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Meta-analysis of the acute effects of nicotine and smoking on human performance

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Abstract

Rationale and objective—Empirical studies indicate that nicotine enhances some aspects of attention and cognition, suggesting a role in the maintenance of tobacco dependence. The purpose of this review was to update the literature since our previous review (Heishman et al. Exp Clin Psychopharmacol 2:345–395, 1994) and to determine which aspects of human performance were most sensitive to the effects of nicotine and smoking.

Methods—We conducted a meta-analysis on the outcome measures of 41 double-blind, placebo-controlled laboratory studies published from 1994 to 2008. In all studies, nicotine was administered, and performance was assessed in healthy adult nonsmokers or smokers who were not tobacco-deprived or minimally deprived (≤2 h).

Results—There were sufficient effect size data to conduct meta-analyses on nine performance domains, including motor abilities, alerting and orienting attention, and episodic and working memory. We found significant positive effects of nicotine or smoking on six domains: fine motor, alerting attention-accuracy and response time (RT), orienting attention-RT, short-term episodic memory-accuracy, and working memory-RT (effect size range=0.16 to 0.44).

Conclusions—The significant effects of nicotine on motor abilities, attention, and memory likely represent true performance enhancement because they are not confounded by withdrawal relief. The beneficial cognitive effects of nicotine have implications for initiation of smoking and maintenance of tobacco dependence.

Keywords

Nicotine; Tobacco; Smoking; Performance; Motor; Attention; Memory; Cognition; Smokers; Nonsmokers

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Introduction

The first Surgeon General's report on the morbidity and mortality associated with cigarette smoking was released 45 years ago (US Public Health Service 1964); however, 20.6% of adults (46 million) in the US are current smokers (Centers for Disease Control and Prevention [CDC] 2009). In 2008, 45% of smokers (21 million) tried to quit smoking (CDC 2009), but only 4–7% was likely successful (Fiore et al. 2008). In most smokers trying to quit, withdrawal symptoms and various nonpharmacological factors (e.g., cigarette availability) typically lead to relapse within a few days or weeks. One component of the nicotine withdrawal syndrome is difficulty concentrating (American Psychiatric Association [APA] 2000), which is generally regarded as a relapse factor and as a factor in the maintenance of smoking in tobacco-dependent individuals not attempting to quit smoking (Heishman et al. 1994). Smokers report that one of the reasons they smoke is for the perceived cognitive benefits of nicotine (West 1993). Experimental investigation for more than 40 years has attempted to validate self-reported claims of performance benefits and to delineate the conditions under which nicotine might enhance the various domains of human performance.

Research in the 1970s and 1980s suggested that tobacco smoking enhanced human performance; however, because of their design, the majority of these studies only demonstrated that smoking reversed withdrawal-induced performance deficits in tobacco-dependent smokers (Heishman et al. 1994). Previous reviews of this literature (Heishman et al. 1994; Heishman 1998; Sherwood 1993) concluded that smoking or nicotine produced small beneficial effects on a limited range of performance measures in nonsmokers and nondeprived or minimally deprived smokers. Behaviors most reliably enhanced were motor responding, focused and sustained attention, and recognition memory.

Nicotine's ability to enhance cognitive processing has led to a greater understanding of the role of cholinergic mechanisms in cognitive functioning. Nicotine binds to presynaptic nicotinic acetylcholine receptors (nAChRs) in the brain and facilitates the release of acetylcholine, dopamine, serotonin, glutamate, and other neurotransmitters known to be involved in cognitive processes (Di Matteo et al. 2007). Cholinergic projections to the prefrontal cortex are involved in attentional processing (Poorthuis et al. 2009). Furthermore, α7 and α4β2 subunits of nAChRs in the hippocampus and basolateral amygdala mediate nicotine's role in memory (Levin et al. 2006; Mansvelder et al. 2006). Nicotine and other nicotinic agents have been suggested as treatment medications for several neuropsychiatric disorders. For example, nicotine has been shown to attenuate certain attentional and cognitive deficits associated with schizophrenia, attention deficit/hyperactivity disorder, Alzheimer's and Parkinson's diseases, and age-related cognitive decline (Evans and Drobes 2008; Levin et al. 2006; Newhouse et al. 2004). Such translational research can be guided by a knowledge of which aspects of cognition are reliably affected by nicotine.

Two extensive literature reviews on the effect of nicotine and tobacco smoking on human performance were published in the early 1990s (Heishman et al. 1994; Sherwood 1993). As noted in these reviews, the effect of nicotine and smoking on cognitive functioning was inconsistent, with nearly an equal number of studies reporting enhancement and no effect. Since then, numerous articles have been published investigating the effects of nicotine and smoking on attention and cognition. The purpose of this study was to conduct a meta-analysis of studies investigating the effects of nicotine on human performance published in the 15 years since our previous review (Heishman et al. 1994). Because many studies have documented the ability of nicotine or tobacco smoking to reverse performance deficits observed following some period of tobacco deprivation (Heishman et al. 1994), we sought to determine which aspects of human performance are enhanced by nicotine or tobacco

smoking without the confound of withdrawal relief. We thus examined data from only those studies testing nonsmokers (never smokers and former smokers), nondeprived smokers, and smokers deprived for less than 2 h (minimally deprived).

The aims of this meta-analysis were (a) to synthesize the human literature on nicotine and performance published from 1994 to 2008, (b) to determine which aspects of performance were most sensitive to the enhancing effects of nicotine and tobacco smoking by calculating effect sizes on all reported outcome measures, and (c) to determine if methodological and design deficiencies noted in our previous review (Heishman et al. 1994) were still evident.

Methods

Literature search

Computerized literature searches were conducted using MEDLINE®, EMBASE™, and PsycINFO®. Searches were limited to peer-reviewed journal articles written in English (book chapters, technical reports, and abstracts were excluded), involving humans, and published in print or online from 1994 through 2008. Key words included *nicotine*, *tobacco*, and *cigarette smoking* in combination with each of the following terms: *performance*, *sensory*, *motor*, *psychomotor*, *attention*, *information processing*, *memory*, and *cognition*. The specific terms used in each database were chosen or modified to take advantage of unique features, such as controlled vocabulary (e.g., MeSH® terms) and available subheadings (e.g., “drug administration”). Additionally, reference sections of review articles were searched for relevant studies. The initial search produced 658 articles. After removing articles that were not pertinent (e.g., epidemiological or medical studies), 256 articles met the above criteria.

