COGNITIVE EFFECTS OF NICOTINE IN NON-SMOKERS

by

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CERTIFICATE OF APPROVAL

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ABSTRACT

Objective: Nicotine reportedly improves aspects of cognition, including spatial attention, but these improvements may be related to the enhanced alertness of subjects on drug. Most nicotine studies have neglected to determine serum levels of nicotine, and have examined habitual smokers, who were perhaps suffering from withdrawal at the time of cognitive testing. The present research explored nicotine effects on measures of spatial attention and alertness in non-smokers. Subjects (non-smokers, 18 – 35 years old, male and female) were expected to show selective improvement in covert orienting of spatial attention with tasks that used peripheral, non-predictive exogenous cue stimuli, because of the high density of cholinergic receptors responsive to nicotine in brain regions associated with exogenous orienting. In contrast, no selective drug effects were expected in covert orienting tasks with centrally presented, predictive endogenous cue stimuli, as cortical brain regions associated with attentional selection contain far fewer receptors. Experiments were also performed to determine whether nicotine would reduce boredom, and speed the perception of time passage in healthy, non-smoking adults.

Methods: Nicotine was delivered to non-smokers by a 7mg transdermal patch. Nicotine's effects on spatial attention were examined using covert orienting tasks with both endogenous and exogenous cue stimuli. The validity effect (the reaction time difference between validly and invalidly cued targets) was examined in order to assess whether nicotine has a selective effect on attention. Event-related potentials were also recorded and analyzed for selective drug effects. Nicotine effects on alertness were examined with EEG and subjective questionnaires. Drug effects on boredom and time perception were examined with visual analog scales, auditory evoked potentials and subjective questionnaires. Blood was drawn and serum levels of nicotine are reported. **Results**: Nicotine non-specifically improved performance on covert orienting tasks in non-smokers, by reducing reaction times and error rates. However, there was no selective effect on spatial attention (i.e., no change in the validity effect) in three covert orienting tasks that used endogenous cue stimuli. Exogenous tasks failed to provoke either a validity effect or an inhibition of return. ERP results were similarly inconclusive. However, nicotine did significantly and consistently improve both EEG and self-rated measures of alertness. Nicotine also reduced the subjective experience of boredom, and speeded the sense of time passage, as assessed by visual analog scales and other subjective instruments. **Conclusion**: Nicotine increases alertness, reduces boredom and speeds the subjective assessment of time passage in non-smokers, but has no selective effect on the covert orienting of spatial attention in response to endogenous cues.

Cognitive Effects of Nicotine in Non-Smokers

Nicotine

Introduction

Tobacco is harvested from the leaves of the tobacco plant *(nicotiniana tabacum),* a native of North and South America, and contains at least 4,000 distinct compounds, including the alkaloid nicotine. Tobacco was used for centuries by Native American tribes, and is now an intimate contributor to global culture and a major export of the United States. Smoking or chewing tobacco (in cigarettes, cigars or snuff) is popular worldwide; Richard Klein has written that "there is nowhere in the world where people do not smoke if they are allowed to" (Klein 1993). It appears for many to be a pleasurable activity. The nature of this pleasure is the central question of this work.

Cholinergic agonist

Nicotine is primarily an agonist at nicotinic cholinergic receptors (nAChR's) in both autonomic ganglia and the central nervous system (CNS). CNS effects presumably reinforce smoking behavior, while dependence is potentially maintained by avoidance of negative withdrawal symptoms and by positive cognitive effects of the drug (LeHouezec and Benowitz 1991). Central nAChR's are mostly presynaptic, capable of stimulating the release of several neurotransmitters, including dopamine (DA), acetylcholine (ACh) and norepinephrine (NE). Presynaptic receptors in the mesolimbic DA system promote the release of DA (Wonnacott 1997), and thus likely mediate the major motivational and reinforcing effects of nicotine (Koob 1992). Yet nAChR's are also found in numerous brain regions thought to carry out specific cognitive functions, such as attentional orienting. In addition, they are found on projections from neurotransmitter-specific brainstem nuclei considered critical for maintaining alertness (Clarke, Schwartz et al. 1985; Wonnacott 1997). Is the pleasure from nicotine derived solely from the drug's influence on the mesolimbic DA system? Or does nicotine selectively enhance attentional orienting, or alertness, and do these cognitive effects also contribute to the popularity and pleasure of the drug?

Addiction

Tobacco represents a major world health problem, and smoking is responsible for approximately 400,000 deaths in the United States each year. Another 50,000 US deaths are attributable to environmental tobacco smoke (ETS), often referred to as "second-hand smoke" (Health 1988). The darker leaf tobacco commonly used by Native Americans before the mid-19th century contained too many unforgiving compounds for deep inhalation; thus the alkaline nicotine was generally absorbed slowly through the buccal lining of the mouth. However, in the mid-19th century, new methods of preparing tobacco resulted in a more acidic and less harsh "Bright Leaf" variety, which when rolled into cigarettes by soldiers suffering through the American Civil War delivered nicotine directly into the lungs, boosting and speeding the dosage of drug (Kluger 1996). During the 20th century, tobacco companies developed new methods of enhancing delivery (reducing harsh tars, increasing nicotine content), further ensuring a large, concentrated, rapid surge of nicotine into the CNS following each deep drag off a cigarette. These changes, coupled with aggressive youth-oriented marketing campaigns, have resulted in higher rates of addiction among adolescents in the United States in recent decades (Kessler 2001).

Cognitive effects?

However, the question of whether nicotine offers cognitive benefit is important. Such benefits may include improvement in attention and/or alertness, or the relief of boredom, or changes in time perception, and these effects could help promote continued use of nicotine independent of its actions on DA circuitry and the associated euphoria. In addition, positive cognitive effects of nicotine might suggest new drug therapies or strategies for addressing cognitive decline in both aging and disease.

Nicotine receptors and distribution

Nicotinic receptors are mostly presynaptic

Acetylcholine receptors are divided into two main classes, muscarinic and nicotinic. Nicotinic receptors are responsive to nicotine. In both the peripheral and central nervous system, nicotinic cholinergic receptors are ligand-gated and ionotropic, and mediate fast excitatory synaptic transmission (Sargent 1993). Ten subunits (alpha-2 – 8; beta-2 – 4) are expressed in vertebrate CNS (Wonnacott 1997), and at least two distinct populations of receptor have been identified: those primarily responsive to nicotine, and those primarily responsive to the chemical alpha-bungarotoxin. Most receptors are located on presynaptic terminals (McGehee and Role 1996; Wonnacott 1997), and stimulate the release of a host of neurotransmitters.

Receptors cause release of multiple neurotransmitters

Nicotine does act on the mesolimbic dopamine circuitry. There are nAChR's on mesolimbic neurons (Clarke and Pert 1985), nicotine excites ventral tegmental area (VTA) neurons (Grenhoff, Aston-Jones et al. 1986), and nicotine infused into the nucleus accumbens increases local extracellular concentrations of DA (Imperato, A et al. 1986; Misfud, Hernandez et al. 1989). While nicotine promotes the release of DA presynaptically (Nisell, Nomikos et al. 1994), many other classical neurotransmitters are also released *in vivo* by the presynaptic action of this drug (Wonnacott 1991; Wonnacott 1997). It has been suggested that these other potential brain sites and neurotransmitter mechanisms could be important for reinforcing nicotine use (Corrigall 1991). In rat brain, iontophoretic application of nicotine to hippocampus elicits ACh release with an EC-50 of 0.9 uM, and the drug also promotes NE release from locus coeruleus projections to cortex (an EC-50 of 6.5 uM)) (Wonnacott 1991; Gray, Rajan et al. 1996; Wonnacott 1997). Other *in vivo* studies have shown that nicotine action at presynaptic receptors is capable of releasing glutamate (McGehee and al 1995) and GABA (Yang, Criswell et al. 1996). While postsynaptic nicotinic receptors also exist, and mediate fast excitatory synaptic transmission, these appear to be fewer in number, and are apparently at least 10 times less sensitive to agonist than pre-synaptic receptors (Lena, Changeux et al. 1993; McGehee and al 1995).

Some receptors are more responsive to nicotine (a4b2 versus a7)

At least two distinct populations of nAChR have been identified in rodents based on radioligand binding studies. One population is particularly responsive to nicotine. The distribution of receptors with high affinity for nicotine as an agonist (Kd = 0.5 – 5 nM) closely matches the distribution of alpha4-beta2 subunit expression (Decker, Brioni et al. 1995), and immunoprecipitation studies have shown that most of these nicotine-preferring sites can be precipitated by antibodies to the same two subunits (Flores, Rogers et al. 1992). Areas with the highest density of these receptors include thalamic nuclei, superior colliculus and medial habenula, with more moderate density in cortex, substantia nigra and the VTA (Clarke, Schwartz et al. 1985; London, Scheffel et al. 1995). A second nAChR population is highly responsive to alpha-bungarotoxin (Kd = 0.5 nM). A good correlation is found between the distribution of the alpha-7 nicotinic subunit, which forms homomeric receptors (Decker, Brioni et al. 1995), and areas of high affinity alpha-bungarotoxin binding (but not nicotine binding). These areas include cerebral cortex, hypothalamus, hippocampus, inferior colliculus, and certain brainstem nuclei (Clarke, Schwartz et al. 1985).

Autonomic effects of nicotine

In addition to its actions at CNS receptors, nicotine is also a ganglionic nicotinic cholinergic agonist in the peripheral nervous system. Most of its effects are biphasic, and dose-dependent, with small doses transiently stimulating the autonomic ganglia, and then reducing activity, and large doses resulting in persistent depression of receptor function. Stimulation of both sympathetic ganglia and the adrenal medulla increases heart rate, blood pressure, stroke volume and cardiac output (LeHouezec and Benowitz 1991). Nicotine also increases the tone and motility of the gastrointestinal tract (1997). This latter effect, in combination with direct nicotine stimulation of the medullary chemoreceptor region in the brainstem, and GI afferent inputs in the vagus nerve, can produce significant nausea in naïve subjects, although tolerance develops with continued use (1997). A common "rite of passage" for new smokers is overcoming the queasiness associated with those first few cigarettes (Kluger 1996).

Cognitive effects of nicotine

Euphoria

Nicotine can cause euphoria similar to that produced by other addictive drugs (Henningfield, Miyasato et al. 1985). As with cocaine and d-amphetamine, nicotine reinforces self-administration (sometimes to the point of toxicity in rats), increases locomotor activity, enhances brain stimulation reward, and reinforces place preference (summarized in (Dani and Heinemann 1996)). However, it has been suggested that this euphoria may not be sufficient for maintaining addiction in human smokers, but that nicotine may improve certain cognitive functions, like accuracy during performance of tasks requiring sustained attention, and that these improvements may also contribute to continued use (Stolerman 1991). A large number of studies have been carried out to document nicotine improvement of various cognitive functions, including memory, vigilance, "rapid visual information processing," and attention, and to investigate the potential benefits of this drug in treating disorders such as Alzheimer's and Parkinson's disease.

Intact cholinergic systems are necessary for accurate performance on a host of cognitive tasks (Everitt and Robbins 1997), although most research has investigated the importance of muscarinic receptors (Levin 1992). Scopolamine, a muscarinic antagonist, increases both reaction times and the error rate in learning and memory tasks, while drugs that enhance cholinergic function (e.g., acetylcholinesterase inhibitors) can counteract these effects (Fibiger 1991; Everitt and Robbins 1997). The discovery of greatly reduced nicotinic receptor density in the brains of those who died suffering from Alzheimer's disease has accelerated research into the involvement of nicotinic receptors in cognition (Lawrence and Sahakian 1995). Nicotinic antagonists have now been shown to impair performance on memory tasks, and nicotine itself is alleged to improve learning, memory, attention, and vigilance (Levin 1992). However, other studies have failed to find nicotine improvement of such function, particularly in non-smokers (e.g., (Hindmarch, Kerr et al. 1990)), or have reported nicotine-induced deficits in cognitive performance (e.g., (Heishman, Snyder et al. 1993)). The picture remains unclear.

Rapid visual information processing and vigilance

A great deal of nicotine research has consistently reported drug enhancement of both "rapid information processing" and vigilance in humans (Levin 1992; Sherwood, Kerr et al. 1992). Vigilance is the ability to maintain goals over an extended period of time (Parasuraman 1998), while information processing has been assessed in tasks reportedly requiring "minimal memory requirements, but depending heavily on the efficient selection and processing of (usually visual) information" (Wesnes and Warburton 1984a). In several studies (e.g., (Wesnes and Warburton 1984a; Wesnes and Warburton 1984b)), acute administration of nicotine was compared to scopolamine, and opposite effects on task performance were observed. In (Wesnes and Warburton 1984b), non-smoking subjects were asked to hold dextrose tablets laced with nicotine and Tabasco sauce, or Tabasco sauce alone, in their mouths for five minutes. After a brief wait, the subjects were presented with a series of numbers on a screen (100 digits/minute) and asked to press a button whenever they detected three consecutive odd or even digits. Non-smokers given nicotine (1.5 mg) maintained consistent reaction times (RTs) during the entire 20-minute task, while those on placebo showed a significant increase in RT. There was no effect on the number of correct detections (there were very few errors overall, so this may have been a "ceiling" effect). Scopolamine, administered in a separate experiment, significantly reduced the number of correct detections as the test progressed, but RTs were not reported. The task used, despite author assertions to the contrary, clearly involves a working memory component (i.e., holding in mind three numbers for comparison), yet nicotine improvements are primarily reflected in the prevention of a vigilance decrement over time.

Memory

Human studies of acute nicotine effects on memory have reported everything from enhancement of task performance (e.g., (Peeke and Peeke 1984; Warburton, Rusted et al. 1992)) to memory deficits (Williams 1980), and the consensus appears to be that the drug has ambiguous effects at best (Jarvik 1991). One study reported that a group of smokers who smoked cigarettes exhibited enhanced primacy and recency effects when compared with a group of non-smokers not on drug (Pineda, Herrera et al. 1998), while another study (Heishman, Snyder et al. 1993) found no drug effect, or a trend towards worsening performance on a series of tasks including digit recall in a group of non-smokers administered nicotine polacrilex gum. Several studies have shown no effect of nicotine on memory performance in human subjects (e.g., (Hindmarch, Kerr et al. 1990; Heishman, Snyder et al. 1993)). In contrast, many animal studies have reported memory improvements, and low doses of nicotine generally facilitate while high doses have no effect on memory or reduce performance on memory tasks (Levin 1992). Yet there appears to be a great deal of variability in individual response, and in terms of what constitutes a "best dose" for each individual animal. Genetic factors undoubtedly play a role. For example, (Marks, Romm et al. 1989) found variation in nicotinic binding in various brain structures, including the hippocampus, among different strains of mice, and other researchers (e.g., (Castellano 1976)) have reported differential nicotine effects on a variety of learning and memory tasks, depending on strain.

