders, but there has been little study of the effects of nicotine on cognitive performance deficits in these patients (Hammar *et al*., 2003). Rates of smoking in clinical studies of mental illness are higher than non-psychiatric controls, and exceed 50% in many major disorders such as bipolar disorder, major depression and panic disorder (George and Vessicchio, 2001). Interestingly, in an examination of 1566 female twin pairs from the Virginia Twin Registry, and using a best-fitting bivariate twin model, Kendler *et al*. (1993) found evidence for shared genetic factors causing the strong association between smoking and major depression, which suggests that there is little evidence for a causal relationship between smoking and major depression. Shytle *et al*. (2002) and Silver *et al*. (2001b) have discussed the role of anti-depressant medications in inhibiting nicotine acetylcholine nAChRs, and suggested that antagonism of these receptors contributes to their effectiveness in reducing symptoms of depression (Table 1). In this regard, an open-label study in clinically depressed non-smokers found that transdermal nicotine patch application lead to a dramatic decrease in depressive symptoms within 3 days (Salin-Pascual *et al*., 1996). It is thought that an increase in depressive symptoms may follow smoking cessation in patients with depression (Niaura *et al*., 1999; Tsoh *et al*., 2000; Killen *et al*., 2003) indicating a potential maintenance role for these receptors in this disorder, and there is also evidence that patients with depression have more difficulty maintaining early abstinence from cigarettes than non-depressed patients (Pomerleau *et al*., 2001).

Most of the research on nicotine and bipolar disorder has been associational in design, and has documented the higher rates of smoking in bipolar patients compared to controls (Gonzalez-Pinto *et al*., 1998; Corvin *et al*., 2001) and examined its association with clinical features of this disorder. For example, it is thought that severity of smoking may predict the severity of psychotic features in this disorder (Corvin *et al*., 2001).

A link between anxiety disorders and nicotine has also begun to be established. Breslau *et al*. (1991) showed that nicotine dependence in young adults was more often associated with anxiety disorders than the non-nicotine dependent population (Breslau *et al*., 1991). Epidemiological studies from the same group later suggested an association between increased daily smoking and risk for first-time occurrence of panic attacks, and that this risk is higher in those actively smoking compared to those who are former smokers (Breslau and Klein, 1999). According to Breslau and Klein (1999), these results also suggest that the presence of panic attacks is not significantly associated with increased risk for the development of smoking and nicotine dependence.

There have been several studies of smoking prevalence, and the association of smoking with psychopathological features, in posttraumatic stress disorder (PTSD) mostly by investigators at Duke University, and confined to Vietnam-era veterans (Beckham, 1999). In initial studies, Beckham *et al*. (1995) found that smoking rates in Vietnam-era veterans with PTSD were approximately 60% (Beckham *et al*., 1995). Furthermore, women with PTSD had higher rates of smoking compared to women with no history of PTSD (Acierno *et al*., 1996). Beckham *et al*. (1997) also found that Vietnam-era combat veterans with PTSD had higher rates of smoking (53%) than those without PTSD (45%). PTSD patients reported higher rates of heavy smoking consumption (> 25 cigarettes/day) than non-PTSD veterans (48% versus 28%). In heavy smokers, there were higher levels of total PTSD symptoms and Cluster C (Avoidance and Numbing) and Cluster D (hyper-arousal) symptoms. Because these studies were cross-sectional, it is not clear whether the higher levels of PTSD symptoms were directly attributable to their heavy smoking, or a trait marker unrelated to smoking. Other studies have shown that nicotine withdrawal symptoms appear to be worse in smokers with PTSD in response to trauma-related stimuli compared to those without PTSD (Beckham *et al*., 1995).