Criteria for review

Studies identified by the database searches were evaluated for inclusion in the meta-analysis according to the following criteria. Inclusionary criteria were (a) administration of nicotine via cigarette smoking or other delivery method during laboratory sessions; (b) measurement of one or more performance variables following nicotine administration; (c) administration of nicotine to healthy adults, aged 18 to 59 years; (d) administration of nicotine to nondeprived smokers, minimally deprived smokers, or nonsmokers; (e) use of a placebo control condition (e.g., denicotinized cigarette and placebo patch); (f) random assignment of participants to experimental and control conditions; and (g) reporting of a statistical test, *p* value, or numeric data that allowed calculation of an effect size. Exclusionary criteria were (a) assessment of nicotine’s effect only on physiological functioning (e.g., evoked potential and acoustic startle); (b) administration of nicotine after more than 2 h of tobacco deprivation; (c) administration of nicotine not under double-blind conditions (i.e., no smoking or sham smoking as a control condition); and (d) administration of nicotine to patient populations. The 256 articles were reviewed independently by two of the authors (SJH and BAK). Cohen’s kappa index (Cohen 1960) was 0.80 (SE=0.06), indicating substantial agreement between the two raters (Landis and Koch 1977). Discrepancies were resolved through discussion. Fifty articles met these criteria.

Coding of variables

The following information was coded for each of the 50 articles: (a) outcome measures; (b) performance domain; (c) route of nicotine administration (inhalation, buccal, transdermal, intranasal, or subcutaneous injection); (d) control condition (denicotinized cigarette or nicotine placebo); (e) degree of tobacco deprivation (none, minimal [0–2 h], or nonsmokers); (f) source statistic or other data used to compute effect size; and (g) whether or not the study indicated funding from the tobacco industry. The following participant

characteristics, if reported, were also coded for each study: (a) mean age; (b) sex (male, female, or both); (c) racial/ethnic composition (Black, White, or Hispanic); (d) mean number of cigarettes smoked per day; and (e) mean number of years smoking. Variables were coded independently by two of the authors (SJH and BAK). Average percent agreement across the variables was 96.7% (range=89–100%). Disagreements were resolved through discussion.

Outcome measures and performance domains

We initially planned to use the same performance categories as used by Heishman et al. (1994) to maintain consistency between the earlier literature (1970–1993) and this update: sensory, motor, attention (focused, selective, divided, and sustained), and cognition (learning, memory, and other). However, we found no studies that measured sensory abilities, and recent trends in the literature allowed us to examine different aspects of attention and memory. Posner's network model of attention provided a theoretical and empirical framework for organizing studies of attentional performance (Posner and Rothbart 2007). The independent networks that comprise this system are termed (a) alerting (maintaining an alert state, as in signal detection tasks), (b) orienting (directing attention to sensory events, as in cued target tasks), and (c) executive function or control (resolving conflict among potential responses, as in the Stroop task; Fan et al. 2009; Posner and Rothbart 2007). We thus categorized attentional outcomes into one of these three domains. The majority of outcomes subsumed under cognition were in memory, with a few studies investigating arithmetic abilities and reasoning. We classified memorial outcome measures as episodic, semantic, prospective, or working memory. Episodic memory refers to personal experiences and information, such as a word list, whereas semantic memory is defined as culturally shared knowledge, such as meaning of words (Tulving 1972). Prospective memory involves intentional processes required to perform a future activity (Ellis and Kvavilashvili 2000). Among these three memory types, we distinguished between short-term memory (retention intervals <3 min) and long-term memory (retention intervals ≥10 min). Working memory is defined as a system that assists in the temporary (<10 s) holding and manipulation of information (Baddeley 1999).

Outcome measures from the 50 articles were classified according to the following 13 performance domains: (a) motor, fine and gross; (b) alerting attention; (c) orienting attention; (d) executive attention; (e) short- and long-term episodic memory; (f) long-term semantic memory; (g) long-term prospective memory; (h) working memory; (i) arithmetic; (j) reasoning; and (k) complex cognition. For most domains, there were sufficient studies to analyze accuracy and response time (RT) separately. If studies reported the effects of nicotine on multiple outcomes, which many did, we categorized all measures in the independent performance domains. If a study reported more than one outcome for a given domain, we selected the most relevant measure or the one consistent with other studies in that domain. Classification of certain outcome measures is somewhat arbitrary because task performance requires multiple performance domains. For example, we categorized the rapid visual information processing test in alerting attention, but the test also requires working memory (Coull et al. 1996).

We included studies using various routes of nicotine administration within each domain because we were interested in determining a generalized effect of nicotine on performance. Most studies administered single doses of nicotine. To include those studies administering multiple doses in the meta-analyses, we used data from the dose producing the greatest effect. Consistent with the analysis of studies using rigorous experimental methodology in our previous review (Heishman et al. 1994), we only included studies that used a placebo control condition; studies using sham smoking or no smoking as a control were excluded. To avoid confounding of nicotine withdrawal, we only included studies that tested nonsmokers, nondeprived smokers, or minimally deprived (≤2 h) smokers. Withdrawal-induced

performance deficits are typically not seen within 2 h of tobacco deprivation (Parrott et al. 1996; Snyder et al. 1989; although see Hendricks et al. 2006).

Data analysis

We used the software Comprehensive Meta-Analysis 2.0 (CMA; Biostat, Inc.; www.MetaAnalysis.com) to conduct a meta-analysis on each performance domain if a minimum of five effect sizes from independent studies were available. We used a random effects model because the studies within any performance domain varied in procedures and outcomes, which precluded an assumption of a common effect size. Additionally, we were interested in generalizing the effects of nicotine beyond the sample of studies (Borenstein et al. 2009). CMA can use sample size and several source statistics to calculate effect size. If multiple source statistics were available, we entered data in this order of preference: (a) means and standard deviations, (b) *t*-statistic and sample size, or (c) *p* value and sample size. If no source statistics were reported for an outcome measure, we excluded that outcome from the analysis. We calculated effect size and variance estimates for each study within each performance domain (accuracy and RT where possible) and then computed a combined effect size for that domain. For all analyses, we computed effect sizes as the standardized mean difference using Hedges's *g* to be able to compare across studies and to correct for bias caused by small sample size (Hedges and Olkin 1985).

We evaluated heterogeneity or inconsistency of effect sizes within each domain in several ways. We defined an outcome as an outlier if the standardized residual *z*-score of the effect size exceeded ±1.96 ($p<0.05$). Because we used a random effects model, we only deleted outliers if the study's methodology was substantially different from the other studies in that domain. The test of the null hypothesis that all studies share a common effect size (homogeneity) is represented by *Q*, which follows a central chi-squared distribution with k-1 degrees of freedom, where k is the number of effect sizes. Tau (T) is the standard deviation of the distribution of effect sizes about the mean effect and thus provides an *absolute* measure of variability. In contrast, I^2 (range=0–100%) is a *relative* measure of the amount of variability and reflects the proportion of observed variance that reflects real differences in effect size. Higgins et al. (2003) suggested that I^2 values of 25%, 50%, and 75% could be considered as low, moderate, and high, respectively. A high I^2 value means that most of the observed variance is real and that a subgroup analysis might explain it (Borenstein et al. 2009). When our analyses indicated a moderate to high I^2, we compared smokers and nonsmokers, if possible, in an attempt to explain the variance.