Attention

Several studies have reported that nicotine improves various aspects of attention in healthy human smokers (e.g., (Peeke and Peeke 1984; Wesnes and Warburton 1984; Hasenfratz, Michel et al. 1989; Bates, Pellett et al. 1994)), in non-smokers (Wesnes and Warburton 1984), in patients with Alzheimer's disease (Jones, Sahakian et al. 1992), and in those suffering from attention deficit/hyperactivity disorder (Levin, Conners et al. 1996). Several of these studies involved the rapid visual information processing task (RVIP) described above, in which subjects are presented with a stream of rapidly changing digits, and are asked to press a button whenever three even or three odd numbers appear consecutively. In the one study involving non-smokers (Wesnes and Warburton 1984), nicotine prevented a vigilance decrement, and was thus interpreted as improving subject ability to sustain attention. In a related study of smokers performing the same RVIP task after smoking either a nicotine or placebo cigarette, nicotine actually reduced RTs from the beginning of the task, without increasing the error rate (Wesnes and Warburton 1984). In one study of memory (Peeke and Peeke 1984), the authors found nicotine facilitation of verbal recall, but only when their smoking subjects received nicotine (via cigarette smoking) *before* viewing a list of words to be later recalled, not after. They interpreted this "pre-trial" exposure effect to nicotine enhancement of both motivation and attention to stimulus details in the experiment. The authors concluded that nicotine has a non-specific effect ("an effect on attention-vigilance-focusing processes"), as opposed to a specific effect on memory storage. An additional study that showed *post-trial* facilitation of verbal recall still offered an attentional explanation, since the effect was lost if subjects were required to perform the RVIP during the post-trial smoking period. The authors reasoned that attention was enhanced by nicotine, not memory, and by engaging attention on the RVIP, the nicotine facilitation effect was blocked (Rusted and Warburton 1992). Another study investigated the effects of nicotine on late-day aviation performance in non-smoking pilots, and concluded that nicotine enhanced the ability of their subjects to attend to their environments (Mumenthaler, Taylor et al. 1998). One recent study (Witte, Davidson et al. 1997) has reported that nicotine improves spatial attention in both primates and human smokers, using a covert orienting of spatial attention task developed by Michael Posner (Posner 1980; Posner and Petersen 1990). In this study, monkeys injected with nicotine and human smokers who inhaled tobacco smoke performed the orienting task faster with nicotine than non-smokers did without drug. The authors interpreted these and other RT results as reflecting nicotine facilitation of the ability of their human and animal subjects to shift attention to various locations in space.

Methodology of nicotine studies of cognitive function

Smokers versus non-smokers

Cognitive improvements are more commonly reported in smokers, although reports of better performance in non-smokers also exist (e.g., (Wesnes and Warburton 1984a; Mumenthaler, Taylor et al. 1998)). However, interpretation of behavioral data from smokers is problematic for several reasons. For one thing, it is known that chronic exposure to nicotine upregulates central nAChR's in both rats (Ksir, Hakan et al. 1987; Pauly, Marks et al. 1996) and humans (Benwell, Balfour et al. 1995), creating a population that is neurophysiologically distinct from non-smokers with respect to the receptors where nicotine acts. Perhaps alterations in density, distribution and/or subunit composition of nAChR's could make smokers more receptive to cognition-enhancing effects of acute doses of drug. In addition, quitting nicotine leads to a predictable constellation of symptoms in habitual smokers, which includes irritability, restlessness, depression, difficulty concentrating, and a craving for cigarettes that manifests in as little as 12 hours (Stolerman and Jarvis 1995). Several researchers (e.g., (West 1993)) have suggested that performance improvements in smokers might be due to the relief of withdrawal symptoms rather than any direct effect of nicotine on vigilance or attention or rapid information processing.

Yet despite a clear withdrawal syndrome, most human studies of nicotine effects on cognition have examined smokers who had abstained from cigarettes for anywhere from 12 to 24 hours before each experiment, and in whom withdrawal relief might underlie their apparently enhanced cognitive performance. This confound has been directly addressed by one study (Warburton and Arnall 1994) that reported no significant difference in RVIP performance between a large group of smokers deprived of nicotine for ten hours and a large group of non-smokers not given any drug (each group consisted of 100 subjects). The authors also found no difference between smokers deprived for ten hours and smokers deprived for one hour. However, while this study cited an American Psychiatric Association announcement from 1987 that suggested a "nicotine withdrawal syndrome" is detectable after as little as two or three hours of abstinence, more recent publications (e.g., (Stolerman and Jarvis 1995)) suggest that at least twelve hours must pass before the syndrome has notable effects on performance. Ten hours of abstinence may not have been sufficiently long to reveal reduced RTs or errors on the RVIP, and a majority of studies reporting cognitive improvement with nicotine have required subjects to abstain for at least twelve hours or more.

Importance of determining blood levels of drug

Only a few published studies (e.g., (Hindmarch, Kerr et al. 1990)) have reported plasma nicotine levels in subjects performing cognitive tasks. Most previous studies of nicotine effects on cognition (including (Peeke and Peeke 1984; Wesnes and Warburton 1984a; Wesnes and Warburton 1984b; Warburton, Wesnes et al. 1986; Hasenfratz, Michel et al. 1989; Jones, Sahakian et al. 1992; Bates, Pellett et al. 1994; Warburton and Arnall 1994; Witte, Davidson et al. 1997)) have neglected to assess the degree of drug exposure during task performance, and many of these same experiments examined habitual smokers asked to inhale tobacco smoke from cigarettes. Differences in the rate of inhalation, depth of inhalation, lung capacity, body weight and a host of other factors can influence drug delivery, and make it difficult to correlate exposure to nicotine with behavioral measures (Benowitz, III et al. 1986; Coultas, Stidley et al. 1993). In general, chronic smokers tend to carefully titrate the level of drug in their system by varying inhalation rates, and how long the smoke is held in the lungs, so while some studies have tried to evaluate the effects of low versus high nicotine cigarettes (e.g., (Wesnes and Warburton 1984)), individual subjects are likely to obtain their commonly preferred dose regardless of which treatment group they are assigned to. Other studies (e.g., (Heishman, Snyder et al. 1993)) have used nicotine gum, and have held subjects to standardized chewing protocols, but similar concerns (differences in the intensity of chewing, vascularization of mouth mucosa, etc.) can increase dose variability. As mentioned previously, dose appears to be critical for determining whether nicotine improves task performance, worsens it or has no discernable effect in most animal studies, so some assessment of how much drug is on board human subjects is warranted in order to interpret these study results.

Nicotine delivery: cigarette, gum, patch

After a cigarette is smoked, arterial blood levels of nicotine can reach 0.5 uM, and the drug is delivered to the CNS less than 10 seconds after absorption in the lungs (Henningfield, Stapleton et al. 1993). It is the fastest method for delivering nicotine to the brain, although blood plasma levels drop by about 50% within a few minutes after finishing each cigarette (Benowitz 1993). Other drug delivery devices used in studies of cognitive function include nicotine polacrilex gum, and the nicotine patch. The patch, which is generally used by individuals attempting to quit smoking, is designed to provide a continuous, transdermal delivery of nicotine, as opposed to the rapidly rising and falling levels of drug that occur with each cigarette (Gupta, Benowitz et al. 1993). These pharmacokinetic aspects of the patch partly explain why it apparently fails to provide the satisfaction of a cigarette, and thus offers reduced addiction potential but also less effectiveness in terms of helping smokers quit (Benowitz 1993). Cigarettes, oral snuff, chewing tobacco and nicotine gum all raise plasma levels to about 15 micrograms/L (this varies from individual to individual) within minutes, while patches operate on the order of hours. Nicoderm CQ patches (from SmithKline Beecham) offer the fastest rise in plasma levels. With application of a 21mg Nicoderm patch (the highest dose), nicotine levels rise to about 10 micrograms/L after 1.5 hours. However, the level eventually reaches a high of 15 micrograms/L at five hours and then slowly declines, stabilizing at about 10 micrograms/L by ten hours post-patch (Benowitz 1993). Most cognitive testing using the transdermal delivery system has been carried out between 1.5 and 4.5 hours post-patch (e.g., (Levin, Conners et al. 1998)), when nicotine plasma levels are rising.

Alertness

“Alertness” is defined as the endogenous, sustained activation of cerebral cortex that non-specifically affects cognitive performance, and it typically ranges from full wakefulness to deep, slow-wave stages of sleep (Oken and Salinsky 1992). Alertness in both animals and humans is in part related to the activity of neuronal pathways originating in the brainstem, hypothalamus and basal forebrain that each primarily release one “classical” neurotransmitter in thalamus (e.g., the reticular nucleus) and/or cortex in a largely non-specific manner (Clark, Geffen et al. 1987; Foote 1987; McCormick 1989; Oken and Salinsky 1992). These include dopaminergic (DA) projections to cortex (primarily frontal cortex) from the VTA, histaminergic (HA) projections to cortex from the hypothalamus, serotonergic (5-HT) projections to cortex from the raphe nuclei, noradrenergic (NE) projections to cortex from the locus coeruleus, and cholinergic (ACh) projections to thalamus and basal forebrain from the pedunculopontine and laterodorsal nuclei in the pons. Additional ACh projections from constituent regions of the basal forebrain (in particular, the nucleus basalis of Meynert) also non-specifically innervate most areas of neocortex. While it has been suggested that glutamate and GABA are employed by the "executive" neuronal networks engaged in stimulus and other forms of information processing, the above transmitters are considered to have a more global, "modulatory" function. Release of DA, HA, 5-HT, NE, and ACh from these ascending projections increases the overall excitability of thalamo-cortical circuitry (McCormick 1992). Many of these effects are slow to manifest, indicating the involvement of second messenger systems, but other responses (e.g., locus coeruleus mediated "startle") can occur more rapidly.

There does appear to be significant specificity of function for each of these individual ascending systems (e.g., (Robbins and Everitt 1998)), and not all projections are state dependent (DA in particular has little correlation with overt alertness). However, activation of all the various pathways, traditionally referred to as the "reticular activating system" (or RAS), does correlate well with whether an individual is fully awake or in the deepest stages of sleep, as well as the many gradations of alertness in between (Steriade and McCarley 1990). These pathways share certain organizational features that support such a modulatory role. For example, they all originate in relatively small, circumscribed brainstem, hypothalamic or basal forebrain nuclei, and project widely to the thalamus and/or cortex. Damage to these nuclei and/or manipulation by drugs leads to changes in sleep and waking cycles, and/or alertness levels (McCormick 1992). Numerous studies have shown that increases in RAS activity and neurotransmitter release in thalamus and cortex is well-correlated with increases in behavioral alertness, which is often measured by EEG (e.g., (Aston-Jones and Bloom 1981; Steriade, Datta et al. 1990; McCormick 1992; Oken and Salinsky 1992)).

EEG measures of alertness

Electroencephalography (EEG) is often used to measure changes in alertness, and is especially useful in separating the various sleep stages from the awake state (Oken and Salinsky 1992). EEG measures cortical electrical activity, summated and detected through scalp electrodes. Certain rhythmic patterns of activity are visible in the EEG, and fall into distinct categories based on frequency (Gotman 1990). Alpha activity is the most easily recognized pattern in a healthy adult, especially from occipital electrodes when a subject's eyes are closed. Alpha frequency ranges from 8 to 13 Hz, and is characteristic of the awake, relaxed state. Beta frequency waves are faster (13 to 30 Hz), and commonly observed in sensory and frontal areas of cortex. Beta activity increases when animals direct their attention to meaningful stimuli (Bouyer, Montaron et al. 1987; McCormick 1992), although barbiturates and benzodiazepines can also enhance beta in some cases (Gotman 1990). Theta activity (4 to 7 Hz) is seen in normal adult EEGs, but not consistently, and only in small quantities. Delta activity (3 Hz or less) is not characteristic of the awake state in healthy young adults. In general, increasing alertness is associated with lower amplitude, faster and less rhythmic EEG waveforms, an effect referred to as "desynchronization" (Oken and Salinsky 1992).

Cholinergic and noradrenergic input from brainstem nuclei modulate the activity of sensory relay neurons in thalamus, which influences the amount of cortical desynchronization detected by the EEG (McCormick 1989; Oken, Kishiyama et al. 1995). If hyperpolarized, thalamic relay neurons are in a "burst mode," with a slow, rhythmic firing rate that contributes to correspondingly slow neuronal firing in cortex, detected on the EEG as rhythmic slow wave (delta and theta) activity. In contrast, when thalamic neurons are depolarized (e.g., by ascending cholinergic projections from the pons), they fire in response to incoming sensory stimuli, in a faster, more complex and meaningful fashion referred to as the "single spike mode" (Steriade, Gloor et al. 1990; Lopes-da-Silva 1991; McCormick 1992; Oken and Salinsky 1992). With a shift from the awake state to drowsiness and sleep, there are dramatic changes in both RAS activity and in the EEG. RAS activity decreases, while EEG changes include attenuation of the alpha rhythm, the appearance of slow, lateral eye movements, less beta activity, and an overall increase in theta and delta waves (Oken and Salinsky 1992). During slow wave sleep (where delta and theta waves predominate), the activity of the non-specific, ascending neurotransmitter projection systems is greatly reduced (Aston-Jones and Bloom 1981; Steriade, Datta et al. 1990; McCormick 1992). In contrast, the shift from slow wave sleep to the awake and alert state correlates with increasing activity in the RAS (McCormick 1992).

Thus, an organism's level of alertness can be grossly "ranked" by the ratio of delta and theta activity (slower waves associated with less alert states) to alpha and beta activity (faster waves linked to more alert states), which is directly modulated by activity of the various ascending non-specific components of the RAS. Increasing alertness and RAS activity are associated with faster EEG waveforms (alpha, beta) and desynchronization. EEG recordings are scored for both clinical and research purposes by direct visual analysis, or by quantitative variables related to alertness (e.g., the theta/alpha ratio), and little difference is found between these two methods (Oken and Salinsky 1992).

Nicotine and the EEG

Only one previous study reported nicotine effects on the EEG (Knott, 1989), and that study examined habitual smokers. The subjects were deprived of nicotine for at least twelve hours before the experiment, and thus may have been experiencing withdrawal when the EEG was recorded. The study found that subjects permitted to smoke cigarettes on "nicotine" test days exhibited increased alpha activity, and decreased theta activity, when compared to their own recordings after they were given "sham" cigarettes (regular cigarettes that were unlit) on separate "no nicotine" test days. While these results suggest enhanced alertness with drug (although this was not a published conclusion of the study), the results may be primarily due to relief of withdrawal symptoms, rather than any direct effect of nicotine on alertness or other cognitive function.