Schizophrenia

Schizophrenia is a chronic psychotic disorder whose essential features include the presence of delusions and hallucinations and thought disorder, in addition to negative symptoms, which include flattening of affect and dysfunction of occupational, social or interpersonal relationships. The link between cigarette smoking and schizophrenia is well-established (Dalack *et al*., 1998; George *et al*., 2003) and, recently, there has been evidence to suggest dysregulation of nAChR systems in schizophrenics, including reduced upregulation of high-affinity nAChRs in the schizophrenic brain (Breese *et al*., 2000) and functional polymorphisms in the promoter region of the low-affinity (α_7) nAChR that alter sensory physiology (Leonard *et al*., 2002).

In terms of studies of the effects of nicotine and smoking on neuropsychological performance in patients with schizophrenia, a human laboratory study in schizophrenic smokers showed that nicotine transdermal patch (0–21 mg/day) could dose-dependently reverse haloperidol-induced working memory, attentional and reaction time impairments (Levin *et al*., 1996b). Furthermore, transdermal nicotine has been shown to reduce haloperidol-induced bradykinesia and rigidity in schizophrenics compared to a placebo patch (Yang *et al*., 2002). Accordingly, it has been suggested that one reason for the high rates of smoking and inability to quit in schizophrenic patients is that they derive specific benefits from nicotine self-administration, such as remediation of antipsychotic-induced cognitive impairments and extrapyramidal symptoms (Dalack *et al*., 1998; George *et al*., 2003). Interestingly, a recent study by Park *et al*. (2000) in non-psychiatric smokers found that acute cigarette smoking may impair spatial working memory, but not spatial selective attention. This is in contrast to data from our group in schizophrenic and control smokers suggesting that smoking cessation impairs visuospatial working memory (VSWM) function in schizophrenic patients (George *et al*., 2002); in healthy control smokers, smoking cessation improves VSWM (George *et al*., 2002), consistent with the results of Park *et al*. (2000). These differential effects of nicotine/smoking on VSWM have been supported by recent laboratory studies in our group, and appear to be mediated by stimulation of high-affinity nAChRs (Sacco *et al*., 2004). Finally, Smith *et al*. (2002) recently showed that nicotine (versus placebo) nasal spray had modest effects on reversing abstinence-induced impairment of complex reaction time and working memory in patients with schizophrenia. Curiously, in the study by Smith *et al*. 2002, some of these modest (Cohen's $d < 0.5$) effects of cigarette smoking on clinical and cognitive outcome measures could also be improved by smoking denicotinized cigarettes, suggesting that non-nicotine (non-pharmacological) aspects of the process of cigarette smoking may contribute to these pro-cognitive effects of smoking.

There are several lines of evidence to suggest that nicotine and smoking enhance attentional processing in schizophrenic subjects and that, in many cases, this enhancement is preferentially seen in schizophrenic patients (and first-degree relatives) compared to healthy controls (Adler *et al*., 1998). Several studies (Adler *et al*., 1993; Leonard *et al*., 2002) from the University of Colorado group have documented that nicotine and smoking can transiently ameliorate deficits in P50 auditory evoked potentials, and that these effects seem to be mediated by α_7-subtype nAChRs, which are enriched in the hippocampus (Stevens *et al*., 1998; Picciotto *et al*., 2000; Leonard and Bertrand, 2001). These deficits in P50 gating are closely linked to the α_7 receptor locus on chromosome 15q14 (Freedman *et al*., 1997). Other studies have shown similar effects of nicotine (Olincy *et al*., 1998; Depatie *et al*., 2002; Sherr *et al*., 2002; Avila *et al*., 2003) and cigarette smoking (Olincy *et al*., 2003) on other pre-attentional measures, such as the leading saccades of smooth-pursuit eye movements and, most recently, that sustained attentional task performance (% Hit Rate) as assessed by Continuous Performance Test (Depatie *et al*., 2002; Sacco *et al*., 2004), and sensorimotor gating, as assessed by pre-pulse inhibition of the acoustic startle response (George *et al*., 2003), could be selectively enhanced by nicotine and cigarette smoking in schizophrenic versus control subjects.