Results

The following performance domains did not have a minimum of five effect sizes necessary to conduct a meta-analysis: (a) gross motor, (b) executive attention, (c) long-term semantic memory-accuracy, (d) long-term prospective memory, (e) arithmetic, (f) reasoning, and (g) complex cognition. The domain of long-term semantic memory-RT initially had five effect sizes, but three were deleted because the studies did not report source statistics associated with no effect of nicotine. Overall, 41 studies (48 experiments) contributed effect size data to meta-analyses of the following nine domains: (a) fine motor, (b) alerting attention-accuracy, (c) alerting attention-RT, (d) orienting attention-accuracy, (e) orienting attention-RT, (f) short-term episodic memory-accuracy, (g) long-term episodic memory-accuracy, (h) working memory-accuracy, and (i) working memory-RT. Table 1 presents effect size, heterogeneity, and variability summary statistics for the nine performance domains. Tables 2, 3, 4, 5, 6, 7, 8, 9, and 10 show individual study characteristics and effect size data for each of the domains.

Characteristics of studies

Sample characteristics—The average sample size of the 48 experiments contributing effect size data to the meta-analyses was 24.6 (SD=18.0, median=19, range=9–130). A majority (58%) of sample sizes were ≤20, which was the same proportion in our previous review (Heishman et al. 1994). Across the nine performance domains, there was no correlation (r=0.03) between effect size and total sample size. Mean age of subjects was 26.1 years (SD=5.6) based on 36 experiments (75% of total); four experiments reported an age range and eight did not report subjects' age. Forty experiments (83%) tested men and women; of those reporting subjects' sex (n= 35), mean percent male subjects was 48%. Six experiments (13%) tested only men, and seven (15%) did not report subjects' sex. Only seven experiments (15%) reported racial or ethnic composition of samples. Mean percentage of White subjects was 80% (SD=12.7, range=57% to 100%) and that of Blacks was 22% (SD=12.3, range=0% to 43%). Two studies reported Asians, comprising 4% and 18% of subjects.

Twenty-nine experiments (60%) tested nonsmokers. Of the 19 experiments (40%) testing smokers, seven reported number of cigarettes smoked per day (M=18.6, SD=3.9); the rest reported a minimum number for study eligibility (range=5 to 20). Seven experiments reported number of years smoking (M=10.0, SD=5.2), two reported a minimum value (4 and 5 years), and ten did not report this information. Five studies reported a score (M=4.5, SD=1.3) on the Fagerström Test for Nicotine Dependence (FTND; Heatherton et al. 1991). Of the 19 experiments testing smokers, six were conducted under conditions of no tobacco deprivation (Houlihan et al. 2001; Kelemen and Fulton 2008; Lawrence et al. 2002; Myers et al. 2008; Phillips and Fox 1998; Tucha and Lange 2004), and 13 experiments required minimal (1–2 h) deprivation. Five studies (eight experiments) tested subjects who were 1-h deprived (Hahn et al. 2007, 2009; Rusted et al. 1995, 1998; Warburton et al. 2001), and five studies (five experiments) tested subjects who were 2-h deprived (Bates et al. 1995; Harte and Kanarek 2004; Krebs et al. 1994; Larrison et al. 2004; McClernon et al. 2003).

Nicotine dosing—The majority of studies (75%) administered nicotine via a medication approved by the Food and Drug Administration. Nicotine gum was used in 16 experiments (33%), transdermal patch in 14 experiments (29%), nasal spray in five experiments (10%), and inhaler in one experiment (2%). Three studies (6%) administered nicotine via subcutaneous injection. Nine experiments (19%) used tobacco cigarettes. According to our inclusion criterion, all studies included a placebo control condition. Studies administering nicotine used an appropriate placebo product, and in those studies using cigarettes, subjects smoked denicotinized cigarettes. The denicotinized cigarettes used in these studies had a nicotine yield less than 0.1 mg.

Most studies (73%) administered single doses of nicotine. For the 11 studies administering multiple doses, we entered data in the meta-analyses from the one dose producing the greatest magnitude of effect (positive or negative difference between condition means). These 11 studies are identified in Tables 2, 3, 4, 5, 6, 7, 8, 9, and 10. Dose–response data are summarized at the end of Results.

Tobacco industry support—In their statements of financial support, three studies (6%) reported support from the tobacco industry (Bates et al. 1995; Houlihan et al. 2001; Levin et al. 1998), whereas 31 studies (76%) indicated no tobacco industry support. Seven studies (17%) did not include an acknowledgment of financial support.

Meta-analysis of performance domains

Fine motor abilities—The seven outcomes comprising the fine motor domain included finger tapping, handwriting, and pegboard performance (Table 2). Such variety in outcomes with so few studies might suggest no basis for commonality. However, there was no evidence of heterogeneity among outcomes, $Q(6)=8.22$, $p>0.2$, and no outcome measure was identified as an outlier. Analysis of the seven effect sizes indicated that nicotine produced a significant positive effect, $g=0.16$, $z=2.21$, $p<0.05$. Because only one study tested smokers, a subgroup analysis was not feasible.

Alerting attention-accuracy—Analysis of the nine effect sizes indicated that nicotine had a significant positive effect on accuracy in alerting attention, $g=0.34$, $z=4.19$, $p<0.001$ (Table 3). One outcome (Barr et al. 2008b) was detected as an outlier, $z=-2.02$, $p<0.04$; however, it was not different methodologically from the other studies. Furthermore, there was no evidence of heterogeneity among the outcomes in this domain, $Q(8)=8.45$, $p>0.3$, and relative variance was low ($I^2=5\%$). A subgroup analysis indicated that nicotine's positive effect was robust in smokers, $g=0.46$, $z=4.18$, $p<0.001$, but just missed significance in nonsmokers, $g=0.21$, $z=1.86$, $p=0.06$. The difference in effect size between smokers and nonsmokers was not significant, $p>0.1$.

Alerting attention-RT—Analysis of the 13 effect sizes indicated that nicotine produced a significant positive effect on RT in alerting attention, $g=0.34$, $z=3.85$, $p<0.001$ (Table 4). One outcome (Foulds et al. 1996) was identified as an outlier, $z=2.89$, $p<0.01$. Foulds et al. administered nicotine as a subcutaneous injection as did one other study in this domain, and their task (rapid visual information processing) was used by four other studies. Because of this similarity with other studies and the lack of evidence of heterogeneity among outcomes, $Q(12)=20.26$, $p=0.06$, we did not delete Foulds et al. The effect of nicotine was significant in nonsmokers, $g=0.39$, $z=3.31$, $p<0.001$, but only a trend in smokers, $g=0.27$, $z=1.79$, $p=0.07$. There was no difference in effect size between smokers and nonsmokers, $p>0.5$.

Orienting attention-accuracy—Analysis of the five effect sizes indicated that nicotine produced a nonsignificant effect on accuracy in orienting attention, $g=0.13$, $z=0.47$, $p>0.6$ (Table 5). Smokers ($p>0.2$) and nonsmokers ($p>0.7$) were similarly unaffected by nicotine. One outcome (Heishman and Henningfield 2000) was identified as an outlier, $z=-1.99$, $p<0.05$. Significant heterogeneity, $Q(4)=16.86$, $p<0.01$, and large relative variance ($I^2=76\%$) suggested that deleting Heishman and Henningfield was appropriate. However, this left only four effect sizes, one less than the minimum required to conduct a meta-analysis.