Alertness and subjective questionnaires

In the human psychological literature, there are a number of often cited subjective questionnaires that are used to measure a subject's "state," including their self-assessed level of alertness. The Stanford Sleepiness Scale (SSS) (Hoddes, Zarcone et al. 1973) asks subjects to choose one out of seven descriptions that best matches how they feel in terms of sleepiness, with the first corresponding to most awake and alert. The Profile of Mood States (POMS) (McNair, Lorr et al. 1992) measures "dimensions" of affect or mood, and requires subjects to rate 65 adjectives describing their feelings and mood on a five-point scale ranging from "not at all" to "extremely." These dimensions include "vigor-activity," thought to reflect vigorousness, ebullience and high energy, as well as "fatigue-inertia," which covers weariness, inertia and low energy level. The POMS has displayed high reliability and validity, and has been used extensively in psychiatric and general population research (McNair, Lorr et al. 1992). Both the POMS and SSS are highly sensitive to changes in subjective alertness as well (e.g., (Oken, Kishiyama et al. 1995)).

Nicotine and Alertness

Since presynaptic nicotinic receptors are present on ascending neurotransmitter-specific pathways to thalamus and cortex, and since nicotine action at these receptors promotes the release of RAS modulatory neurotransmitters, including ACh and NE (Clarke and Pert 1985; Clarke, Schwartz et al. 1985; Wonnacott 1997), it is hypothesized that nicotine has a general "alerting" effect in non-smokers, one that can be assessed using both EEG methods and subjective questionnaires.

PREDICTION #1, ALERTNESS: Nicotine will maintain or increase alertness in non-smokers, as measured by EEG measures, and the results of subjective questionnaires, due to its action at projections from neurotransmitter-specific brainstem nuclei that contribute to alertness. Improved alertness may contribute to faster RTs and/or reduced error rates on various cognitive tasks administered to subjects (but non-specifically, with no selective effect on any particular cognitive function).

Attention

Attention is a central function of the brain. It has been described in multiple ways over a century of psychological and cognitive investigation, since William James first offered his observations in 1890 (James 1890). James wrote that "Everyone knows what attention is. It is the taking possession by the mind, in clear and vivid form, of one out of what seem several simultaneous objects or trains of thought." However, many current researchers consider attention a much broader term for a set of discrete brain processes that permit the maintenance of goal-directed behavior despite the presence of multiple distractions (e.g., (Posner and Petersen 1990; Oken and Salinsky 1992; Parasuraman 1998)).

These processes include attentional selection; that is, the differential processing of information based on certain selective criteria (e.g., (Parasuraman 1998)). For example, when you search a crowd for your friend who is wearing a bright red coat, you selectively direct your attention based on stimulus color. Attempting to detect a target stimulus appearing on either side of a computer screen also requires the differential processing of visual information, in this case based on the target's spatial location. The RVIP task described earlier, used in a number of studies examining nicotine effects on cognition, requires differential processing of the last two numbers plus the current number on screen in order to determine whether all three numbers are even or odd. Selection involves "top-down" or "endogenous" influences; e.g., you have to know in advance that your friend is wearing a red coat and direct your attention accordingly. Such an "executive" system of attention is considered necessary because there are limits to how much we can attend to given the overwhelming amount of sensory information we are exposed to at any one time (Posner 1998).

The "orienting reflex" is another brain process that falls under the broad rubric of attention (Posner 1980; Posner and Petersen 1990; Oken and Salinsky 1992). Orienting involves the rapid deployment of processing resources towards the source of an external stimulus. The stimulus might be a sudden flash of light, and the orienting response would involve rapidly shifting one's attention towards the illumination source. In an orienting task where target stimuli appear randomly on the left or right side of a computer screen, subjects can orient by shifting their eyes (foveating) towards the spatial location where a target appears. Orienting permits the allocation of processing resources to behaviorally relevant stimuli, and it is driven by the stimuli themselves. In other words, orienting is more of an involuntary, “bottom up” or “exogenously” directed form of attention than selective attention, which requires some higher level control.

Networks of Attention

Attention is such a large and hotly contested field (see (Parasuraman 1998) for an overview) that the discussion here is limited to visual attention. While visual attention is still a broad area, and includes multiple subcomponents, there is nevertheless general agreement among cognitive researchers as to some of its basic features. Numerous investigators (e.g., (Mesulam 1981; Mesulam, Mufson et al. 1983; Parasuraman 1998; Posner 1998)) have suggested that “systems” of attention exist, and that brain networks that subserve attentional functions are at least partially separate from those areas involved in the initial processing of visual input.

Nevertheless, attention does appear to influence these early visual processing areas, particularly in extrastriate regions of visual cortex. For example, attention appears to enhance neuronal activity in extrastriate regions engaged in response to an attended feature of a visual stimulus. One often-cited study utilized positron emission tomography (PET) to examine brain regions involved in discriminating the color, shape and speed of visual stimuli (Corbetta, Miezin et al. 1991). When subjects specifically attended to stimulus color, for example, the authors detected increased activity in the human homologue of macaque area V4, the region critical for the processing of color information. Another PET study (Haxby, Horowitz et al. 1994) found enhanced activation in occipitotemporal regions required for object recognition when subjects directed their attention to photos of human faces. In that same study, subjects attending to a particular spatial location exhibited enhancement of activity in parietal regions important for the "mapping" of extrapersonal space. These results have led to the general idea that attention acts to enhance neuronal activity in those extrastriate areas responsible for processing an attended visual feature.

Another way to examine neural activity underlying attentional enhancement of extrastriate processing is to look at event related potentials (ERPs), voltage deflections recorded at the scalp that are time-locked to the appearance of a visual stimulus or other cognitively important stimulus event. Studies examining ERPs produced in response to visual stimuli presented at specific spatial locations have found that attention enhances early components of the ERP provoked by the stimulus (e.g., (Heinze, Mangun et al. 1994; Luck 1995; Clark and Hillyard 1996)). These components include the P1 and the N1, which follow presentation of a visual stimulus by 80-200ms. ERPs reflect the summation of synchronous post-synaptic potentials from cortex and are thus a direct measure of neural activity. Studies have localized these P1 and N1 generators to extrastriate cortex (e.g., (Clark and Hillyard 1996)), lending further support to the general idea that attention acts to enhance neuronal activity in those extrastriate areas responsible for processing an attended visual feature.

However, in most cases where attention to a particular stimulus feature was experimentally required, a "network" of other brain regions was also activated by each attention task (e.g., (Corbetta, Miezin et al. 1991; Haxby, Horowitz et al. 1994; Heinze, Mangun et al. 1994; Nobre, Sebestyen et al. 1997); reviewed in (Parasuraman 1998; Posner 1998)). Cortical areas that are consistently enhanced in PET and fMRI studies include the posterior parietal cortex, dorsolateral prefrontal cortex, and the anterior cingulate gyrus. All have been previously implicated in visual attention because stroke or tumor damage to these regions is known to produce a syndrome known as visuospatial neglect, in which patients fail to attend to objects or events on the side of space contralateral to the lesion. Such unilateral visuospatial deficits occur most often following damage to the right hemisphere, suggesting right hemisphere dominance for attentional function in humans (Mesulam 1981). Subcortical areas where damage can produce neglect symptoms, and that exhibit enhanced activity in PET and single cell recording studies of visual attention, include superior colliculus, the pulvinar nucleus of the thalamus, and the basal ganglia (e.g., [Goldberg, 1972 #135; Colby, 1991 #132).

Marcel Mesulam (Mesulam 1981; Mesulam 1990) and Michael Posner (Posner 1980; Posner and Petersen 1990; Posner 1998) have each developed theories that ascribe particular functional characteristics to various components of the attentional "network" or, in the case of Posner, "networks." Mesulam (Mesulam 1981) notes that, due to massive input from visual sensory processing areas, the posterior parietal lobe is ideally situated anatomically to establish an internal "map" of the perceptual aspects of extrapersonal space. Patients with damage to right posterior parietal cortex do appear to have this internal map biased in favor of the ipsilateral hemispace. They tend to ignore everything on their left, and some go so far as to neglect the left half of their own bodies, failing to dress or clean the left arm, leg or side of the face (e.g., (Rafal and Robertson

1998)). Posterior parietal cortex is directly connected with the cingulate gyrus, a component of the limbic system and, according to Mesulam, the potential source for a "motivational" mapping of objects and events in extrapersonal space. Posterior parietal cortex is also linked to both superior colliculus and pre-motor areas of frontal cortex, which are involved in planning and execution of eye and limb movements for motivationally relevant events in space. Thus, according to Mesulam and others (e.g., (Rafal, Posner et al. 1988)), posterior parietal cortex appears critical for the perceptual aspects of visual attention, cingulate gyrus for the motivational or limbic aspects of visual attention, and frontal cortex/superior colliculus for the motor aspects of visual attention.

Michael Posner has argued (Posner 1980; Posner and Petersen 1990; Posner 1998) that these same regions can be grouped into two anatomically distinct networks subserving two functionally distinct aspects of visual attention, in particular visuospatial attention. He has proposed that an "anterior" network of brain regions, including the anterior cingulate cortex and dorsolateral prefrontal cortex, is involved in the "top-down," "endogenous" or "executive" control of attention. When you attend to a particular spatial location, these frontal regions are selectively activated, and serve to direct your attention based on relevant spatial characteristics, leading to enhanced activation of neurons in parietal areas engaged in mapping space. In contrast, a "posterior" attentional network, which includes evolutionarily older structures such as the superior colliculus and the pulvinar nucleus of the thalamus, along with the posterior parietal cortex, is selectively activated when an individual orients to an external stimulus. This theoretical anterior-posterior division gains support from studies of stroke patients. Those with damage to anterior cingulate, for example, often report a "loss of control" over their own thoughts and behaviors (e.g., (Goldberg 1981)). In contrast, subjects with superior colliculus or pulvinar lesions experience difficulty with orienting to external stimuli (e.g., (Posner 1998)).

Covert orienting of visuospatial attention

Visuospatial attention is the differential processing of visual stimuli based on spatial location, and much of Posner's research on these two attentional networks has involved the study of "covert orienting" of visuospatial attention. Covert orienting is the ability to concentrate visual attention on a particular spatial location, without moving the eyes, thus enhancing stimulus processing in that spatial location relative to others. In a covert orienting task, used to assess a subject's ability to attend, subjects fixate centrally (their eyes never move) while covertly directing their attention to an area of a monitor screen based on a cue stimulus. If a cue indicates the subsequent location of a target stimulus that must be responded to (e.g., with a button press), it is "valid"; if it indicates a site where the target does not appear, it is "invalid." In general, reaction times (RTs) for a motor response to the appearance of a target decrease when attention is covertly directed to the site of target presentation by a valid cue in humans (e.g., (Posner 1980; Oken 1994); (Murphy and Klein 1998)), monkeys (e.g., (Petersen, Robinson et al. 1987; Witte, Davidson et al. 1997)) and rats (e.g., (Phillips, McAlonan et al. 2000)). Invalid trials require a shift of spatial attention from the incorrectly cued location to the actual target location, while valid trials do not. The RT difference between these two trial types is referred to as the "validity effect," and is thought to reflect the speed required to "shift" attention from one spatial location to another (Posner 1980; Posner and Petersen 1990).

Two types of visuospatial attentional "shifting" may be investigated using covert orienting tasks, according to Posner, depending upon the type of cues used in the task. Attention may be shifted in a top down or endogenous fashion if the cue is meaningful, and provides predictive information about where a target stimulus will later appear. This is most often accomplished by providing arrow cues at fixation that indicate subsequent target location at least 62% of the time. An "expectation" that the target will appear in the indicated location is established, and the subject covertly shifts their attention to the expected visuospatial position in advance. In contrast, attention shifted in an exogenous or bottom up fashion involves the appearance of a cue stimulus in the periphery, one that does not predict subsequent target appearance (e.g., there is a 50% chance that the target will emerge at the cued location) yet draws attention because its sudden emergence provokes an orienting response. There are several lines of evidence supporting the existence of these two distinct systems. For example, subjects appear to be more efficient (i.e., they exhibit faster RTs) at detecting exogenously cued targets than endogenously cued targets, because of the automatic nature of the former and the more effortful, higher order character of the latter (e.g., (Jonides 1981; Rafal and Henik 1994)). In addition, subjects exhibit a phenomenon known as inhibition of return (IOR) at longer cue-target intervals (or stimulus onset asynchronies, SOAs) in exogenously cued orienting tasks, in which their responses are longer to valid rather than invalidly cued targets (sort of a "reverse validity effect"). IOR is thought to be due to the active inhibition of the return of attention to a previously attended location (Posner and Cohen 1984), and it is not observed with tasks using central, endogenous cues. According to Posner, the endogenous covert orienting paradigm primarily engages the anterior attentional network, while the exogenous cue paradigm primarily engages the posterior attentional network.

Nicotine and Visuospatial Attention

What are the effects of nicotine on visuospatial attention? Nicotine is a cholinergic agonist, and the loss of cholinergic input to cortex is known to compromise visuospatial attention. As mentioned earlier, intact cholinergic systems are necessary for accurate performance on a host of cognitive tasks, including those examining covert orienting (Everitt and Robbins 1997). Alzheimer's disease in humans is characterized by spatial attention deficits, and by loss of nicotinic cholinergic receptors in the CNS (e.g., (Nebes and Brady 1989); [Parasuraman, 1992 #143); however, the wide range of neurotransmitter and neuronal loss in this form of dementia makes it difficult to draw any direct connection between the two. However, in studies of patients with Alzheimer's disease (Parasuraman, Greenwood et al. 1992; Oken 1994), subjects were selectively impaired in responding to invalidly cued targets. Parasuraman tested subjects on both an endogenous and an exogenous version of their covert orienting task, and found the same result in both cases. In other words, regardless of whether subjects had covertly directed their attention to the wrong (i.e., non-target) location based on a predictive, central cue, or if their attention had been drawn to that location by a non-predictive, peripheral cue, it took Alzheimer's patients longer to shift their attention from the incorrectly cued location to the actual target location. The validity effect (the reaction time difference between validly and invalidly cued targets) was greater in both paradigms for patients, with their presumably less functional cholinergic systems, than for controls. (Yet a caveat is warranted here, since patients also presumably possess less functional NE systems and neuronal losses in higher association areas, including parietal regions implicated in attentional networks.)

In many studies of covert orienting, however, the tasks used do not neatly test one proposed network or the other. The cues involved, especially in animal studies, tend to be peripheral, and thus apt to engage the putative posterior orienting network. Yet they are often informative as well, which might simultaneously engage the anterior executive network. Nevertheless, a reduction in cholinergic activity seems to worsen attentional performance. For example, in one study in which basal forebrain cholinergic projections to cortex were lesioned in monkeys (Voytko, Olton et al. 1994), the authors found selective impairment on performance of a covert orienting task, but not on an extensive series of memory and perceptual tasks. The covert orienting task involved peripheral cues that presumably engaged the posterior network, but the cues were also predictive, which potentially engaged the anterior network as well.