It is important to address the body of literature on the common genetic foundations of many of these disorders with respect to the specific example of nicotine use and psychiatric comorbidity. Independent of psychiatric diagnosis, in a review of factors influencing initiation of smoking, genetic liability accounted for 50% of the variance in risk of becoming a regular smoker (Tsuang *et al*., 2001), whereas a meta-analysis of genetic and environmental influences on liability to schizophrenia by Sullivan *et al*. (2003) estimated high heritability (81%). Kendler *et al*. (2003) suggest that genetic risk factors principally account for the comorbidity of many common psychiatric and substance use disorders. Thus, although it has not been rigorously studied, the hypothesis that comorbid smoking and major mental illness share common genetic risk factors appears to be likely and warrants further investigation (Kendler *et al*., 2003).

Dose–response effects of nicotine on cognitive function in human subjects

To date, there have been few studies of the dose–response effects of nicotine on cognitive performance in humans. Only two studies in normal controls (Parrott and Craig, 1992; Foulds *et al*., 1996) and single studies in patients with AD (Newhouse *et al*., 1988), PD (Kelton *et al*., 2000) and schizophrenia (Levin *et al*., 1996b) have conducted a careful examination of the dose–response effects of nicotine on cognitive performance. Interestingly, in the control studies, nicotine appeared to dose-dependently (either subcutaneously or with nicotine gum) improve sustained attention on the RVIP task (Foulds *et al*., 1996), but this was not the case on the Stroop task (Parrott and Craig, 1992). In AD patients given i.v. nicotine, there were inverted-U effects of nicotine on a verbal memory task (Newhouse *et al*., 1988), while in Parkinson's patients, i.v. nicotine dose-dependently improved psychomotor performance, reaction times and extrapyramidal symptoms (Kelton *et al*., 2000). Finally, in schizophrenic patients who had haloperidol-induced cognitive deficits, a transdermal nicotine patch (7–21 mg/day) dose-dependently reversed such working memory and attentional deficits (Levin, 1996). Therefore, there may be different dose– response effects of nicotine across different cognitive tasks, but this may also depend on the route of nicotine administration, and these dose–response effects on cognitive function will require further study.

Conclusions and recommendations for further study

Taken together, there is emerging evidence to suggest that nicotine may enhance cognitive performance in humans, although such cognitive enhancement may only be observed in patients with neuropsychiatric disorders who exhibit defined neuropsychological and psychophysiological deficits that are intrinsic to their illness. A review of the available evidence

of nicotinic effects on cognition in healthy human subjects (Table 2) suggests that, with the exception of positive gains in general psychomotor performance, there is little, if any, evidence to support nicotinic effects on most domains of cognitive performance. By contrast, there appears to be stronger evidence for nicotinic modulation of cognitive dysfunction in several neuropsychiatric disorders (Table 3), including ADHD, AD, PD and schizophrenia. For other neuropsychiatric disorders, nicotinic enhancement of cognitive function is less clear, although there is evidence that nicotine may improve certain clinical symptoms associated with these disorders (e.g. motor tics in TD, mood symptoms in affective disorders), and the role for nAChR stimulation in remediating clinical and cognitive dysfunction in these disorders will require further study.