Orienting attention-RT—Analysis of the 11 effect sizes indicated that nicotine produced a significant positive effect on RT in orienting attention, $g=0.30$, $z=3.93$, $p<0.001$ (Table 6). No outcome measure was identified as an outlier, and there was no evidence of heterogeneity among outcomes, $Q(10)=7.35$, $p>0.6$. Because only one study tested smokers, a subgroup analysis was not feasible.

Short-term episodic memory-accuracy—Analysis of the eight effect sizes indicated that nicotine produced a significant positive effect on accuracy in short-term recall tasks, $g=0.44$, $z=3.19$, $p<0.01$ (Table 7). One outcome (Phillips and Fox 1998) was identified as an outlier, $z=2.28$, $p<0.05$. Phillips and Fox reported outcome data separately for smokers and nonsmokers; the outlier measure was from the smokers. The methodological aspects of the study were similar to others in the domain, and there was no evidence of heterogeneity among outcomes, $Q(7)=9.65$, $p>0.2$. Thus, we did not delete Phillips and Fox. The effect of nicotine was significant in smokers, $g=0.46$, $z=2.25$, $p<0.05$, but only a trend in nonsmokers,

g=0.43, z=1.89, p=0.06. There was no difference in effect size between smokers and nonsmokers, p>0.9.

Long-term episodic memory-accuracy—Analysis of the 12 effect sizes indicated that nicotine did not significantly affect accuracy in delayed episodic recall tasks, g=0.17, z=1.14, p>0.2 (Table 8). One outcome (Warburton et al. 2001) was identified as an outlier, z=3.07, p<0.01. Significant heterogeneity, $Q(11)$=58.11, p<0.001, suggested that deleting Warburton et al. was appropriate; however, this study was nearly identical to the others with respect to methodology. Deleting Warburton et al. from the analysis did not change the nonsignificant effect size result, nor did it eliminate the heterogeneity among the outcomes. Large relative variance (I^2=81%) supported the inconsistency of effect sizes in this domain. A subgroup analysis indicated that nicotine's effect was not significant in nonsmokers, g= −0.04, z=−0.19, p>0.8, but revealed a trend toward significance in smokers, g=0.40, z=1.86, p= 0.06. There was no difference in effect size between smokers and nonsmokers, p>0.1.

Working memory-accuracy—Analysis of the nine effect sizes indicated that nicotine produced a nonsignificant negative effect on accurate performance in working memory, g= −0.11, z=−0.61, p> 0.5 (Table 9). No outcome measure was identified as an outlier. However, there was significant heterogeneity among outcomes, $Q(8)$=35.95, p<0.001, and large relative variance (I^2=78%). Because only one study tested smokers, a subgroup analysis was not feasible.

Working memory-RT—Analysis of the ten effect sizes indicated that nicotine produced a significant positive effect on RT in working memory, g=0.34, z=3.40, p<0.01 (Table 10). No outcome measure was identified as an outlier, but there was significant heterogeneity among outcomes, $Q(9)$=18.17, p<0.05. A moderate relative variance (I^2=50%) suggested a subgroup analysis between smokers and nonsmokers. The effect of nicotine was significant in both smokers, g=0.45, z=2.01, p<0.05, and nonsmokers, g=0.31, z=2.64, p<0.01. There was no difference in effect size between smokers and nonsmokers, p>0.5.

Dose–response relationships—There was little consistency in dose–response functions within and across the performance domains. Linear effects were reported for fine motor performance (Tucha and Lange 2004), alerting and orienting attention (Foulds et al. 1996; Myers et al. 2008), and working memory (Foulds et al. 1996; Heishman and Henningfield 2000; Perkins et al. 2001, 2008). Curvilinear (typically an inverted U) effects were reported for fine motor skills (Perkins et al. 1994), alerting attention (Foulds et al. 1996), and long-term episodic memory (Perkins et al. 1994). However, most studies reported no dose–response effects for fine motor performance (Foulds et al. 1996; Perkins et al. 2001, 2008), alerting and orienting attention (Griesar et al. 2001; Heishman and Henningfield 2000; Kleykamp et al. 2005; Myers et al. 2008; Thiel et al. 2005), episodic memory (Foulds et al. 1996; Krebs et al. 1994; Perkins et al. 2001, 2008), and working memory (Kleykamp et al. 2005; Myers et al. 2008).

Discussion

The purpose of this meta-analytic synthesis was to update our previous narrative review (Heishman et al. 1994) and to determine which aspects of human performance were most sensitive to the enhancing effects of nicotine or tobacco smoking. There were sufficient effect size data to conduct meta-analyses on nine performance domains, including fine motor abilities, alerting and orienting attention, and episodic and working memory. We found significant positive effects of nicotine or smoking on six domains: fine motor, alerting attention-accuracy and RT, orienting attention-RT, short-term episodic memory-accuracy, and working memory-RT (effect size range=0.16 to 0.44). The enhanced performance on

motor and attentional tasks is consistent with the earlier literature (Heishman et al. 1994; Sherwood 1993), whereas the salutary effect of nicotine on memory was not recognized previously. This is likely attributable to improved methodology and more refined tests, rather than to more studies investigating memory. For example, no studies in our previous review (Heishman et al. 1994) used the n-back task as a measure of working memory.

Previous reviews (Heishman et al. 1994; Sherwood 1993) concluded that nicotine enhanced motor responding more reliably than task accuracy. The meta-analysis revealed a small, but significant effect size (0.16) for fine motor abilities. We also observed significant positive effects of nicotine on RT in alerting and orienting attention and working memory and failed to obtain significant effects on accuracy in orienting attention, long-term episodic memory, and working memory. These results suggest that much of nicotine's enhancing effects are mediated via facilitation of motoric responding, which is consistent with expression of nAChRs in the peripheral musculature, striatum, and motor cortex (Dani and Bertrand 2007; Mansvelder et al. 2006). The remaining significant effect sizes for attention and memory were in the medium range (Cohen 1988), suggesting that nicotine's effect on cognition is not as subtle as previously thought (Heishman et al. 1994; Sherwood 1993). Because we only included studies testing nonsmokers and smokers who were not tobacco-deprived or deprived for less than 2 h, the observed performance enhancement likely represents true facilitation, not withdrawal relief (Heishman et al. 1994; Hughes 1991). The significant effect sizes of nicotine on motor abilities, attention, and memory have implications for maintenance of tobacco dependence and initiation of smoking.