Loss of cholinergic input also produces spatial attention deficits in rats. In one study (Muir, Everitt et al. 1995), rats were trained to discriminate a brief visual stimulus presented randomly in one of five spatial locations. A light would come on above one of the five locations, and the rat would run forward to poke its nose in an aperture under that light, which would provoke delivery of a food pellet. Following AMPA lesioning of basal forebrain projections to cortex, there were significant reductions in both choice accuracy and response latency, which were attributed to a decrease in the rat's ability to attend to relevant locations in space. Interestingly, these deficits were reversed by both nicotine, and the cholinesterase inhibitor physostigmine. Presumably both posterior and anterior attentional networks were recruited by this task, since the cues were simultaneously peripheral, and 100% predictive of subsequent target location.

Nicotine effects on covert orienting have been assessed in three recent studies, two involving humans and/or primates (Witte, Davidson et al. 1997; Murphy and Klein 1998), and one involving rats (Phillips, McAlonan et al. 2000). In all cases, nicotine selectively reduced reaction times to invalidly cued targets. The validity effect was thus reduced, indicating a specific drug effect on the ability to shift attention from the incorrectly cued location to the actual target location. In Witte, et al. (1997), two rhesus monkeys trained to perform a covert orienting task exhibited a smaller validity effect (i.e., faster shifting) when injected with nicotine than when injected with saline. Also in Witte, et al. (1997), a group of human smokers permitted to smoke a cigarette before testing had a smaller validity effect than a group of non-smokers who did not receive any drug. The authors interpreted these results as reflecting nicotine facilitation of spatial attentional shifting. In Murphy and Klein (1998), smokers permitted to smoke cigarettes immediately before performance of a covert orienting task had smaller validity effects (faster shifting) than smokers deprived of nicotine for one hour, or for 24 hours. These last two studies have weaknesses. Both investigated nicotine effects in smokers, who are neurophysiologically distinct from non-smokers with respect to the cholinergic receptors where nicotine acts (Benwell, Balfour et al. 1995), and for whom nicotine exposure via cigarettes may have relieved withdrawal symptoms that contributed to improved behavioral performance. Additionally, in Witte, et al. (1997), it is difficult to conclude much based on highly variable RT measurements from only two monkeys. Finally, in both studies, neither covert orienting task was purely endogenous or exogenous; each used predictive, peripheral cues that presumably engaged both the anterior and posterior attentional networks.

In Phillips, et al. (2000), rats were trained to stick their noses in a center hole, with one hole to either side, while a cue light appeared above either the left or right hole. This was followed by a bright target light above one hole or the other, and the rat had to quickly poke its nose into the hole beneath the target in order to receive a sucrose pellet reward. Unlike most of the covert orienting tasks described above, this task was purely exogenous, because the cue light never predicted the subsequent target location. In other words, this study potentially avoided the influence of endogenous anterior network activity on posterior network orienting. The authors reported that mean RT decreased as a function of increasing nicotine dose, and that this decrease was limited to invalidly cued targets. Thus, nicotine, in a purely exogenous covert orienting task selectively engaging the posterior attentional network, results in a reduced validity effect (i.e., faster shifting, as a consequence of faster response to the invalidly cued targets alone).

Attentional networks have different nicotinic receptor distributions

Brain regions associated with the two functionally distinct attentional networks proposed by Michael Posner appear to differ in their distribution of nAChR's. In the rat, receptors particularly responsive to nicotine (those containing alpha 4 and beta 2 subunits) are found in high density in thalamus (including the pulvinar nucleus) and superior colliculus (Clarke, Schwartz et al. 1985; London, Scheffel et al. 1995), two key components of the posterior network critical for the exogenous orienting response. In contrast, these receptors are found in much lower density in cortical regions, such as the anterior cingulate gyrus and dorsolateral prefrontal cortex, both considered essential structures in the anterior network responsible for top down or endogenous attention. Nicotinic cholinergic receptors composed of homomeric assemblies of the alpha 7 subunit, which are far less sensitive to nicotine and are usually labeled by alpha-bungarotoxin (Clarke, Schwartz et al. 1985); (Decker, Brioni et al. 1995), are more abundant in cortical regions associated with the anterior network than in subcortical components of the posterior network. Therefore, nicotine may have more influence on structures associated with the posterior orienting network than on those associated with the anterior attentional network, and the use of covert orienting tasks that selectively engage one system or the other might help to reveal these potentially differential effects. The recent study of covert orienting in rats (Phillips, McAlonan et al. 2000), which used peripheral, non-predictive cues designed to selectively engage the posterior network, reported nicotine enhancement of attention. Other studies reporting enhancement (e.g., (Witte, Davidson et al. 1997; Murphy and Klein 1998)) used tasks that presumably engaged both networks.

Nicotine effects on event-related potentials (ERPs) influenced by spatial attention

Studies examining ERPs produced in response to target stimuli at particular spatial locations have found that the amplitudes of both contralateral P1 and N1 components increase when subjects attend to the stimulus presentation site (Luck, Fan et al. 1993). In covert orienting experiments, the P1 decreases in amplitude to invalidly cued target stimuli compared to neutrally cued targets, perhaps indicating suppression of stimulus processing at unattended locations. The N1, in contrast, increases in amplitude to validly cued targets, perhaps reflecting enhancement of processing at the attended location (Mangun and Hillyard 1987; Luck, Heinze et al. 1990; Luck 1995). While there is a correlation between ERP amplitudes and RTs, the P1 and N1 occur prior to any decision-making and prior to movement initiation. Since nicotine may directly affect these early processes, ERPs might provide information about when in the information processing stream the drug exerts any effects.

PREDICTION #2, SPATIAL ATTENTION: Nicotine will selectively enhance covert orienting of spatial attention in an exogenous, but in not an endogenous cueing task, due to the greater density of nAChR's with high affinity for nicotine in the exogenous network. Improvement in orienting will be indexed by a reduced validity effect (invalid RTs - valid RTs) in the exogenous task alone. It is further predicted that nicotine will reduce the typically observed suppression of P1 amplitude on invalidly cued trials in the exogenous task (but have no selective effect in the endogenous task), indicating enhanced processing of invalidly cued targets, and potentially reflecting the underlying neural activity contributing to a reduced validity effect in that task.

EXPERIMENT #1: NICOTINE EFFECTS ON ALERTNESS AND ENDOGENOUS ORIENTING OF SPATIAL ATTENTION

Introduction: Experiment #1

Nicotine, extracted from the leaves of the tobacco plant, acts largely as an agonist at nicotinic cholinergic receptors (nAChR's), both at autonomic ganglia and in the central nervous system (CNS). CNS effects presumably reinforce smoking behavior, while dependence is potentially maintained by avoidance of negative withdrawal symptoms and by the positive cognitive effects of the drug (LeHouezec and Benowitz 1991). Central nAChR's are mostly presynaptic, capable of stimulating release of several neurotransmitters, including acetylcholine (ACh), dopamine (DA), and norepinephrine (NE). Presynaptic receptors in the mesolimbic DA system promote the release of DA (Wonnacott 1997), and likely mediate the major motivational and reinforcing effects of nicotine (Koob 1992). Yet nAChR's are also found in numerous brain regions thought to carry out specific cognitive functions, such as attentional orienting. In addition, they are found on projections from neurotransmitter-specific brainstem nuclei considered critical for maintaining alertness (e.g., (Clarke, Schwartz et al. 1985; Wonnacott 1997)).

Covert orienting of spatial attention is the ability to concentrate visual attention on a particular spatial location, without moving the eyes, thus enhancing stimulus processing in that spatial location relative to others. In a covert orienting task, subjects fixate centrally while covertly directing attention to an area of a monitor screen based on a cue stimulus. If a cue indicates the subsequent location of a target stimulus, it is "valid"; if it indicates a site where the target does not appear, it is “invalid.” In general, reaction times (RTs) for a motor response to the appearance of a target decrease when attention is covertly directed to the site of target presentation by a valid cue in humans (e.g., (Posner 1980; Oken 1994)), monkeys (Petersen, Robinson et al. 1987; Witte, Davidson et al. 1997) and rats (Phillips, McAlonan et al. 2000). Invalid trials require a shift of spatial attention from the incorrectly cued location to the actual target location, while valid trials do not. The RT difference between these trial types is called the “validity effect,” and is thought to reflect the speed of attentional shifting (Posner 1980; Posner and Petersen 1990).

Nicotine facilitation of “attention” in humans has been examined using rapid visual information processing and vigilance tasks (Levin 1992). Nicotine reportedly improves performance on both tasks in smokers (Peeke and Peeke 1984; Wesnes and Warburton 1984a; Wesnes and Warburton 1984b; Hasenfratz, Michel et al. 1989; Jones, Sahakian et al. 1992; Bates, Pellett et al. 1994); (Warburton and Mancuso 1998), and in patients with attention deficit/hyper-activity disorder (ADHD) (Levin, Conners et al. 1996). Nicotine also reportedly improves attentional performance in non-smokers performing Conner’s Continuous Performance Test, a go/no-go task used to assess childhood ADHD (Levin, Conners et al. 1998). Animal studies support specific nicotine effects on spatial attention. Selective lesions of the cholinergic basal forebrain produce spatial attention deficits in rats (Muir, Everitt et al. 1995) and primates (Voytko, Olton et al. 1994), deficits reportedly reversed by nicotine in rats (Muir, Everitt et al. 1995). A study by Witte, et al. (1997) that examined monkeys injected with nicotine and human smokers who inhaled tobacco smoke reported that nicotine decreased RTs in a covert orienting task. In addition, the human smokers exhibited a significantly smaller validity effect than a group of non-smokers who did not receive drug. The authors interpreted these results as reflecting nicotine facilitation of spatial attentional shifting.

Giving up nicotine leads to a predictable constellation of symptoms in habitual smokers, including irritability, restlessness, depression, difficulty concentrating, and craving for cigarettes that manifests in as little as 12 hours (Stolerman and Jarvis 1995). Yet despite this clear withdrawal syndrome, many human studies of attention have examined smokers who abstained from cigarettes for anywhere from 12 to 24 hours before each experiment, and in whom withdrawal relief might underlie enhanced cognitive performance. The current study involved non-smokers to avoid this potentially confounding issue. In addition, most previous studies failed to report plasma nicotine levels in subjects, making it unclear how much nicotine they were exposed to during testing. In this experiment, serum was analyzed to determine whether subjects received consistent, detectable levels of nicotine, and to assess the reliability of transdermal delivery of drug.

Two types of spatial attentional “shifting” are investigated using covert orienting tasks, according to Posner (1980), depending on the type of cues used in the task. Attention may be shifted in a “top down” or endogenous fashion if a cue is meaningful, and provides predictive information about where a target stimulus will later appear. In contrast, attention shifted in an exogenous or “bottom up” fashion involves the appearance of a cue stimulus in the periphery, one that does not predict subsequent target appearance yet draws attention because its sudden emergence provokes an orienting response. There are several lines of evidence supporting the existence of these two distinct systems. For example, subjects appear to be more efficient (i.e., they exhibit faster RTs) at detecting exogenously cued targets than endogenously cued targets, because of the automatic nature of the former and the more effortful, higher order character of the latter (e.g., (Jonides 1981; Rafal and Henik 1994)).

Brain regions associated with these two functionally distinct attentional networks differ in their distribution of nAChR's. Receptors particularly responsive to nicotine are found in high density in thalamic nuclei and superior colliculus (Clarke, Schwartz et al. 1985; London, Scheffel et al. 1995), two key components of a proposed posterior network of brain regions critical for the exogenous orienting response (Posner and Petersen 1990; Posner 1998). In contrast, these receptors are found in lower density in cortical regions like anterior cingulate gyrus and dorsolateral prefrontal cortex, both considered essential structures in an anterior network responsible for top down or endogenous attention. Receptors far less sensitive to nicotine (Clarke, Schwartz et al. 1985); (Decker, Brioni et al. 1995) are more abundant in cortical regions associated with the anterior network than in subcortical components of the posterior network. Therefore, nicotine may have more influence on structures associated with the posterior orienting network than on those associated with the anterior network, and the use of covert orienting tasks that selectively engage one system or the other might help to reveal these potentially differential effects. A recent study of covert orienting in rats (Phillips, McAlonan et al. 2000), which used peripheral, non-predictive cues designed to selectively engage the posterior network, reported nicotine enhancement of attention. Other studies reporting enhancement (e.g., (Witte, Davidson et al. 1997; Murphy and Klein 1998)) used tasks that presumably engaged both networks. This experiment was designed to test the hypothesis that nicotine would not specifically enhance the covert orienting of spatial attention in non-smokers in a task involving predictive, centrally presented, endogenous cues.

Earlier studies primarily relied on RT measures to assess drug effects on spatial attention. Yet experiments examining performance on spatial attention tasks have found that attention results in selective amplification of cortical activity in primates. Single cell recording studies (e.g., (Robinson, Bowman et al. 1995)), PET studies (e.g., (Corbetta, Miezin et al. 1991; Heinze, Mangun et al. 1994)) and event-related potential (ERP) studies (e.g., (Mangun and Hillyard 1987; Luck 1995; Clark and Hillyard 1996)) have shown that attention to visual stimuli enhances neuronal activity and/or blood flow in selected extrastriate areas. ERPs are scalp-recorded electrical potentials that reflect summation of synchronous post-synaptic potentials from cortical neurons and are thus a direct measure of the neural activity involved in attention tasks (Ruchkin 1988). In covert orienting experiments, the contralateral P1 ERP component (the first long latency positive waveform deflection after stimulus presentation that is related to cognitive processing) decreases in amplitude to invalidly cued targets compared to neutrally cued targets, reflecting suppression of stimulus processing at unattended locations. The contralateral N1 (the first negative deflection), in contrast, increases in amplitude to validly cued targets (versus neutrally cued targets), reflecting enhanced processing at the attended location (Luck, Heinze et al. 1990; Luck 1995; Clark and Hillyard 1996). In order to account for a lack of specific nicotine effect on the endogenous orienting of spatial attention, it was predicted that nicotine would not selectively alter contralateral P1 amplitude on the invalidly cued trials, or contralateral N1 amplitude on the validly cued trials.