To date, several pre-clinical (e.g. rodent and primate) studies suggest positive effects of nicotine on working memory and attentional performance. However, further study of the effects of nicotine on neurocognitive deficits in animal models of neuropsychiatric disorders (e.g. induced by pharmacological agents, transgenic strains of mice, anatomical lesions) would be useful, particularly because such studies, in the light of their translational nature, would help to define basic mechanisms and support further hypothesis testing, which could have important therapeutic implications. The use of well-defined animal models of cognition that have analogues in humans, such as the radial arm maze (working memory), the five-choice serial reaction time test (attention), and sensory gating/pre-attentional measures, such as event-related potentials (e.g. N40) and pre-pulse inhibition, coupled with standardized methods for administering nicotine, both acutely and chronically (to model the situation in tobacco users), is highly recommended. Furthermore, more controlled studies of the direct administration of nicotine or nicotinic agents on cognitive deficits in neuropsychiatric disorders are required. This would include an evaluation of nicotinic agent dose–response effects, which would be important in the light of the propensity of nAChRs to desensitize and upregulate, especially because there is some evidence for nicotine administration leading to inverted-U dose–response effects on some cognitive measures (Newhouse *et al*., 1988). Furthermore, additional systematic study of the effects of nicotinic on various domains of cognitive dysfunction (e.g. attention, verbal and non-verbal memory, working memory and executive function) is suggested, especially because stimulation of different nAChR subtypes may lead to differential effects on various types of cognitive performance. Because cigarette smoking status (and nicotine withdrawal) may be a significant confounding variable in the assessment of the pro-cognitive effects of nicotine, these clinical ‘proof of principal’ studies will have to control carefully for smoking status and nicotine deprivation effects, which appear to be clinically significant. The ethics of administering nicotine to healthy non-smokers (including never smokers) and non-smoking patients with neuropsychiatric disorders also needs further consideration. In most cases, the abuse liability of nicotine administered by nicotine replacement therapies (other than cigarette smoking) is negligible (Henningfield and Keenan, 1993; West *et al*., 2000), and relevant regulatory agencies (e.g. government funding agencies, institutional review boards) will need to be appropriately educated about these issues because careful implementation of critical safeguards and safety measures will ensure that the true therapeutic effects of nicotine and other nicotinic agents in various neuropsychiatric disease entities will be safely ascertained, and then translated to clinical treatment in a timely manner. Nonetheless, it appears highly likely that several novel nAChR-based pharmacological treatments for cognitive dysfunction in neuropsychiatric disorders could become available within the next 5–10 years.

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Table 1

Binding affinities (K_d or K_i, μM) of various nicotinic agents to nicotinic acetylcholine receptor (nAChR) subtypes

Nicotinic agent	nAChR Subtypes (K_d or K_i, μM)			
	$\alpha_4\beta_2$ (brain)	$\alpha_3\beta_4$ (brain)	$\alpha_1\beta_1$ (muscle)	α_7 (brain)
Acetylcholine[a]	7–20	34	—	1100
Nicotine[a]	4.2	10.2	> 1000	40–83
Mecamylamine[b]	2.5	0.6	30	6.9
Dihydro-β-erythroidine[b]	3.5	23.1	—	20.0
Galanthamine[a]	10	17		0.9
Epibatidine[b]	3.0×10^{-5}	3.0×10^{-4}	2.7×10^{-3}	2.1×10^{-2}
ABT-594[a]	$3.7–5.5 \times 10^{-5}$	—	10.0	1.6
Bupropion[b]	10.0	1.4	10.5	50
Fluoxetine[b]	2.2	2.5	2.1	10.7

nAChR, Nicotinic acetylcholine receptor

[a] K_d, concentration for half-maximal binding

[b] K_i, concentration for half-maximal inhibition of binding. Data adapted from Bertrand *et al.* 1992; Harvey *et al.* 1996; Donnelly Roberts *et al.* 1998; Parker *et al.* 1998; Fryer and Lukas (1999a,b); Maelicke *et al.* 2001; Shytle *et al.* 2002a; Eaton *et al.* 2003; Samochocki *et al.* 2003; Zhao *et al.* 2003.

Table 2

Summary of evidence of nicotinic modulation of cognition in healthy human subjects: is there evidence for nicotinic enhancement of cognitive function?