Implications for tobacco dependence

Difficulty concentrating is a valid symptom of nicotine withdrawal (APA 2000; Hughes 2007). Deficits in task performance, the related objective withdrawal sign, have been observed in the laboratory as soon as 30 min to 2 h after tobacco deprivation begins (Hendricks et al. 2006; Parrott et al. 1996); clinical reports of difficulty concentrating peak a few days after abstinence and can last for several weeks (Hughes 2007). Smoking can reverse withdrawal-induced performance deficits (Heishman et al. 1994) as can nicotine replacement and other medications when used during a quit attempt (Henningfield et al. 2009). For this reason, difficulty concentrating and consequent declines in performance are regarded as relapse factors in smokers trying to quit and as factors in the maintenance of smoking in those not attempting to quit. Evidence for these findings came from studying tobacco-deprived smokers (Heishman et al. 1994; Sherwood 1993); however, the focus of this meta-analysis was the effects of nicotine and smoking in nonsmokers and in smokers not experiencing withdrawal, which might have bearing on the initiation of smoking.

We previously concluded that because nicotine enhanced a limited range of behavior in nonsmokers and nondeprived smokers and that these effects were small in magnitude, performance enhancement was not likely to be an important factor in the initiation of smoking among adolescents (Heishman 1998; Heishman et al. 1994). To our knowledge, this hypothesis has not been empirically tested, but the results of this meta-analysis indicate that performance facilitation might play a role in the rewarding effects of nicotine during the initiation of tobacco dependence. In contrast to the subtle, inconsistent performance effects shown in the earlier literature (Heishman et al. 1994; Sherwood 1993), we observed significant positive effect sizes of nicotine on motor abilities, attention, and memory, which likely represent true performance facilitation. In most of the performance domains where a subgroup analysis was possible, we observed significant effect sizes for non-smokers and no differences between nonsmokers and smokers. The result in nonsmokers is indirect evidence that nicotine's performance enhancing effects might be one reason people decide to start smoking. However, the question of whether the cognitive enhancing effects of nicotine reinforce cigarette smoking remains to be answered.

Neurobiological mechanisms

Consistent with our findings, numerous studies have shown that nicotine improves attention and memory in various animal models (Kenney and Gould 2008; Levin et al. 2006). Although little is known about the specific mechanisms underlying the performance enhancing effects of nicotine, cholinergic neurons in the basal forebrain send projections into multiple subcortical structures and cortical regions (Woolf 1991), thus influencing numerous behaviors, including motor and cognitive functions via interactions with all neurotransmitter systems (for excellent reviews see Debski 2008; Mansvelder et al. 2006; Poorthuis et al. 2009). The α7 and α4β2 subunits of nAChRs, and perhaps other cholinergic receptor subtypes, have been implicated in cognitive functioning (Levin et al. 2006; Mansvelder et al. 2006). A detailed consideration of the neurobiological mechanisms of nicotine's role in cognition is beyond the scope of this paper, but recent imaging studies are beginning to shed light on brain regions involved in nicotine's effects on human attention and memory.

The cognitive effects of nicotine are related to its activation of the prefrontal cortex, parietal cortex, thalamus, and hippocampus, areas known to be involved with attention and memory and that contain relatively high densities of nAChRs (Brody 2006; Levin et al. 2006; Azizian et al. 2009). The alerting/arousal network, including the locus coeruleus, right frontal cortex, and parietal cortex, uses norepinephrine as a primary neurotransmitter (Fan et al. 2005; Posner and Rothbart 2007). Nicotine alters norepinephrine activity (Mitchell et al. 1990; Toth et al. 1992) and neural activity associated with the locus coeruleus (Egan and North 1986; Sun et al. 2004). Frontal, parietal, and cingulate cortex and the hippocampus are also associated with working memory (Cohen et al. 1997; Kumari et al. 2003; Levin et al. 2006). For example, Kumari et al. (2003) reported that nicotine increased activity in the anterior cingulate when volunteers were performing an easy working memory task, but increased parietal activity during a more difficult version of the task.

In contrast to data suggesting that nicotine facilitates cognition by increasing neural activity are recent findings showing that nicotine-induced improvements in attention were associated with neural deactivation (Hahn 2007, 2009). These findings suggest that a neural network model might more fully explain the relationship between nicotine and cognition (Hong et al. 2009; Mansvelder et al. 2006; Poorthuis et al. 2009). Such a model postulates that nicotine functions to synchronize high frequency neural activity, a role that might include simultaneous excitation and inhibition in particular brain regions (Hong et al. 2009; Mansvelder et al. 2006). How a neuronal network is affected by nicotine might depend on which neurons in the network express nAChRs, the type of nAChRs that are expressed, and/or the cellular location of these neurons (Mansvelder et al. 2006; Poorthuis et al. 2009). Individual differences in these aspects of neuroanatomy might explain the variability observed for some cognitive outcomes (see below for a discussion of this variability). Jacobsen et al. (2006) reported that genetic variation in the dopamine D2 receptor altered nicotine's effect on working memory. Future research will undoubtedly rely on such pharmaco-genetic interactions to fully explain nicotine's effects.

Methodological considerations

Sample size was ≤20 in 58% of the experiments. Power analyses indicate that a single study with 20 subjects has 14% power to detect a small (0.20) effect, 56% power to detect a medium (0.50) effect, and 92% power to detect a large (0.80) effect at α=0.05, two-tailed. None of the single studies had adequate power (≥80%) to detect a small effect. Four percent had adequate power to detect a medium effect, and 79% had adequate power to detect a large effect. Only 14% had adequate power to detect the estimated effect size found in the

study. When designing future studies, investigators should perform power calculations to determine the required sample size for meaningful results.

One inclusion criterion for the meta-analysis was use of a placebo control, which allows a study to be conducted under double-blind conditions. The majority (74%) of studies in our previous review (Heishman et al. 1994) in which subjects smoked did not use a placebo smoking condition. The development of denicotinized cigarettes in the 1990s provided an effective placebo for smoking studies (Robinson et al. 2000). Surprisingly, 30% of the original 256 studies reviewed for this analysis were excluded because they lacked a placebo control or were not conducted under double-blind conditions. This hallmark of experimental design is critical for unambiguous interpretation of future results.

Because the enhancing effects of nicotine are difficult to determine when smokers are experiencing nicotine withdrawal, we excluded studies in which smokers were tobacco-deprived for more than 2 h. Performance deficits after a few hours of deprivation are well-documented (Parrott et al. 1996; Snyder et al. 1989). Again, we were surprised that 40% of the 256 identified studies tested subjects after more than 4 h of tobacco deprivation and were thus excluded. We previously found that 70% of studies administered nicotine via ad libitum smoking, and we recommended that future research use nicotine medications for more precise dosing (Heishman et al. 1994). In the meta-analysis, we found that 75% of included studies used some form of nicotine medication. Although this is a positive design trend, only a small increase in the percentage of studies investigating multiple active doses of nicotine to explore dose–response relationships is seen from the 1994 review (11%) to the present analysis (27%). We observed linear, curvilinear, and no dose–response functions within and across the performance domains. This aspect of nicotine's performance effects clearly needs more research.