While nicotine was not expected to affect the endogenous orienting of spatial attention, it was predicted that the drug would directly affect a subject's level of alertness, the tonic activation of cerebral cortex. Cholinergic receptors responsive to nicotine are found in subcortical neurotransmitter-specific projection systems that underlie alertness, including cholinergic axons from the pontine nuclei and basal forebrain, and noradrenergic axons from the locus coeruleus (Foote 1987; Oken and Salinsky 1992). In fact, ACh release fluctuates with alertness level, and is higher in awake and REM sleep states, and suppressed during slow wave sleep (Foote 1987). Norepinephrine promotes alertness (Aston-Jones, Foote et al. 1984; Posner and Petersen 1990), and nicotine also acts to release NE (Wonnacott 1997). In addition, stimulation of the basal forebrain depolarizes cortical neurons, and shifts subthreshold membrane potential fluctuations from large amplitude, slow oscillations to low-amplitude, fast oscillations (McCormick 1992). Increasing alertness is associated with a similar shift in the EEG, from high amplitude, rhythmic activity to low amplitude, faster, less rhythmic activity. It was predicted that subjects given nicotine would exhibit enhanced alertness, as measured by both quantitative and subjective analysis of EEG recordings made after completion of the task, when compared to subjects on placebo.

To further examine nicotine effects on alertness, two subjective questionnaires, the Profile of Mood States (POMS) (McNair, Lorr et al. 1992) and the Stanford Sleepiness Scale (SSS) (Hoddes, Zarcone et al. 1973) were administered to subjects before and after the task. An earlier study in ADHD patients taking nicotine reported an increased vigor score on the POMS (Levin, Conners et al. 1996), as did a more recent study in non-smokers (Levin, Conners et al. 1998). It was predicted that nicotine would similarly increase subjectively reported alertness as measured by these two tests, matching results from the EEG.

Methods: Experiment #1

Participants. Subjects were 17 non-smokers (8 male, 9 female) from the Oregon Health Sciences University (OHSU), Reed College, and the University of Portland. This research received prior approval from the Oregon Health Sciences University institutional review board, and all subjects gave their informed consent before inclusion in the study. No subject had used nicotine during the last three years, and most (13) had never smoked regularly at all. Subjects ranged in age from 20 - 33 years (average of 24), were right-handed, and averaged 19 years of education. Young adults were selected because potentially confounding changes in electrophysiological correlates of attention and alertness occur with increasing age (Oken and Salinsky 1992). Each subject experienced all three test conditions: high nicotine, low nicotine, and placebo. Subjects were asked to avoid alcohol for 24 hours before each session. Subjects drank their normal dose of caffeine each day, but had no caffeine for at least three hours before testing.

Drug Treatment. Nicotine was delivered by transdermal patches. Nicoderm CQ patches (SmithKline Beecham), are rectangular, 0.6 mm-thick, multi-layer structures that release nicotine into the skin. Each patch is designed to deliver 7 mg of nicotine over 24 hours. Nicoderm patches were chosen because they deliver nicotine faster than other brands; maximal plasma levels are reached in 2-4 hours (Benowitz 1993). Placebo patches were rectangular Band-Aids cut to resemble Nicoderm patches. Plasma concentrations at the time of cognitive testing (1.5 - 2.0 hours after patch application) were expected to be about 12-14 ng/ml for the high dose (two patches) and 6-8 ng/ml for the low dose (one patch); levels shown to cause attentional improvements in past studies (Levin 1992; Levin, Conners et al. 1996; Levin, Conners et al. 1998). Cognitive testing was begun at this time in order to strike a balance between receptor activation by adequate nicotine plasma levels and potential desensitization of receptors by prolonged drug contact.

Procedure. Subjects completed one practice and three experimental sessions at the same time of day, each session at least two days after the last (in order to assure nicotine elimination before the start of each session). In the practice session, subjects performed the same covert orienting task they performed during each experimental session (although the order of stimuli was different each time they performed the task). Each subject was given a 7mg nicotine patch at the practice session, to screen out those likely to experience adverse side effects (e.g., nausea) during subsequent sessions involving the same or a higher dose. The three experimental sessions were identical except for the nicotine dose. A high dose session involved application of two 7mg nicotine patches to the underside of the subject's upper arm (on the non-dominant side). One 7mg nicotine patch and one placebo patch were applied at the low dose session, and two placebo patches at the control session. Both subject and principal investigator were blind to the dose. Patches were applied and removed by a third person not directly involved in the study, and covered by paper tape. Session order was counterbalanced, yet the low dose session always preceded the high dose session so that subjects experiencing side effects at the low dose (e.g., nausea) wouldn't receive the high dose of nicotine.

The three experimental sessions proceeded as follows:

0:00 Profile of Mood States (POMS), Stanford Sleepiness Scale (SSS)
0:10 Nicotine patch application
0:15 Electrode attachment and testing
1:10 Eyes closed EEG recording 1
1:40 25-minute endogenous covert orienting task
2:10 Eyes closed EEG recording 2
2:20 POMS, SSS
2:30 Blood drawing

EEG and ERP Recording. Fourteen gold EEG electrodes were attached to the subject, according to the International 10 - 20 System (Daly and Pedley 1990), at the following scalp sites: Fz, Cz, Pz, Oz, C3, C4, P3, P4, T5, T6, O1, O2, and linked mastoids. Four electrodes were attached above and below one eye and over each lateral canthus to record electrooculogram, to exclude artifact in EEG and ERP analysis. Electrode impedance was kept below 3000 ohms, and calibration was performed using 100μV sine waves. The analog filter range was 0.3 to 70 Hz, amplitude step size for digitization was 0.1μV, and the digital sampling rate was 256 per second.

All sites were referenced to balanced noncephalic electrodes on the neck and chest for later examination of ERPs. ERPs were recorded from T5 and T6, because previous studies had indicated that these electrodes produce high amplitude early waveforms (e.g., (Mangun and Hillyard 1987; Luck, Heinze et al. 1990; Clark and Hillyard 1996)). ERP latency was measured from target stimulus onset, and peak amplitudes were determined by comparison with a 200 ms pre-cue baseline. Each baseline value was determined by computer averaging of the activity recorded during the entire 200-ms baseline period. A post-stimulus window of 60-120 ms was used to detect the P1 ERP component, while a window of 140-190 ms was used to detect the N1.

One hour after patch application, six minutes of EEG was recorded while the subject rested comfortably with their eyes closed. A second six minutes of EEG was recorded after completion of the covert orienting task (two hours after patch application), and this EEG recording was analyzed for nicotine effects on alertness. The EEG was segmented into 2-second epochs, edited for excessive eyeblink movement and other artifact, windowed using a cosine taper occupying 40% of each epoch, and Fast Fourier Transform was applied. The square root of power for each frequency band in each epoch was averaged across epochs. Markers for increased alertness include a decreased (delta + theta)/(alpha + beta) (DT/AB) ratio (i.e., 2–7.5Hz/8-20Hz), increased peak alpha power (peak power frequency between 5 and 15 Hz) and higher median power frequency (50th percentile of power between 2 and 20 Hz) (Oken, Kishiyama et al. 1995). To reduce the number of variables for statistical analysis, only P3-O1 and P4-O2 averaged together were used in the analysis (these electrodes were chosen because attenuation of the alpha rhythm with decreasing alertness is generally more robust at posterior recording sites). The recording was divided into 60, ten-second epochs, and the number of sleep episodes (stage 1A, 1B or 2) was recorded. The EEG was scored for sleep according to standard EEG criteria using posterior alpha rhythm, amount of theta and delta frequencies, lateral eye movements and blinks (from (Rechtstaffen and Kales 1968)).

Heart Rate. Heart rate was recorded to provide another physiologic measure of nicotine exposure using a single channel of electrocardiogram.

Covert Orienting Task. Ninety minutes after patch application, subjects performed a 25-minute covert orienting of spatial attention task adapted from that of Posner (1990) and Oken (1995), to examine nicotine's behavioral effects on attention (RT changes with drug). Subjects sat 70cm in front of a color monitor in a dimly lit room, and maintained fixation at the center of the screen. A series of 360 images (320 circles, 40 squares) was presented with equal frequency 7 degrees to the left and right of fixation in six, four-minute periods, each period followed by a 30-second rest. Both cues and targets were black on a white background. Cues subtended a visual angle of 1 degree, while the target circles and non-target squares subtended an angle of 1.8 degrees. Subjects pressed a button with their dominant hand whenever a circle appeared. Subjects were asked to respond as rapidly as possible without sacrificing accuracy. Stimulus sequence was randomized so that subjects could not predict the order of stimuli from one experimental session to the next. In no case were more than two invalid stimuli presented in a row. In the majority of trials, images were preceded by a predictive, centrally presented cue stimulus (~ 85% validity). Cues consisted of a left arrow, a right arrow and two crossed lines (the neutral cue). The inter-stimulus interval was varied to prevent subjects from anticipating stimulus onset. The interval from cue onset to stimulus onset was 800ms, and each stimulus was on-screen for 100ms. Of 360 images presented, 200 were validly cued circles, 40 were neutrally cued circles, 40 were invalidly cued circles, 40 were validly cued squares, and 40 were circles not preceded by a cue. EEG continued to be recorded at this time, in order to collect data for another study.

Subjective Mood Measures. The Profile of Mood States (McNair, Lorr et al. 1992) and the Stanford Sleepiness Scale (a seven point self-rating scale of alertness; (Hoddes, Zarcone et al. 1973)) were administered to subjects immediately upon arrival at each experimental session (prior to nicotine patch attachment), and immediately after the second eyes closed EEG recording session. This was done in order to examine nicotine effects on changes in subjective levels of alertness (the vigor measure on the POMS, and the SSS in particular) following performance of the covert orienting task. Previously, vigor, fatigue and confusion measures were found to be sensitive to single doses of methylphenidate and diphenhydramine (Oken, Kishiyama et al. 1995). The POMS administered in this study was slightly altered from the original, as subjects were asked to report how they felt at the moment of the test, rather than during the preceding two weeks.

Phlebotomy. Blood (10cc) was drawn from the antecubital vein of the subject's left or right arm after the second eyes closed rest period. Blood was centrifuged for 15 minutes, and at least 2ml of plasma was siphoned off and kept frozen. Plasma nicotine was detected by capillary gas chromatography/mass spectrometry, which can detect nicotine levels as low as 1 ng/ml (Jacob 1981). This procedure was performed by MedTox Laboratories in St. Paul, Minnesota. Plasma drug levels were later correlated with RTs, sex, weight and electrophysiologic (EEG) measures of alertness.

Analysis. In all cases, ANOVA with repeated measures was performed, after determining that all assumptions of ANOVA were met. To address nicotine's behavioral effects on attention, a repeated measures ANOVA was performed on RTs across drug condition (0, 7, 14mg) and trial type (valid, invalid, neutral, no cue). To determine if nicotine improved attentional shifting, the RT difference between valid and invalid trials (validity effect) was compared across drug condition. To learn if nicotine increased subject impulsiveness, a repeated measures ANOVA on the number of incorrect target responses (i.e., false hits) across drug condition was performed. To address nicotine's electrophysiologic effects on alertness, a repeated measures ANOVA across drug condition assessed the (delta + theta)/(alpha + beta) ratio, all from the second, post-task, EEG recording period. Additional electrophysiologic alertness measures were examined with repeated measures ANOVA across drug condition, including median power frequency and peak alpha power. To address nicotine's effects on subjective measures of alertness, ANOVAs on POMS and SSS scores across drug condition were performed.

Results: Experiment #1

Participants. Out of 17 subjects tested, five were dropped from the study due to nausea following attachment of nicotine patches. Four of these five were those subjects who reported having smoked regularly in the past, but all more than three years prior to this study. Two of the five experienced significant nausea during the practice session, after receiving a single 7mg patch. Two others did not report nausea during the practice, but felt nauseous during the first experimental session involving the low dose (7mg) patch. The last subject felt nauseous on the high (14mg) dose, and vomited. Of the 12 subjects whose results are reported here, two experienced some nausea, but not until at least 30 minutes after completion of their last experimental session.

Blood Nicotine. In contrast to previous studies of nicotine effects on cognition in human subjects, blood plasma levels of nicotine were determined after completion of all tasks. Results were obtained for 10 of 12 subjects (results from two subjects were lost due to lab error, and none of the 5 subjects who were dropped from the study due to significant nausea had their blood drawn, Figure 1). When subjects were administered placebo patches, no nicotine was detected in their blood. When one 7mg patch was applied in the low nicotine condition, a mean of 7.14 ng/ml was detected (SD=3.9), and when two 7mg patches were attached in the high nicotine condition, a mean of 13.86 ng/ml was detected (SD=5.9). There was no significant difference between men and women in this study (t-test, $p=0.2$). There was also no correlation between body weight and plasma level ($r=-0.17$, $p=0.37$).

Heart Rate. Nicotine dose-dependently increased heart rate ($F(2, 22) = 19.09$, $p < 0.0001$). The mean heart rate of subjects during the second eyes closed EEG recording period was 63.3bpm (SD = 8.0) on placebo. At the low dose of nicotine it was 70.4bpm (SD = 8.7) and at the high dose it was 78.1bpm (SD = 8.9).

Reaction Times. To examine nicotine's behavioral effects on attention, a repeated measures ANOVA was performed on RTs across drug condition (placebo, low dose, high dose) and trial type (valid, invalid, neutral, no cue). There was, as shown previously, a significant effect of validity, with the mean of the median RTs to valid targets consistently faster than to neutral targets, which were faster than RTs to invalid targets, which were faster than RTs to uncued (no cue) targets ($F(3,33) = 97.91$, $p<0.0001$). In addition, there was a significant *within subjects* effect of drug condition ($F(2,22) = 5.09$, $p = 0.015$), with nicotine decreasing RTs to all targets. Results are presented in Figure 2. Post-hoc comparison of the placebo versus low nicotine dose condition revealed a significant difference (e.g., valid placebo RT = 298.5ms (SD = 51.5) versus valid low dose RT = 280.5 (SD = 45.5)) ($F(1,11) = 8.88$, $p = 0.013$), while the placebo versus high dose comparison was also significant (e.g., valid high dose RT = 284.3 (SD = 54.1)) ($F(1,11) = 6.74$, $p = 0.025$). The difference between RT on placebo and RT on nicotine (both low and high dose) in the various task conditions is presented in Figure 3. There was no significant RT difference between the two nicotine conditions.

To determine if nicotine improved attentional shifting, the within subjects RT difference between valid and invalid trials (the validity effect) was compared across drug condition. There was no significant effect of drug condition (F(2,22) = 2.74, p = 0.087); however, there was a trend towards an increased valid/invalid RT difference with drug (placebo mean = 42.3ms, SD = 15.7; low dose = 46. 8ms, SD = 16.9; high dose = 49.5ms, SD = 16.4). The benefit provided by the neutral cue versus the no cue condition (no cue – neutral RTs), often termed the "alerting effect" (Fernandez-Duque and Posner 1997), did not change with drug condition (F(2,22) = 1.57, p = 0.231, mean alerting effect = 104.4ms, SD = 6.7).