	Domain	Findings	Reference
Healthy subjects (smokers and non-smokers)	Attention (sustained) Rating = 1	Acute smoking improved response time on RVIP and overall DSST performance in 12 smokers	Petrie and Deary (1989)
		Smoking deprivation for 24 h increased reaction time, reaction time variability and commission errors on CPT	Hatsukami *et al.* 1989
		Attentional measures of vigilance (reaction time, target detection) in the RVIP task were dose-dependently improved by nicotine gum (0, 2 and 4 mg), cigarette smoking	Parrott and Craig (1992)
		Subcutaneous nicotine (0.0, 0.3 and 0.6 mg) administration in deprived smokers improved correct responses on logical reasoning, vigilance and accuracy on RVIP, and improved word recognition. Positive effects in never smokers were confined to reaction times in RVIP and digit recall	Foulds *et al.* 1996
		Transdermal nicotine (21 mg/24 h) compared to placebo improved hit rate on the RVIP task, and this was accompanied by task-induced activation of regions associated with visual arousal, attention and motor activation, including parietal cortex, thalamus, caudate and occipital cortex	Lawrence and Ross (2002)
		Administration of transdermal nicotine patch significantly improves performance on CPT in non-smoking adults without attentional deficits	Levin *et al.* 1998
		Smoking enhanced P300 ERPs under non-deprived conditions, these effects were reduced with 12-h deprivation	Pineda *et al.* 1998
		Transdermal nicotine (21 mg) increased electroencephalogram arousal, reduced reaction times and increased P300 ERP amplitudes relative to placebo	Knott *et al.* 1999
		Acute and repeated cigarette smoking improves visuospatial expectancies, but not non-spatial expectancies	Murphy and Klein (1998)
	Attention (selective) Rating = 2	Nicotine administration, or smoking faciltitates classical Stroop Test (1935) performance, whereas abstinence impairs it	Wesnes and Revell (1984); Provost and Woodward (1991); Pomerleau *et al.* 1994
		Neither high- or low-nicotine content cigarettes modifies classical Stroop performance; Nicotine gum (0, 2 and 4 mg) and acute smoking or smoking abstinence did not alter Stroop performance	Suter *et al.* 1983; Parrott and Craig (1992); George *et al.* 2002
		Smoking improves smoking-context specific Stroop performance (e.g. reduce Stroop interferenceSI), whereas abstinence impairs smoking-word related Stroop interference	Gross *et al.* 1993; Rusted *et al.* 2000; Powell et al. (2002)
		Transdermal nicotine improved reaction times and interference scores on the classical Stroop, but not other attentional measures	Mancuso *et al.* 1999
	Sensorimotor gating (pre-attentional) Rating = 2	Smoking abstinence reduces, and acute smoking increases PPI of the startle response	Kumari *et al.* 1996; Della Casa *et al.* 1998; Kumari and Gray (1999); Duncan *et al.* 2001
		Acute smoking of high-nicotine content cigarettes (versus nicotine-free) inhibits PPI in deprived smokers	Hutchison *et al.* 2000
		Subcutaneous administration improves PPI in non-smokers	Kumari *et al.* 1997
	Verbal learning Rating = 3	Increasing doses of mecamylamine yielded more errors on repeated acquisition task in non-smokers	Newhouse *et al.* 1992
		Administration of oral cotinine (nicotine's proximal metabolite) dose-dependently impaired performance on a verbal recall task, while also decreasing N100 ERP latencies and reaction time	Herzig *et al.* 1998
		Smoking abstinence slowed responses on a letter search test, while acute smoking reversed letter test performance to baseline	Bell *et al.* 1999
		Acute smoking (1–2 cigarettes) had negligible effects on Buschke's selective reminding task and a letter fluency task in both smokers and non-smokers	Sakurai and Kanazawa (2002)
	Nonverbal learning Rating = 3	Acute smoking (1–2 cigarettes) had negligible effects on mental arithmetic task in both smokers and non-smokers	Sakurai and Kanazawa (2002)
	Processing Rating = 1	Smoking deprivation (up to 24 h) increased response latencies (reaction times) on a variety of tasks including attention, recall, working memory and logical reasoning speed	Snyder *et al.* 1989
		In non-smokers, nicotine improved reaction times without changes in accuracy on a reaction time task	Le Houezec *et al.* 1994
		Nicotine polacrilex (4 mg) showed improvements in reaction time on the two letter search task (visual attention), rather than in accuracy for smokers and non-smokers	Ernst *et al.* 2001a
		Low dose transdermal nicotine (7 mg/24 h) maintained choice reaction time performance through increasing overall arousal	Davranche and Audiffren (2002)