Many studies were deficient in reporting demographic and smoking history variables. Of the 48 experiments included in the meta-analysis, 25% did not report average age of subjects, 15% did not report sex ratio, and only 15% reported the racial or ethnic composition of the sample. Of the 19 experiments testing smokers, 63% did not report average cigarettes smoked per day or number of years smoking, and only 26% reported a measure of nicotine dependence (FTND). Incomplete reporting of such basic demographic and smoking history data impedes an analysis of variables moderating the performance effects of nicotine.

Limitations of meta-analysis

Seven performance domains were not included in the meta-analysis because they did not have a minimum of five effect sizes (see Results). Four of these domains, executive attention, long-term semantic memory, arithmetic, and complex cognition, had at least one study reporting significant positive effects of nicotine. Two studies investigating the effects of nicotine on driving (Sherwood 1995) and flight (Mumenthaler et al. 1998) simulation were difficult to categorize; however, both reported positive effects of nicotine on composite performance measures. We encourage investigators to continue research in these areas so that a more complete picture of nicotine's effects can be achieved.

Of the six performance domains revealing a significant effect size, significant heterogeneity and moderate relative variance was observed for working memory-RT, which casts some doubt on the reliability of the observed effect size. Not surprisingly, the three domains that did not show a significant effect of nicotine had significant heterogeneity, large relative variance, and large standard deviation (Table 1). Of the four attentional domains, only orienting attention-accuracy did not reveal a significant effect, likely because of the small number of studies and the one significant outlier. Elimination of that outlier resulted in a

significant effect, g=0.39, p<0.01, but this result was based on four effect sizes, one less than our criterion.

An additional limitation was our decision to exclude studies with patient samples in an effort to determine the effect of nicotine in the absence of any premorbid cognitive deficits. Nicotine and nicotinic ligands have been tested as treatments for several neuropsychiatric disorders, including schizophrenia, attention deficit/hyperactivity disorder, Alzheimer's and Parkinson's diseases, and age-related cognitive decline (Evans and Drobes 2008; Levin et al. 2006; Newhouse et al. 2004). Using the same rationale, we also excluded studies with subjects older than age 59 years. Reviews of the association between smoking and cognitive decline in the elderly conclude that smokers, compared with never smokers, are at significantly greater risk for Alzheimer's disease, vascular dementia, and yearly cognitive decline (Anstey et al. 2007; Peters et al. 2008); oxidative stress, inflammation, and atherosclerosis are likely mechanisms (Swan and Lessov-Schlaggar 2007). Cigarette smoking is also associated with reduced psycho-motor and visual search speed, cognitive flexibility, and verbal memory in middle-aged cohorts (Kalmijn et al. 2002; Richards et al. 2003). These data and those reported here highlight the distinction between the positive and potentially therapeutic effects of acute nicotine and the deleterious effects of chronic smoking on cognition.

A final limitation encountered by all literature reviews, whether narrative or meta-analytic, is that studies with statistically significant effects are more likely to be published than those without significant findings. Any such publication bias in the literature will likely be reflected in the meta-analysis. One approach shown to minimize this bias is to perform a comprehensive search of the literature (Borenstein et al. 2009). We conducted multiple computerized literature searches using a range of relevant search terms and identified over 650 articles. Although we did not search the unpublished literature (technical reports and dissertations), we think we obtained a sample of peer-reviewed articles that was as unbiased as possible.

Future research directions

As was the case in our previous reviews (Heishman 1998; Heishman et al. 1994), the most obvious current research gap is the lack of studies examining specific performance domains. As noted above, we were unable to conduct meta-analyses on seven domains because of a paucity of studies. No studies that met our inclusion criteria investigated learning or executive functions, such as decision-making and planning. A related deficiency is the lack of studies attempting to relate laboratory tasks to real-world performance (criterion validity) or attempting to model complex performance in the laboratory. Methodologies exist for conducting research in applied settings (Parrott 1987) and for simulating complex behavior in the laboratory (Sauer et al. 2003; Streufert et al. 1988). Such research would complement our knowledge of nicotine's enhancing effect on laboratory tests of attention and memory.

A secondary goal of this meta-analysis was to explore the potential influence of moderator variables on performance outcomes. With few exceptions, however, investigators have not systematically examined the interactive influence of moderator variables (e.g., emotional state, arousal, stress, environmental context, and expectancy) on the performance effects of nicotine. In contrast to state variables, trait or individual differences between subject populations have been investigated more widely. For example, studies have examined differences between smokers and nonsmokers (McClernon et al. 2003; Tucha and Lange 2004) and the influence of neuropsychiatric disorders (discussed above), impulsivity (Perkins et al. 2008), or genetic polymorphisms (Jacobsen et al. 2006) on the performance effects of nicotine. A greater emphasis on state moderator variables would increase our

understanding of the direct vs. indirect mechanisms underlying the effects of nicotine on performance (cf. Waters and Sutton 2000).

Finally, much more research is needed for a complete understanding of the cellular and neurobiological mechanisms by which nicotine enhances cognition. The discovery of the role of nAChRs in cognition has led to the testing of nicotinic analogs as potential cognitive enhancing agents in patient populations with cognitive deficits (Levin et al. 2006; Newhouse et al. 2004). Empirical information about nicotine's ability to enhance elements of cognition in healthy individuals, as revealed by this meta-analysis, might inform novel therapeutic uses of nicotine and nicotinic agents in cognitively impaired populations.

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†Article met inclusion/exclusion criteria but was not used in meta-analyses.

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Table 1

Summary effect size data for nine performance domains

Performance domain	*k*	*N*	Hedges's *g*	95% CI	*Q*	I^2	*T*
Fine motor	7	294	0.16	+0.02/+0.31	8.22	27.0	0.10
Alerting attention-accuracy	9	207	0.34	+0.18/+0.50	8.45	5.4	0.06
Alerting attention-RT	13	311	0.34	+0.17/+0.52	20.26	40.8	0.20
Orienting attention-accuracy	5	78	0.13	−0.41/+0.67	16.86	76.3	0.53
Orienting attention-RT	11	187	0.30	+0.15/+0.44	7.35	0	0
Short-term episodic memory-accuracy	8	199	0.44	+0.17/+0.71	9.65	27.4	0.20
Long-term episodic memory-accuracy	12	436	0.17	−0.13/+0.47	58.11	81.1	0.45
Working memory-accuracy	9	155	−0.11	−0.46/+0.24	35.95	77.7	0.47
Working memory-RT	10	281	0.34	+0.14/+0.53	18.17	50.5	0.21

RT response time

Table 2

Studies contributing effect size data for the meta-analysis of fine motor abilities