To determine if nicotine reduced RT by encouraging greater subject impulsiveness (i.e., subjects were faster because they indiscriminately hit the button to both target circles and non-target squares), Friedman's Test was performed on the percentage of non-target squares incorrectly hit across drug condition. Accuracy was very high (greater than 99%), and there was no significant effect of drug condition (X^2 = 1.167, p = 0.558).

Subjective Mood Measures. A within subjects ANOVA of Stanford Sleepiness Scale (SSS) scores with two factors (drug condition, and pre versus post-drug administration) revealed a significant effect of drug condition (F(2,22) = 6.38, p = 0.007), and pre- versus post-testing (F(2,22) = 12.07, p = 0.001). In addition, there was a significant drug condition by pre/post interaction (F(2,22) = 18.89, p = 0.000). An ANOVA of baseline pre-drug, pre-task SSS scores revealed no differences among subjects (F(2,22) = 0.38, p

= 0.689), while an ANOVA of post-drug SSS scores revealed a significant effect of drug condition (F(2,22) = 5.86, p = 0.009). Post-drug scores decreased (indicating greater alertness) at the low dose of nicotine compared to baseline (F(1,11) = 15.4, p = 0.002), while it increased from baseline (indicating decreasing alertness) after the high dose (F(1,11) = 11.88,p = 0.005). There was no significant change in score from the pre-drug to post-drug SSS in the no drug control condition, yet there was a trend towards an increased score (decreased alertness) (F(1,11) = 3.48, p = 0.089). Results are presented in Figure 4.

An ANOVA of baseline pre-drug POMS vigor, confusion and total mood disturbance scores (from tests administered before cognitive testing) revealed no significant difference between the three sessions (F(2,22) = 1.09, p = 0.353). When these pre-drug scores were subtracted from post-drug scores to produce change scores for these measures, significant within subject differences were found. The change score for vigor was positive at low dose of nicotine (1.3, SD = 2.9), indicating increased self-assessment of vigor after the experiment, while it was negative in both the placebo (-3.1, SD = 3.5) and the high dose condition (-4.9, SD = 3.2), indicating a loss of vigor (F(2,22) = 4.47, p = 0.023) over the course of the testing session.

ERP Amplitudes. To determine if nicotine improvement of RTs was reflected in ERP changes, a repeated measures ANOVA across drug condition and trial type was used to examine the amplitude of the P1 ERP component (using a post-stimulus window of 60-120ms), and the N1 (post-stimulus window of 140-190ms) at temporal electrodes T5 and

T6. There were no hemispheric differences so data was collapsed over left and right. In addition, there was no significant difference in baseline amplitudes across trial type (F(7,245)= 0.39, p=0.909). However, there were sufficient data points to conduct a within subjects ANOVA on contralateral ERP waveforms only. There was a low signal to noise ratio, and relatively few invalid trials to average. The ipsilateral waveforms could not be reliably measured in all trial types in most subjects (9 of 12), again due to a low signal/noise ratio. However, ANOVA did reveal a significant within subjects effect of trial type (F(3,21)=8.13, p=0.001). In particular, the amplitude of the contralateral P1 was higher in the no cue trials (across all drug conditions) than in valid trials (F(1,10)=14.54, p=0.003). As mentioned above, invalid trials could not be reliably examined because there were too few of them to average. Finally, ANOVA revealed no significant within subjects effect of drug condition (F(2,14)=1.56, p=0.245).

ERP Latencies. To further explore whether nicotine improvement of RTs was reflected in ERP changes, a repeated measures ANOVA across drug condition and trial type was used to examine the latency of the P1 ERP component (using a post-stimulus window of 60-120ms), and the N1 (post-stimulus window of 140-190ms) at electrodes T5 and T6. There were no hemispheric differences so data was collapsed over left and right. As with the amplitude data, there was sufficient data to conduct an ANOVA on contralateral ERPs only. The ANOVA revealed no significant effect of drug condition (F(2,16)=0.43, p=0.349). There was also no significant effect of trial type on latency of the P1 (F(3,24)=0.11, p=0.451). A post-hoc examination of latency of the N1 also revealed no significant effect of drug condition (F(2,18)=0.75, p=0.231).

EEG Measures. To examine nicotine's electrophysiologic effects on alertness, an ANOVA with repeated measures was performed on the (delta + theta)/(alpha + beta) ratio across drug condition. The analysis revealed a near significant effect of drug condition (F(2,22) = 2.76, p = 0.085), with a trend towards decline in the ratio with drug. An ANOVA with repeated measures performed on the median power (50th percentile) between 2 and 20Hz revealed a significant effect of drug condition (F(2,22) = 7.48, p = 0.003), with median power increasing at both doses of drug. Nine out of twelve subjects showed increased median power at the low dose of nicotine, while ten out of twelve showed increased median power at the high dose. In addition, peak alpha power (between 5 and 15Hz) increased significantly with drug (F(2,22) = 3.039, p = 0.05). Results are in Table 1. A repeated measures ANOVA across drug condition was also used to determine whether the number of sleep epochs detected by clinical scoring was related to the quantitative EEG results. The number of sleep epochs (stage 1A, 1B or 2) from eleven subjects were analyzed; the twelfth subject's EEG was too difficult to score, due to excessive heart rate artifact from the non-cephalic reference electrodes. An ANOVA with repeated measures revealed a reduction in the number of sleep epochs with increasing doses of nicotine (F(2,22) = 3.96, p = 0.034).

Discussion: Experiment #1

This experiment found that nicotine reduced RTs in non-smokers performing a covert orienting of spatial attention task using central, predictive cue stimuli. RTs were significantly faster in subjects given either a low dose (one 7mg patch) or a high dose (two 7mg patches) of nicotine than in those given placebo patches. This effect was not dose-dependent, since low and high nicotine produced similar benefits in RT. This effect was not due to greater impulsiveness by subjects on nicotine, or a clear change in strategy, since there were no significant effects of drug condition on the error rate.

Previously, Witte, et al. (1997) found that smokers smoking cigarettes had a smaller validity effect than non-smokers without drug (i.e., the smokers had faster RTs in the invalid condition versus the valid condition), and suggested that this represented an improvement in spatial attention (i.e., the smokers shifted their attention faster). In contrast, this study found no evidence of attentional improvement with nicotine. There was no decrease in the validity effect at either drug dose; in fact, there was a trend towards an increased validity effect with drug (i.e., slower shifting of attention with nicotine). More subjects might provide sufficient power to detect a significant change in this measure, but the current results are inconclusive. However, the lack of a nicotine effect on validity may be related to the lower density and affinity of nAChR's in cortical regions associated with the endogenous orienting of attention (Posner and Petersen 1990). Past experiments in which human or animal subjects exhibited significant drug effects on validity involved either purely exogenous tasks (e.g., (Phillips, McAlonan et al. 2000)), or tasks that simultaneously recruited both endogenous and exogenous attentional networks (e.g., (Witte, Davidson et al. 1997; Murphy and Klein 1998)).

As predicted, the non-specific decrease in RTs was not accompanied by selective changes in early components of ERP's to targets. The fact that the ipsilateral waveforms could not be reliably measured in all trial types in most subjects (9 of 12), was a complicating factor that limited statistical approaches to the data. However, there was no significant effect of drug condition on the amplitude of either the P1 or the N1. The predicted reduction of the typically encountered suppression of contralateral P1 in the invalid trials (thought to reflect reduced processing of unattended targets) was not observed. The predicted increase in N1 amplitude on valid trials (reflecting enhanced processing of attended stimuli) was also not observed. Failure to find significance may be partly due to the small number of stimuli averaged for certain trial types. In order to keep the length of the overall orienting task below thirty minutes, the number of invalid, neutral and no cue trials was only 20 each/session. Several of these trials were ultimately lost due to contamination by movement artifact. The resulting waveform averages were occasionally difficult to measure, and the variability introduced may have reduced statistical power. In the future it might help to use longer orienting tasks, with a sufficient number of stimuli for averaging.

Unlike several previous studies, our experiment compared non-smokers exposed to nicotine with the same non-smokers on placebo. While studies by Levin (1996, 1998) and some others (e.g., (Grobe, Perkins et al. 1998; Mumenthaler, Taylor et al. 1998)) have examined the effects of nicotine in non-smokers, Witte (1997), and most other researchers (including Peeke and Peeke 1984; Wesnes and Warburton 1984; Wesnes and Warburton 1984; Hasenfratz, Michel et al. 1989; Jones, Sahakian et al. 1992; Bates, Pellett et al. 1994); (Warburton and Mancuso 1998)) have focused their investigations on habitual smokers. It is known that chronic exposure to nicotine upregulates central nAChR's in both rats (Ksir, Hakan et al. 1987; Pauly, Marks et al. 1996) and humans

(Benwell, Balfour et al. 1995). The Witte (1997) study compared smokers inhaling tobacco smoke with non-smokers, two populations that are neurophysiologically distinct with respect to the receptors where nicotine acts. Perhaps selective upregulation in cortical regions linked to the orienting network contributed to the reduced validity effect observed in that study.

In addition, Witte (1997) and other studies examining smokers (e.g., (Grobe, Perkins et al. 1998)) required subjects to refrain from tobacco smoking for 12 to 24 hours prior to each experiment. A predictable withdrawal syndrome occurs in habitual smokers in as little as 12 hours (Stolerman and Jarvis 1995). Thus, previously reported RT improvements might be partly attributable to the relief of withdrawal. In contrast, the within subjects design of this study examined only non-smokers, each of whom was given placebo and nicotine in separate experimental sessions. The RT improvements observed in this study cannot be attributed to withdrawal relief, or to receptor changes resulting from chronic nicotine use. Finally, the Witte (1997) study used a covert orienting task with peripheral, not central cues. Nicotine may speed attentional shifting in tasks that draw attention using predictive peripheral cues, but not in tasks requiring attentional shifts based on informative, centrally presented cues.

Most previous studies of nicotine effects (Peeke and Peeke 1984; Wesnes and Warburton 1984a; Wesnes and Warburton 1984b; Hasenfratz, Michel et al. 1989; Jones, Sahakian et al. 1992; Bates, Pellett et al. 1994; Witte, Davidson et al. 1997; Warburton and Mancuso 1998) neglected to assess the degree of drug exposure during task performance, and many of these experiments examined smokers asked to inhale tobacco smoke from cigarettes. Differences in the rate of inhalation, depth of inhalation, lung capacity and a host of other factors can complicate drug delivery, and make it difficult to correlate exposure to nicotine with behavioral measures (Benowitz, III et al. 1986; Coultas, Stidley et al. 1993). Some studies have asked subjects to chew nicotine gum (Heishman, Snyder et al. 1993), but similar issues (rate of chewing, vascularization of mouth mucosa) arise. In this study, gas chromatography/mass spectrometry of plasma samples drawn 2.5 hours after patch application provided a quantitative measure of nicotine exposure. The levels obtained (0ng/ml on placebo, 7.1ng/ml on low dose, 13.9ng/ml on high dose) matched levels reported in the literature for this brand of patch (Benowitz 1993). However, there was no correlation between body weight and plasma level, or between gender and plasma level. This individual variation in nicotine levels from transdermal patches has been noted (Gourlay, Benowitz et al. 1997). Many factors aside from body weight, including the amount of subcutaneous fat and the degree of local vascularization, may contribute to this variability.

While nicotine had no selective effect on spatial attention in non-smokers, it did improve EEG measures of alertness. It was predicted that nicotine would maintain or increase alertness, as measured by a lower (delta + theta) / (alpha + beta) ratio. There was a near significant decrease in this ratio with nicotine. Yet in order for this ratio to be significantly affected, brain oscillations need to cross the 8Hz threshold from theta to alpha activity (or vice versa). Subtle changes in oscillation frequency are perhaps missed by this ratio. An ANOVA performed on the median power between 2 and 20Hz provides support, revealing a significant effect of drug condition, with median power increasing at both doses of nicotine. In addition, peak alpha power frequency (defined as the peak power frequency between 5 and 15Hz) increased significantly with nicotine. Sleep scoring of the EEG recordings also supported the hypothesis that nicotine promotes alertness. The number of sleep epochs during a rest recording was significantly higher in subjects given placebo patches than either dose of drug. Other studies have found a similarly close correlation between quantitative and subjective scoring of state from EEG (e.g., (Oken and Salinsky 1992)). Nicotine promotes the activity of ascending brainstem fibers known to non-specifically enhance cortical activity (Aston-Jones, Foote et al. 1984; Foote 1987; Posner and Petersen 1990; Oken and Salinsky 1992; Wonnacott 1997). This increased activity may underlie the improved alertness of subjects taking drug.

Results from the self-rated Stanford Sleepiness Scale and Profile of Mood States also suggest significant alerting effects of nicotine. Nicotine improved alertness in the SSS at the low dose, a gain reversed at the high dose. Vigor change scores from the POMS reflected enhanced vigor in subjects taking the low dose of nicotine, a gain again reversed at the high dose. The enhanced POMS vigor of non-smokers on a 7mg (low dose) patch has been previously reported (Levin, Conners et al. 1998). Perhaps subjective measures fail to follow RT and EEG results at the high dose because the side effects of nicotine are more detectable and more apt to affect subject mood at this dose. Only three subjects guessed correctly that they were on nicotine at the low dose. In contrast, all twelve subjects guessed correctly that they were on drug at the high dose, and most reported dizziness, increased heart rate, and itching around the patch site at this dose. In addition, the two subjects who developed significant nausea after all tasks were completed were the only subjects to show longer RTs on drug.

The non-specific improvements in RT without specific effects on attention, along with improved EEG and subjective measures of alertness were similar to results previously reported in a study of methylphenidate (Oken, Kishiyama et al. 1995). This suggests that nicotine's mechanism of action may be due in part to its effect on monoamine systems.

EXPERIMENT #2: NICOTINE EFFECTS ON ENDOGENOUS AND EXOGENOUS ORIENTING OF SPATIAL ATTENTION

Introduction: Experiment #2

Experiment #2 was designed to directly compare the effects of nicotine on performance of both an endogenous and an exogenous covert orienting of spatial attention task. The tasks were matched for stimulus parameters and differed only in the nature of the cues used. Nicotine was expected to have a specific attentional influence, and reduce the validity effect in the exogenous task. In contrast, based on the results of Experiment 1, no attentional effect was expected in performance of the endogenous task. However, an overall decrease in RT was expected in this task due to increased subject alertness. Subjective questionnaires were again administered in order to confirm enhancement of alertness with nicotine. Since nicotine promotes DA release (Wonnacott 1997), and since drugs that release DA are known to decrease RTs on motor tasks (Koob 1992), subjects also performed a finger tapping task to examine whether the RT improvement detected in Experiment 1 may have been due to faster motor responses on the button. Electrodes were again attached and EEG data was collected for an additional study.