Domain	Findings	Reference
Working memory Rating = 3	Acute smoking after overnight abstinence impaired spatial working memory performance in smokers	Park *et al.* 2000
	Smokers showed deficits in working memory, independent of nicotine gum administration	Ernst *et al.* 2001b
	Prolonged smoking abstinence for up to 8 weeks improved spatial working memory performance in non-psychiatric smokers	George *et al.* 2002
	Recognition memory improved with higher doses of mecamylamine in non-smokers	Newhouse *et al.* 1992
Executive function Rating = 3	Smoking deprivation for 4 and 24 h led to decrements in Trails B performance, but this was likely related to impairment of psychomotor performance	Hatsukami *et al.* 1989
	In smokers, logical reasoning was unchanged by deprivation, but improved once participants resumed smoking	Bell *et al.* 1999

RATINGS: 1 = Strong Evidence; 2 = Modest Evidence; 3 = Little or No Evidence. CPT, Continuous Performance Test; DSST, Digit Symbol Substitution Test; ERP, event-related potential; PPI, pre-pulse inhibition; RVIP, rapid visual information processing.

Table 3

Summary of evidence for nicotinic modulation of cognition in patients with neuropsychiatric disorders: is there evidence for nicotinic enhancement of cognitive function?

	Domain	Findings	Reference
ADHD	Attention Rating = 1	TNP improved CPT reaction time and hit rate variability in adults with ADHD, but more so in smokers than nonsmokers	Conners *et al.* 1996; Levin *et al.* 1996a, 2001
	Clinical outcomes Rating = 1	Nicotine increased self-reported vigor on POMS	Conners *et al.* 1996; Levin *et al.* 1996a, 2001
		TNP improved symptoms as measured by CGI in both smokers and nonsmokers	Conners *et al.* 1996; Levin *et al.* 1996b
		The nicotinic agonist ABT-418 improved clinical measures of attentiveness and impulsivity in adults with ADHD	Wilens *et al.* 1999
		TNP reduced symptoms on Conners' Parent Rating Scale in 'Learning Problems and 'Hyperactivity' domains in children and adolescents with ADHD	Shytle *et al.* 2002b
Alzheimer's disease	Attention Rating = 1	Intravenous nicotine (0.125, 0.25 and 0.50 mg/kg/min) dose-dependently improved intrusion errors on a verbal recall task in non-smokers with AD, with maximal benefits at the 0.25 mg/kg/min dose, suggesting an 'inverted U' dose effect	Newhouse *et al.* 1988
		TNP improved performance on CPT by reducing errors of omission after 1 day, and this effect was sustained with chronic nicotine exposure. Also reduced variability of response speed in patients with AD	White and Levin (1999)
		MMN's amplitude increases with nicotine gum (2 mg) and MMN latencies shortened by nicotine treatment in patients with AD	Engeland *et al.* 2002
		Nicotine gum (2 mg) did not alter auditory P300 in either Tacrine treated or non-treated AD subjects	Knott *et al.* 2002
		Patients with AD improved detection performance on a flicker fusion test compared to control groups with i.v. nicotine, as well as discriminative sensitivity and reaction times	Sahakian *et al.* 1989
		Subcutaneous administration of nicotine improved sustained visual attention (RVIP and delayed response matching tasks) and perception (flicker fusion task) in AD patients	Jones *et al.* 1992
	Learning and memory Rating = 2	TNP improved acquisition of information compared to placebo patch in patients with probable AD	Wilson *et al.* 1995
		TNP did not improve performance of a letter memory test (Sternberg) in patients with AD	White and Levin (1999)
		Subcutaneous nicotine versus saline administration did not improve verbal or visual Stroop test memory in patients with AD	Jones *et al.* 1992
		No difference between TNP and placebo patch on measures of short-term memory	Snaedal *et al.* 1996
	Executive function Rating = 3	TNP did not improve performance on the DRS compared to PLA in patients with probable AD	Wilson *et al.* 1995
	Psychomotor performance Rating = 2–3	Subcutaneous nicotine improved finger tapping performance in patients with AD in this single-blind study	Jones *et al.* 1992
Parkinson's disease	Attention Rating = 1	Acute intravenous nicotine (up to 1.25 μg/kg/min) in comparison to saline significantly dose-dependently improved reaction time, processing speed, and reduced tracking errors	Kelton *et al.* 2000
	Clinical outcomes Rating = 2–3	Chronic treatment with TNP (14 mg/day) compared to placebo improved extrapyramidal symptoms	Kelton *et al.* 2000
		NRT did not significantly alter ratings of timed walking, fine motor skills, hand tremor, or depressive symptoms in a nonsmoking sample with PD	Vieregge *et al.* 2001
		After 12 h of exposure to NRT, 16 patients with PD demonstrated a worsening of motor performance compared to placebo	Ebersbach *et al.* 1999
Schizophrenia	Attention (sustained) Rating = 1	SCZ smokers showed improved sustained attention (on CPT Hits) with administrated of 14 mg patch compared to non-psychiatric controls	Depatie *et al.* 2002
		Cigarette smoking improved abstinence-induced impairment of CPT Hit Rate and Attentional Variability Index in Schizophrenics compared to smoking controls. These improvements were blocked by the high-affinity nAChR antagonist mecamylamine	Sacco *et al.* 2003
	Attention (selective) Rating = 3	SCZ patients quitting smoking for up to 10 weeks did not have alteration of Stroop test performance	George *et al.* 2002
	Attention (sensory gating) Rating = 1	P50 auditory-evoked ERPs are transiently improved by nicotine administration and cigarette smoking. Such effects are related to stimulation of a_7 nAChRs (encoded by CHRNA7)	Adler *et al.* 1993; Leonard *et al.* 2002
		Nicotine administration (to smokers and nonsmokers), or smoking in SCZ patients demonstrated improved leading saccade acceleration in the smooth pursuit eye movement task, with no significant effects in non-psychiatric subjects	Olincy *et al.* 1998; Sherr *et al.* 2002; Depatie *et al.* 2002;