Study	Task/outcome	Hedges's *g*	Standard error	*n*	Age[a]	% male	Smoking status	Cigarettes per day	Nicotine dose	Route of administration
Barr et al. 2008a	Pegboard	0.16	0.17	32	40	53	NSm	NA	14 mg	Transdermal
Foulds et al. 1996[b]	Finger tapping	−0.15	0.23	18	25	50	NSm	NA	0.6 mg	Subcutaneous
Perkins et al. 1994[b]	Finger tapping	0.48	0.24	18	23	50	NSm	NA	5–20 μg/kg	Intranasal
Perkins et al. 2001[b]	Finger tapping	0.11	0.22	20	34	50	NSm	NA	10–20 μg/kg	Intranasal
Perkins et al. 2008[b]	Finger tapping	0.04	0.09	130	25	39	NSm	NA	5–10 μg/kg	Intranasal
Tucha and Lange 2004[b]	Handwriting	0.21	0.16	38	24	50	NSm	NA	4 mg	Buccal
Tucha and Lange 2004[b]	Handwriting	0.43	0.17	38	24	50	Sm	≥15	4 mg	Buccal

Nsm nonsmoker, *Sm* smoker, *NA* not applicable

[a] Mean value

[b] Administered multiple active nicotine doses

Table 3

Studies contributing effect size data for the meta-analysis of alerting attention-accuracy

Study	Task/outcome	Hedges's *g*	Standard error	*n*	Age[a]	% male	Smoking status	Cigarettes per day[a]	Nicotine dose, mg	Route of administration
Barr et al. 2008b	Signal detection	0.00	0.18	30	39	53	NSm	NA	14	Transdermal
File et al. 2001	RVIP	0.51	0.35	32	21	50	NSm	NA	2	Inhalation-inhaler
Foulds et al. 1996[b]	RVIP	0.24	0.23	18	25	50	NSm	NA	0.6	Subcutaneous
Harte and Kanarek 2004	CPT	0.76	0.29	14	19	36	Sm	14	2	Buccal
Kelemen and Fulton 2008	RVIP	0.31	0.18	32	24	69	Sm	>10	2	Buccal
Lawrence et al. 2002	RVIP	0.42	0.26	15	22	53	Sm	22	21	Transdermal
Levin et al. 1998	CPT	0.62	0.31	11	23	91	NSm	NA	7	Transdermal
Myers et al. 2008[b]	CPT	0.55	0.21	25	36	52	Sm	22	2	Intranasal
Poltavski and Petros 2006	CPT	0.11	0.36	30	20	100	NSm	NA	7	Transdermal

Nsm nonsmoker, *Sm* smoker, *NA* not applicable, *RVIP* rapid visual information processing, *CPT* continuous performance test

[a] Mean value

[b] Administered multiple active nicotine doses

Table 4

Studies contributing effect size data for the meta-analysis of alerting attention-response time

Study	Task/outcome	Hedges's *g*	Standard error	*n*	Age[a]	% male	Smoking status	Cigarettes per day[a]	Nicotine dose, mg	Route of administration
Barr et al. 2008b	Signal detection	0.38	0.19	30	39	53	NSm	NA	14	Transdermal
Bates et al. 1995	Choice RT	0.47	0.23	19	21	32	Sm	5–25	0.8	Inhalation-cigarette
File et al. 2001	RVIP	0.37	0.35	32	21	50	NSm	NA	2	Inhalation-inhaler
Foulds et al. 1996[b]	RVIP	1.42	0.33	18	25	50	NSm	NA	0.6	Subcutaneous
Kelemen and Fulton 2008	RVIP	0.28	0.18	32	24	69	Sm	>10	2	Buccal
Kleykamp et al. 2005[b]	ANT	−0.16	0.22	20	20	45	NSm	NA	4	Buccal
Lawrence et al. 2002	RVIP	0.07	0.24	15	22	53	Sm	22	21	Transdermal
Le Houezec et al. 1994	Choice RT	0.50	0.29	12	27	100	NSm	NA	0.8	Subcutaneous
Levin et al. 1998	CPT	0.10	0.28	11	23	91	NSm	NA	7	Transdermal
Myers et al. 2008[b]	CPT	0.27	0.20	25	36	52	Sm	22	2	Intranasal
Poltavski and Petros 2006	CPT	0.38	0.36	30	20	100	NSm	NA	7	Transdermal
Rusted and Alvares 2008	RVIP	0.64	0.29	48	22	44	NSm	NA	1	Intranasal
Thiel et al. 2005[b]	Cued target detection	0.27	0.22	19	24	42	NSm	NA	2	Buccal

Nsm nonsmoker, *Sm* smoker, *NA* not applicable, *RVIP* rapid visual information processing, *ANT* attention network test, *CPT* continuous performance test

[a] Mean value

[b] Administered multiple active nicotine doses

Table 5

Studies contributing effect size data for the meta-analysis of orienting attention-accuracy

Study	Task/outcome	Hedges's *g*	Standard error	*n*	Age[a]	% male	Smoking status	Cigarettes per day[a]	Nicotine dose, mg	Route of administration
Ernst et al. 2001b	Letter search	0.00	0.30	9	21–45	33	NSm	NA	4	Buccal
Hahn et al. 2007	Spatial attention	0.49	0.25	17	33	35	Sm	21	21	Transdermal
Heishman and Henningfield 2000[b]	Letter search	−1.00	0.34	12	31	100	NSm	NA	8	Buccal
Larrison et al. 2004	Antisaccades	0.43	0.25	16	NR	NR	Sm	NR	4	Buccal
Vossel et al. 2008	Cued target detection	0.71	0.41	24	25	54	NSm	NA	2	Buccal

Nsm nonsmoker, *Sm* smoker, *NA* not applicable, *NR* not reported

[a] Mean value

[b] Administered multiple active nicotine doses

Table 6

Studies contributing effect size data for the meta-analysis of orienting attention-response time

Study	Task/Outcome	Hedges's *g*	Standard error	*n*	Age[a]	% male	Smoking status	Cigarettes per day[a]	Nicotine dose, mg	Route of administration
Colzato et al. 2005	Cued target detection	0.27	0.23	18	20–30	NR	NSm	NA	7	Transdermal
Ernst et al. 2001b	Letter search	0.61	0.30	9	21–45	33	NSm	NA	4	Buccal
Griesar et al. 2001[b]	Spatial attention	0.35	0.24	17	24	47	NSm	NA	14	Transdermal
Hahn et al. 2009	Selective attention	0.65	0.25	18	30	50	Sm	21	21	Transdermal
Heishman and Henningfield 2000[b]	Letter search	0.23	0.27	12	31	100	NSm	NA	8	Buccal
Kleykamp et al. 2005[b]	ANT	0.01	0.22	20	20	45	NSm	NA	4	Buccal
Meinke et al. 2006-study 1	Cued target detection	0.49	0.23	20	24	40	NSm	NA	2	Buccal
Meinke et al. 2006-study 2	Cued target detection	0.05	0.23	17	23	29	NSm	NA	2	Buccal
Thiel et al. 2005[b]	Target detection	0.37	0.23	19	24	42	NSm	NA	2	Buccal
Thiel and Fink 2008	Target detection	0.25	0.26	13	26	85	NSm	NA	2	Buccal
Vossel et al. 2008	Target detection	0.73	0.41	24	25	54	NSm	NA	2	Buccal