Methods: Experiment #2

Participants. Subjects were 12 non-smokers (8 female, 4 male) from OHSU and the general public. Because most subjects who experienced nausea in Experiment 1 had smoked previously, no subject in Experiment 2 had any history of regular tobacco use. Subjects were age 22 - 32 (average age of 26), and had, on average, 17 years of education. Eleven out of 12 subjects were right-handed. Each subject experienced both test conditions: nicotine and placebo control. Subjects were asked to avoid alcohol for 24 hours before each session, and caffeine for at least three hours prior to each session.

Drug. Nicotine was delivered by transdermal patch as described for Experiment 1. Since subjects receiving a single, 7mg patch showed drug effects and the 14mg dose produced subjective side effects, only the 7mg dose was administered in Experiment 2.

Procedure. Subjects completed two practice and two experimental sessions at the same time of day. Experimental sessions were separated by at least two days, in order to assure complete nicotine elimination between sessions. In practice sessions, subjects performed the same two covert orienting tasks and the finger tapping task that they performed during each experimental session. The two experimental sessions were identical except for the administered nicotine dose. A nicotine session involved application of one 7mg nicotine patch to the underside of the subject's upper arm (on the non-dominant side). One placebo patch (a square Band-Aid) was applied at the placebo control session. Drug condition was counterbalanced, as was the order of the two orienting tasks, although each subject experienced the same task order in all sessions. Both subject and principal investigator were blind to the administered nicotine dose. Patches were applied and removed by a third person not directly involved in the study, and covered by paper tape.

The two experimental sessions proceeded as follows:

0:00	Nicotine patch application
0:05	Stanford Sleepiness Scale (SSS)
0:10	Electrode attachment and testing
1:15	25-minute covert orienting task (endogenous or exogenous)
1:45	Finger tapping task
2:00	25-minute covert orienting task (endogenous or exogenous)
2:25	SSS and questionnaire

EEG. Electrodes were attached as in Experiment 1. The data was collected for another study.

Covert Orienting Tasks. Seventy five minutes after patch application, subjects performed the first of two 25-minute covert orienting of attention tasks adapted from that of Posner (1990) and Oken (1995) to examine nicotine's behavioral effects on attention (RT changes with drug). The second covert orienting task was performed 115 minutes after patch application. A letter discrimination paradigm was chosen because previous studies demonstrated a validity effect in the exogenous condition using this approach (Henderson 1991; Parasuraman, Greenwood et al. 1992). However, our tasks differed from previous tasks in that a fixation stimulus did not appear before the onset of each cue; our software was limited in the number of images that could be presented on each trial. For both tasks, subjects sat 70cm in front of a color monitor in a dimly lit room, and maintained fixation at the center of the screen. In both tasks, a series of 384 target images was presented with equal frequency 7 degrees to the left and right of fixation in six, approximately four-minute periods, each period followed by a 30-second rest. In both tasks, cue stimuli were on-screen for 71ms, target stimuli were on-screen for 114ms, and the cue-target interval (or stimulus onset asynchrony (SOA)) was either 128ms or 671ms, each 50% of the time. Stimulus sequence was randomized so that subjects could not predict the order from one experimental session to the next. In the endogenous task, no more than two invalid stimuli were presented in a row. Subjects pressed one of two buttons on a computer mouse in response to the presentation of a target letter. There were two different target letters in each task. In the endogenous task, subjects pressed the left mouse button when they saw an “E,” and the right mouse button when they saw an “X.” In the exogenous task, subjects pressed the left button in response to an “N,” and the right button in response to an “A.” Subjects were asked to respond as rapidly as possible without sacrificing accuracy. In the endogenous task, the cue was presented at fixation, and was a leftward pointing arrow half the time, and a rightward pointing arrow the other half. The arrows indicated the correct target location 81.25% of the time (i.e., 81.25% of the arrows were valid cues, and 18.75% were invalid). In the exogenous task, the cue was always an upward pointing arrow presented 7 degrees to the right or left of fixation (50% of the time in each direction). Exogenous cues did not predict the subsequent target location; 50% of the time they were correct, 50% of the time they were incorrect. Both cues and targets were black on a white background. Target letters and endogenous arrow cues subtended a visual angle of 1 degree, while the exogenous cue subtended an angle of 0.3 degrees. The exogenous cue was smaller because a previous study suggested that smaller cue stimuli draw attention to more circumscribed spatial locations, instead of attracting attention to a wider region that could include both target locations (Henderson 1991).

Finger Tapping Task. Between the two covert orienting tasks, subjects performed a finger tapping task to assess nicotine effects on motor performance. Subjects were presented with two counter buttons (Veeder-Root, Part #727235-001) spaced 20cm apart, and were asked to tap back and forth on each as quickly as they could for 60 seconds with the index finger of their dominant hand. They repeated this task with the index finger of their non-dominant hand. The total number of taps on each counter with each hand was recorded.

Subjective Mood Measures. The Stanford Sleepiness Scale (Hoddes, Zarcone et al. 1973) was administered to subjects upon arrival at each experimental session (prior to nicotine patch attachment), and after performance of all tasks. This was done in order to examine and confirm nicotine effects on subjective levels of alertness. Subjects were also given a questionnaire at the end of each experimental session, in which they were asked whether they had experienced any boredom, euphoria, difficulty with the task, increased or decreased heart rate, nausea, dizziness, or were ever "physically ill in any way" compared to when they first arrived. Subjects indicated their responses on a five point scale, in which 1 represented "a lot" and 5 represented "not at all." Subjects were also asked whether their ability to concentrate had changed, which of the two tasks was more difficult, and whether they believed they had received nicotine.

Analysis. In all cases, ANOVA with repeated measures was performed, after determining that all assumptions of ANOVA were met. To address nicotine's behavioral effects on attention, a repeated measures ANOVA was performed on RTs across drug condition (0, 7mg), SOA (128ms, 671ms) and trial type (valid, invalid) for both the endogenous and exogenous task. To determine if nicotine improved attentional shifting, the RT difference between valid and invalid trials was compared across drug condition in both tasks. To examine nicotine effects on task performance and to determine whether nicotine influenced subject accuracy, the non-parametric Wilcoxon Signed Ranks Test was performed on the number of incorrect target responses across drug condition. To determine whether nicotine improved simple motor performance, an ANOVA on the number of finger taps in 60 seconds (from both right and left index fingers) across drug condition was performed. To address nicotine's effects on subjective measures of alertness, an ANOVA on SSS scores across drug condition was performed. In addition, the Mann-Whitney U Test was used to determine whether drug condition affected subject responses about boredom, euphoria, difficulty with task, increased or decreased heart rate, nausea, dizziness, physical illness, ability to concentrate, and whether or not they received drug.

Results: Experiment #2

Participants. Out of twelve subjects tested, one experienced some nausea, but not until at least thirty minutes after completion of their last experimental session. All twelve subjects completed the study.

Reaction Times. To examine nicotine's effects on attention, a repeated measures ANOVA was performed on RTs across drug condition (0, 7mg), SOA (128ms, 671ms) and trial type (valid, invalid) for both the endogenous and exogenous task. In the endogenous task there was, as shown previously, a significant within subjects effect of validity (F(1,11) = 23.67, p = 0.000), with median RTs faster to valid targets than to invalid targets. Unlike results from Experiment 1, there was no significant within subjects effect of drug condition (F(1,11) = 2.94, p = 0.114), although there was a trend towards reduced RTs with drug. In fact, the RT decrement was greater in milliseconds than in Experiment 1, but since the RTs were longer the SD was greater and thus the decrease was not significant. However, a post-hoc within subjects ANOVA of RTs from those subjects who performed the endogenous task first, at 75 minutes after patch application, did reveal a significant effect of drug (F(1,5) = 21.87, p = 0.005). Results are presented in Figure 5. Yet there was no drug effect on validity in this group (F(1,5) = 0.0, p = 0.962); nicotine reduced both valid and invalid RTs. There was also a significant effect of SOA (F(1,11) = 47.68, p = 0.000) for all 12 subjects, with RTs faster at the long (671ms) SOA. In the exogenous task, there was no effect of validity (F(1,11) = 0.9, p = 0.362) or drug condition (F(1,11) = 0.32, p = 0.583). However, there was a significant effect of SOA (F(1,11) = 10.11, p = 0.009), with RTs faster at the long (671ms) SOA.

To determine if nicotine affected accuracy, a Wilcoxon Signed Ranks test was performed on the number of incorrect button hits across drug condition in both tasks. All mean error rates were less than 3%. In the endogenous task, there was a significant within subjects effect of drug condition (Z = -2.415, p = 0.016), with nicotine reducing the number of errors (mean of 10 errors on placebo (SD = 9), 7.2 errors with nicotine (SD = 7.5)). Results are shown in Figure 6. There was no drug effect on errors in the exogenous task, although the error rate was lower (5.2 errors on placebo, 6.1 errors with nicotine).

Finger Tapping Task. There was no significant effect of nicotine on the total number of finger taps for the right hand (F(1,22) = 0.003, p = 0.957) or the left hand (F(1,22) = 0.002, p = 0.966). Results are presented in Figure 7.

Subjective Mood Measures. An ANOVA of baseline pre-drug SSS scores (from tests administered before cognitive testing) revealed no differences among subjects regardless of drug condition (F(1,22) = 0.373, p = 0.548), while post-drug SSS scores revealed a significant effect of drug condition (F(1,22) = 8.587, p = 0.008). Post-drug SSS scores did not change from baseline (indicating maintained alertness) when subjects were given nicotine, while SSS scores increased from baseline (indicating decreased alertness) when subjects did not receive drug. Results are in Figure 8.

When subjects were given nicotine, four out of twelve guessed correctly that they had received drug. One subject guessed that they were on nicotine when they were given a placebo patch, and the remaining seven subjects reported (incorrectly) that they never received nicotine at all. Results are presented in Figure 9. Subjects were asked if their ability to concentrate changed during the experiment, with 1 indicating improvement, 5 indicating a decrement, and 3 indicating no change. A Mann-Whitney U Test revealed significant improvement in self-rated concentration with nicotine ($p = 0.036$). Subjects were asked if they experienced boredom during the experiment, with 1 indicating "a lot" and 5 indicating "not at all." A Mann-Whitney U Test revealed significantly less reported boredom with nicotine ($p = 0.022$). Results are displayed in Figure 10. In contrast, there was no significant effect of nicotine on subjective assessments of euphoria, difficulty with task, increasing/decreasing heart rate, nausea, or dizziness.

Discussion: Experiment #2

This experiment found a trend towards reduced RTs in non-smokers taking nicotine while performing a covert orienting of spatial attention task using central, predictive cue stimuli. Unlike results from Experiment 1, this was not a significant effect. However, subjects taking nicotine did make significantly fewer errors on the endogenous task, indicating some drug facilitation of performance. While no reduction in error rate was seen in Experiment 1, that task was significantly easier than the letter discrimination task in Experiment 2, with subjects performing at greater than 99% accuracy.

Furthermore, in those subjects who performed the endogenous task before the exogenous task, nicotine did significantly reduce RTs. Perhaps immediate, previous exposure to the exogenous task, where cues are non-predictive, encouraged subjects to approach the endogenous task in a different manner. This is somewhat unlikely, as there was still a validity effect. Thus, perhaps these results reflect the time course of nicotine effects in non-smokers. Subjects who performed the endogenous task first did so at 75 minutes after application of the patch. In Experiment 1, subjects began the endogenous task at 90 minutes after receiving the patch, and also exhibited faster RTs. Yet subjects who began the task at 115 minutes did not show nicotine facilitation of RT. Nevertheless, Levin (1998) reported increased performance in non-smokers on the Conner's Continuous Performance Task (CPT), a task requiring subjects to press a button when they see a target stimulus and withhold a response when they see a non-target stimulus, at a full three hours and ten minutes after an identical 7mg nicotine patch was attached. Yet this task does not require spatial attention, as both stimuli are consistently presented in the same location on-screen. Perhaps nicotine loses its ability to enhance spatial attention tasks faster, or perhaps the subjects on placebo are far less alert at three hours after patching compared to those on nicotine, and this lack of alertness, not reduced attentional performance, is responsible for the results on the CPT. Finally, RT improvement does not appear related to non-specific improvement in motor performance, since there was no effect of nicotine on the finger tapping task.

There was, as in Experiment 1, no significant change in the validity effect with nicotine in either the entire group of twelve subjects or in the subset of six subjects taking the endogenous task first who exhibited significantly faster RTs on drug. This provides further support for the hypothesis that nicotine has no specific attentional effect on the orienting of spatial attention based on endogenous cue stimuli, perhaps partly because of the relatively moderate density of nAChR's in cortical regions thought to underlie this function.

In the exogenous task, neither a validity effect nor a drug effect was demonstrated. Without a validity effect, it is impossible to examine nicotine's influence on RT measures of attentional shifting. Subjects were expected to exhibit faster responses in valid trials compared to invalid trials at the shorter SOA, as attention was exogenously drawn by the cue to the target on valid trials, while invalid trials would require a shift from the incorrectly cued location to the actual target site. In addition, subjects were expected to show inhibition of return (IOR) at the longer SOA, with slower responses on valid trials versus invalid trials illustrating a disinclination to return spatial attention to a recently attended site. Both validity at short SOAs and IOR at long SOAs have been demonstrated in previous studies (Posner, Cohen et al. 1982; Henderson 1991; Parasuraman, Greenwood et al. 1992). Their absence in this study may have been due to our failure to include a fixation stimulus prior to the start of each trial, as several previous studies have done (Henderson 1991; Parasuraman, Greenwood et al. 1992). While eye movements were monitored throughout the experiment, and subjects did maintain fixation, their attention may have wandered around the monitor screen, and the time required to shift towards each peripheral cue may have varied accordingly. In addition, the absent fixation stimulus may have served a critical alerting role in previous studies, providing a baseline level of cortical activation necessary for consistent exogenous orienting of attention on each trial during long cognitive tasks.

There was, in addition, no reduction in the number of errors in the exogenous task, as there was in the endogenous task. This may be explained by a ceiling effect due to the lower error rate in the exogenous task.