	Domain	Findings	Reference
			Avila *et al.* 2003; Olincy *et al.* 2003
		Acute cigarette smoking selectively improves pre-pulse inhibition in SCZ compared to non-psychiatric controls; these effects are blocked by the high-affinity nAChR antagonist mecamyamine	George *et al.* 2003a
	Learning and memory Rating = 2	SCZ smokers treated with haloperidol demonstrated dose-related impairment in delayed matching to sample accuracy, and poorer response time on a complex reaction task. Nicotine dose-dependently reversed these medication induced impairments	Levin *et al.* 1996
	Working memory or spatial organization Rating = 1	SCZ smokers had baseline impairments in VSWM compared to SCZ nonsmokers, and after quitting smoking, SCZ smokers had further impairments in VSWM while control quitters had improvements	George *et al.* 2002
		Administration of nicotine to SCZ smokers improved performance on a spatial organization task (ANAM battery)	Smith *et al.* 2002
	Clinical outcomes Rating = 2	In a group of SCZ patients, smoking high nicotine cigarettes decreased negative symptoms of SCZ more than smoking de-nicotinized cigarettes. However, neither type of cigarettes significantly altered positive symptoms, anxiety, or depression	Smith *et al.* 2002
		SCZ patients demonstrated decreased haloperidol-induced bradykinesia-rigidity when administered 21 mg/24 h TNP versus placebo	Yang *et al.* 2002

Ratings: 1 = Strong Evidence; 2 = Modest Evidence; 3 = Little of No Evidence. ADHD, attention-deficit hyperactivity disorder; ANAM, Automated Neuropsychological Assessment Metrics; CGI, Clinical Global Improvement; CPT, Continuous Performance Test; DRS, Dementia Rating Scale; ERP, event-related potential; MMN, mismatch negativity; NRT, nicotine replacement therapy; POMS, Profile of Mood States; RVIP, rapid visual information processing; SCZ, schizophrenic; TNP, transdermal nicotine patch; VSWM, visuospatial working memory.