Nsm nonsmoker, *Sm* smoker, *NA* not applicable, *NR* not reported, *ANT* attention network test

[a] Mean value

[b] Administered multiple active nicotine doses

Table 7

Studies contributing effect size data for the meta-analysis of short-term episodic memory-accuracy

Study	Task/outcome	Hedges's *g*	Standard error	*n*	Age[a]	% male	Smoking status	Cigarettes per day[a]	Nicotine dose, mg	Route of administration
Jubelt et al. 2008	Word recognition	0.15	0.27	12	35	33	NSm	NA	14	Transdermal
Krebs et al. 1994[b]	Prose recall	0.21	0.36	30	NR	100	Sm	13	1.5	Inhalation-cigarette
McClernon et al. 2003	Word recall	0.80	0.41	24	20	50	NSm	NA	7	Transdermal
McClernon et al. 2003	Word recall	−0.03	0.39	24	20	50	Sm	17	14 or 21	Transdermal
Phillips and Fox 1998	Word recall	0.48	0.36	30	28	50	NSm	NA	2	Buccal
Phillips and Fox 1998	Word recall	1.41	0.40	30	28	50	Sm	>5	2	Buccal
Poltavski and Petros 2005	Prose recall	0.46	0.49	17	20	100	NSm	NA	7	Transdermal
Rusted et al. 1998	Word recall	0.39	0.18	32	20–44	25	Sm	>5	0.6	Inhalation-cigarette

Nsm nonsmoker, *Sm* smoker, *NA* not applicable, *NR* not reported

[a] Mean value

[b] Administered multiple active nicotine doses

Table 8

Studies contributing effect size data for the meta-analysis of long-term episodic memory-accuracy

Study	Task/outcome	Hedges's *g*	Standard error	*n*	Age[a]	% male	Smoking status	Cigarettes per day	Nicotine dose	Route of administration
File et al. 2001	Picture recall	−0.42	0.35	32	21	50	NSm	NA	2 mg	Inhalation-inhaler
Foulds et al. 1996[b]	News recall	−0.33	0.23	18	25	50	NSm	NA	0.6 mg	Subcutaneous
Kelemen and Fulton 2008	Word recall	−0.07	0.17	32	24	69	Sm	>10	2 mg	Buccal
Perkins et al. 1994[b]	Word recognition	0.48	0.24	18	23	50	NSm	NA	5–20 μg/kg	Intranasal
Perkins et al. 2001[b]	Word recognition	−0.29	0.22	20	34	50	NSm	NA	10–20 μg/kg	Intranasal
Perkins et al. 2008[b]	Word recognition	−0.26	0.09	129	25	39	NSm	NA	5–10 μg/kg	Intranasal
Rusted et al. 1995- study 1	Word recall	0.14	0.35	32	NR	NR	Sm	>5	0.6 mg	Inhalation-cigarette
Rusted et al. 1995- study 2	Word recall	0.00	0.35	32	NR	NR	Sm	>5	0.6 mg	Inhalation-cigarette
Rusted et al. 1995- study 3	Word recall	−0.06	0.24	16	NR	NR	Sm	>5	0.6 mg	Inhalation-cigarette
Rusted et al. 1995- study 4	Word recall	0.80	0.26	19	NR	NR	Sm	>5	0.6 mg	Inhalation-cigarette
Rusted and Alvares 2008	Word recall	0.67	0.29	48	22	44	NSm	NA	1 mg	Intranasal
Warburton et al. 2001	Word recall	1.92	0.38	40	18– 23	40	Sm	>10	0.6 mg	Inhalation-cigarette

Nsm nonsmoker, *Sm* smoker, *NA* not applicable, *NR* not reported

[a] Mean value

[b] Administered multiple active nicotine doses

Table 9

Studies contributing effect size data for the meta-analysis of working memory-accuracy

Study	Task/outcome	Hedges's *g*	Standard error	*n*	Age[a]	% male	Smoking status	Cigarettes per day[a]	Nicotine dose	Route of administration
Barr et al. 2008a	Number sequence	−0.12	0.17	32	40	53	NSm	NA	14 mg	Transdermal
Ernst et al. 2001a	n-back	−0.24	0.28	11	30	45	NSm	NA	4 mg	Buccal
Ernst et al. 2001b	n-back	0.90	0.37	9	21–45	33	NSm	NA	4 mg	Buccal
Foulds et al. 1996[b]	Digit recall	−0.72	0.26	18	25	50	NSm	NA	0.6 mg	Subcutaneous
Heishman and Henningfield 2000[b]	Digit recall	−1.07	0.35	12	31	100	NSm	NA	8 mg	Buccal
Jacobsen et al. 2006	n-back	−0.28	0.26	14	NR	NR	NSm	NA	3.5 or 7 mg	Transdermal
Kleykamp et al. 2005[b]	n-back	−0.43	0.23	20	20	45	NSm	NA	4 mg	Buccal
Kumari et al. 2003	n-back	0.92	0.34	11	20–40	100	NSm	NA	12 μg/kg	Subcutaneous
Myers et al. 2008[b]	n-back	0.22	0.19	28	36	50	Sm	22	2 mg	Intranasal

Nsm nonsmoker, *Sm* smoker, *NA* not applicable, *NR* not reported

[a] Mean value

[b] Administered multiple active nicotine doses

Table 10

Studies contributing effect size data for the meta-analysis of working memory-response time

Study	Task/outcome	H s *g*	Standard error	*n*	Age[a]	% male	Smoking status	Cigarettes per day[a]	Nicotine dose	Route of administration
Ernst et al. 2001a	n-back	0.09	0.28	11	30	45	NSm	NA	4 mg	Buccal
Ernst et al. 2001b	n-back	0.15	0.30	9	21–45	33	NSm	NA	4 mg	Buccal
Foulds et al. 1996[b]	Digit recall	0.88	0.27	18	25	50	NSm	NA	0.6 mg	Subcutaneous
Heishman and Henningfield 2000[b]	Digit recall	1.05	0.34	12	31	100	NSm	NA	8 mg	Buccal
Houlihan et al. 2001	Sternberg	0.83	0.25	20	26	60	Sm	>20	1.1 mg	Inhalation-cigarette
Jacobsen et al. 2006	n-back	0.00	0.25	14	NR	NR	NSm	NA	3.5 or 7 mg	Transdermal
Kleykamp et al. 2005[b]	n-back	0.15	0.22	20	20	45	NSm	NA	4 mg	Buccal
Myers et al. 2008[b]	n-back	0.16	0.19	28	36	50	Sm	22	2 mg	Intranasal
Perkins et al. 2001[b]	Sternberg	0.29	0.22	20	34	50	NSm	NA	10–20 μg/kg	Intranasal
Perkins et al. 2008[b]	Sternberg	0.21	0.09	129	25	39	NSm	NA	5–10 μg/kg	Intranasal

Nsm nonsmoker, *Sm* smoker, *NA* not applicable, *NR* not reported

[a] Mean value

[b] Administered multiple active nicotine doses