As in Experiment 1, nicotine again improved subjective measures of alertness. Subjects on nicotine reported no change in their SSS score from baseline after completing both cognitive tasks, while subjects on placebo were significantly less alert at the end of each session. While the same dose of nicotine increased reported alertness in Experiment 1, subjects in that experiment performed only one, 25-minute task as opposed to two tasks in Experiment 2. Two tasks take more effort than one, and thus subjects maintained, rather than increased, alertness. There was only a trend towards an increased SSS score (decreased alertness) in the placebo condition in Experiment 1, while subjects on placebo reported a significantly higher score after completing tasks in Experiment 2, offering further evidence that Experiment 2 was more demanding than Experiment 1. When subjects were asked to indicate whether a session improved or reduced their ability to concentrate, those on nicotine tended to report improvement, while those on placebo reported a reduction or no change. When subjects were asked to indicate whether a session provoked boredom, those on nicotine tended to report no, while those on placebo reported significant boredom. Nicotine in non-smokers appears to improve alertness and the ability to concentrate, and it reduces boredom, at least by subjective assessment.

In both the endogenous and exogenous task, RTs were consistently faster at the long (671ms) SOA than they were at the short (128ms) SOA. If the cue acted as an alerting stimulus, it may have activated cortical neurons and facilitated performance at the longer SOA. In contrast, there may have been insufficient time during the short SOA to prepare the system for a faster response to the target.

Experiment 2, as opposed to the two-patch, high dose condition in Experiment 1, was truly double blind. Subjects had difficulty determining whether they had received nicotine during the study; in fact only five out of twelve subjects reported that they had received nicotine on the day that they actually did receive drug (seven thought they had received placebo). The decision to examine non-smokers without any history of regular tobacco smoking appeared to prevent the occurrence of significant nausea in response to the nicotine patch. While the four subjects with a significant past history of tobacco use all developed nausea in Experiment 1, none of the twelve naïve subjects in Experiment 2 developed nausea that precluded their continued participation in the study.

General Discussion: Experiments #1 and #2

Nicotine improves alertness in non-smokers. Subjects given nicotine in Experiment 1 exhibited increased median power frequency and peak alpha power in their EEG and a declining number of sleep epochs with increasing doses of drug. In addition, results from subjective questionnaires, including the POMS and SSS, in both experiments, strongly suggest that subjects felt less bored, more vigorous and more alert while on drug. These results match those from previous nicotine studies in non-smokers (e.g., (Levin, Conners et al. 1996; Levin, Conners et al. 1998)). Improved alertness is probably responsible for the RT improvements observed in the endogenous spatial orienting task in Experiment 1. In Experiment 2, subjects who performed the endogenous task at 75 minutes after receiving nicotine also exhibited decreased RTs, and all subjects reduced their number of errors, results likely related to their enhanced alertness on nicotine as well. Nicotine promotes the activity of ascending brainstem fibers known to non-specifically enhance cortical activity, including noradrenergic projections from the locus coeruleus and cholinergic projections from the pons and basal forebrain (Aston-Jones, Foote et al. 1984; Foote 1987; Posner and Petersen 1990; Oken and Salinsky 1992; Wonnacott 1997), and release of these neurotransmitters may underlie the improved alertness of subjects on drug.

In contrast, nicotine had no specific attentional effect in tasks designed to engage the proposed endogenous orienting network (Posner and Petersen 1990), with its moderate density of nicotinic cholinergic receptors (Clarke, Schwartz et al. 1985). The validity effect, the RT difference between validly and invalidly cued target stimuli, did not change with the reduction in RT, suggesting that the time required to shift attention did not change either. While the Witte (1997) study did report a reduction in the validity effect, this may have been due to the ambiguous nature of their cue stimuli, which were both peripheral and predictive, presumably provoking activity in both attentional networks. Further work is required to test the hypothesis that nicotine has an attentional effect on the exogenous orienting network, by using a task able to demonstrate both validity and IOR.

While studies by Levin (1996, 1998) and a few others (e.g., (Mumenthaler, Taylor et al. 1998)) have examined the effects on nicotine in non-smokers, Witte (1997) and most other researchers (including (Peeke and Peeke 1984; Wesnes and Warburton 1984a; Hasenfratz, Michel et al. 1989; Jones, Sahakian et al. 1992; Bates, Pellett et al. 1994; Bates, Mangan et al. 1995; Murphy and Klein 1998; Warburton and Mancuso 1998)) have focused their investigations on habitual smokers. It is known that chronic exposure to nicotine upregulates central nAChR's in both rats (Ksir, Hakan et al. 1987; Pauly, Marks et al. 1996) and humans (Benwell, Balfour et al. 1995). The Witte (1997) study compared smokers inhaling tobacco smoke with non-smokers, two populations that are neurophysiologically distinct with respect to the receptors where nicotine acts. Perhaps selective upregulation in cortical regions linked to the endogenous orienting network contributed to the reduced validity effect observed in Witte (1997). In addition, Witte (1997) and other studies examining smokers required their subjects to refrain from tobacco smoking for 12 to 24 hours prior to each experimental session. A predictable withdrawal syndrome occurs in habitual smokers in as little as 12 hours (Stolerman and Jarvis 1995). Thus, these previously reported RT improvements might be at least partly attributable to the temporary relief of withdrawal symptoms. In contrast, the within subjects design of these experiments examined only non-smokers, each of whom was given placebo and nicotine in separate sessions. The RT improvements observed in these studies cannot be attributed to withdrawal relief, or to neurophysiological changes resulting from chronic nicotine use.

The improvement in RT is probably not due to faster motor action related to increased dopamine release, since performance on the finger tapping task was not influenced by the drug. The conclusion is that behavioral and electrophysiologic changes in response to nicotine primarily reflect increased alertness. Since the experiments involved non-smokers, these effects are not related to the relief of withdrawal symptoms.

Directions for Experiments 3 and 4

Nicotine promotes alertness in non-smokers, but in these experiments did not appear to specifically affect the orienting of spatial attention based on endogenous cues. The non-specific improvements in cognitive performance observed with nicotine (indexed, for example, by faster RTs and reduced error rates in the orienting tasks) suggest that the drug offers at least some cognitive benefit to those subjects unaffected by unpleasant autonomic side effects like nausea. Yet is the nature of that benefit limited to increased alertness? Or are additional drug effects, perhaps related to changes in alertness, or mood, also contributing to improved cognitive performance? A number of results from Experiments 1 and 2 suggested further directions for research, including:

1. *Boredom and Engagement:* In Experiment 2, subjects given an opportunity to "rate" their level of boredom on a five point scale reported significantly more boredom with the experimental tasks when on a placebo patch than when on a nicotine patch. How does boredom relate to alertness and attention? Does nicotine reduce the subjective experience of boredom? If so, could nicotine-induced relief of boredom contribute to greater effort and performance in covert orienting or other cognitive tasks?
2. *Time Perception:* In Experiment 2, when subjects were asked to add "additional comments," five out of the six subjects given nicotine on their second day of testing reported that the experiment "went faster" than the first experiment. In contrast, three out of six subjects given nicotine on their first day of testing wrote that their second, placebo day took "longer." Does nicotine speed up the sense of time passage in non-smokers? Does it speed it up objectively (i.e., do subjects think that a half hour has passed after twenty minutes), or subjectively (i.e., do they realize that twenty minutes has passed, but believe it only felt like fifteen?)?
3. *Motor Performance:* Could the non-specific improvement in RT observed in both Experiments 1 and 2 be due to a faster motor response (i.e., hitting the response button more quickly), perhaps because of nicotine-evoked DA release? Results from a simple finger tapping task in Experiment 2 suggest not, since subjects did not tap any faster while on nicotine than on placebo. However, perhaps the simple task was too simple, and subjects on placebo already performed it at peak level. In contrast, a more complex motor performance task that subjects found more challenging might potentially show benefit from nicotine where the simple task did not.

4. *Functional exogenous task:* The exogenous task in Experiment 2 failed to work properly (there was, for one thing, no validity effect; i.e., no benefit to valid cueing). As described in the Discussion for Experiment 2 above, this was perhaps due to the lack of a fixation stimulus, a feature often used in other reports of exogenous cueing. Would a new exogenous task with a fixation stimulus carried through each trial produce a validity effect, and reveal nicotine effects on attentional performance?

Boredom and Engagement

What is boredom? According to Carlo Maggini, a psychologist at the University of Parma, boredom is "the suspension of intentionality, fidgety indifference, frustration, and painful estrangement from a reality experienced as meaningless" (Maggini 2000). Other researchers have described it as "an unpleasant subjective state which has cognitive (subjective monotony) and affective components" (Gordon, Wilkinson et al. 1997). For most individuals, it is a disagreeable, but temporary loss of interest or engagement in one's surroundings that is quickly overcome by either changing one's environment, or by cognitively generating interest or entertainment given the environment at hand (e.g., (Csikszentmihalyi and Csikszentmihalyi 1988); (DeChenne 1988)). Bertrand Russell has pointed out the dangers of both techniques, warning that boredom is "a vital problem for the moralist, since half the sins of mankind are caused by the fear of it" (Russell 1930). Pathologic boredom, in contrast to the acute or occasional variety, occurs chronically regardless of external circumstances (Maggini 2000), and is highly correlated with drug abuse (Samuels and Samuels 1974).

Acute boredom is usually associated with situations that are monotonous and repetitive, and that offer little external stimulation (e.g., (Davies 1926; Berlyne 1960; Geiwitz 1966; O'Hanlon 1981; Mikulas and Vodanovich 1993; Seib and Vodanovich 1998)). (Farmer and Sundberg 1986) have written that "…boredom is maintained by an environment that is perceived as static, with the actor remaining largely disconnected from the processes that describe his or her environment." A lack of "mental arousal" or alertness has been proposed as one potential source of boredom (e.g., (Zuckerman 1969; DeChenne 1988)). (Zuckerman 1969) postulates that each individual has an optimal level of alertness, at which they feel most engaged and involved in their surroundings, and which they will expend energy and effort to maintain. If one's alertness level drops below this apparent, homeostatic "set point," one experiences boredom, and generally takes steps to alter the environment to increase alertness (e.g., see a movie, start a war, read a book, procreate, etc.). As noted above, in both acute and chronic forms, boredom is also a risk factor for drug abuse (Samuels and Samuels 1974; Leong and Schneller 1993), including the abuse of cigarettes (e.g., (Tuakli, Smith et al. 1990; Sarramon, Verdoux et al. 1999)).

Boredom has also been theoretically linked to a failure of attention (Maggini 2000); [Hamilton, 1981 #169; (Hamilton, Haier et al. 1984). Carlo Maggini writes (Maggini 2000) that "efficient attention (or the development of an adequate attention style) is considered crucial to experiencing satisfaction (intrinsic enjoyment) and avoiding boredom (boredom coping)." That is, the ability to direct one's attention to objects or events of interest in one's environment, no matter how impoverished, is a cognitive skill that can help prevent or alleviate boredom. Studies have also shown that boredom is induced whenever subjects are required to maintain attention on a repetitive stimulus for an extended period of time (Seib and Vodanovich 1998). For example, subjects in one study of boredom (Ahmed 1990) were asked to spend 50 minutes crossing out all the vowels in a series of newspaper articles. In another study (Watt 1991), boredom was induced by requiring subjects to circle certain digits on pages filled with numbers (e.g., in one case, subjects were asked to circle all the 3's, and every 6 followed by a 7). According to (Leary, Rogers et al. 1986), "Boredom occurs only as a result of attending to stimuli that are not intrinsically captivating, and the level of boredom experienced is a direct function of the cognitive effort required to sustain focused attention on the stimulus." The "focused attention" of Leary is probably most akin to the vigilance required in long, repetitive attention tasks like the RVIP of Wesnes and Warburton (e.g., (Wesnes and Warburton 1984a)), or an extended version of the covert orienting task of Posner (e.g., (Posner and Petersen 1990)). Yet boredom is probably not just a failure of vigilance, as one can imagine a highly motivated individual (for example, a fighter pilot over Iraq) experiencing fatigue in monitoring radar signals (i.e., performing less well on a vigilance task), yet remaining far from bored. However, under less motivating conditions, using stimuli with less import (or threat), it is possible to design an explicitly boring task, one that involves maintaining vigilance over a long period of time, using repetitive stimuli that lack intrinsic allure. Presumably, such a task would promote boredom in many individuals, boredom that might be prevented or alleviated by increasing subject alertness.

Boredom Proneness Scale

"The threshold of boredom must be like the threshold of pain, different in all of us," wrote Martha Ellis Gellhorn (Gellhorn 1979), a US journalist and novelist, and the first wife of Ernest Hemmingway. The Boredom Proneness Scale (BPS), developed by (Farmer and Sundberg 1986), ranks individuals based on their answers to a series of 28 true or false questions about behaviors, thoughts and feelings related to boredom. This scale has been convincingly validated and shows strong test/retest reliability [Leong, 1993 #174; (Gordon, Wilkinson et al. 1997); Farmer, 1986 #171], indicating that its construct of boredom proneness is a stable and measurable personality trait. Men (particularly young men) have higher BPS scores than women (e.g., (Polly, Vodanovich et al. 1993; Seib and Vodanovich 1998)). Boredom proneness, in most cases measured by the BPS, is positively correlated with depression, hopelessness and loneliness (Farmer and Sundberg 1986), anxiety (Vodanovich, Verner et al. 1991), and feelings of alienation (Tolor 1989), and negatively correlated with curiosity (Maggini 2000), "attentiveness" (Gordon, Wilkinson et al. 1997), activity (McGiboney and Carter 1988) and arousal/alertness (Smith 1981). Notably, in a study examining induced boredom (Gordon, Wilkinson et al. 1997), there was no relationship detected between those with high BPS scores and self-reported levels of induced boredom.

Auditory evoked potentials and boredom

When a series of paired auditory clicks are presented to normal subjects, auditory evoked potentials (AEPs) recorded after the second click often show habituation when compared to AEPs recorded in response to the first. This has been shown to occur with the P50 midlatency waveform, and it is considered evidence of "pre-attentive" sensory gating (e.g., (Adler, Pachtman et al. 1982)). In some schizophrenic populations, such gating is diminished, and is thought to reflect the increased neuronal sensitivity of these patients to sensory stimuli (Adler, Pachtman et al. 1982). Two studies (Adler, Hoffer et al. 1992; Adler, Hoffer et al. 1993) have shown that nicotine normalizes this deficient gating, both in schizophrenics and in relatives of schizophrenics. The authors suggest that the nicotinic cholinergic system may contribute to the typically observed habituated response to repeated stimuli in normal subjects. Less pre-attentive sensory gating results in less cognitive processing of the second auditory stimulus, and researchers have shown similar habituation in later, cognitive ERP waveforms influenced by attention (e.g., (Lukas and Siegel 1977; Lutzenberger, Schandry et al. 1979; Wang, Timsit-Berthier et al. 1996)), including the P1 and N1. In rats, low doses of nicotine both increase the acoustic startle response (ASR) (Acri, Grunberg et al. 1991), and increase pre-pulse inhibition of the ASR, further indicating enhanced sensory gating with this drug. Thus, perhaps subjects who are more engaged and alert are responding to auditory stimuli in a more effective manner, and will show greater habituation to the second of two paired auditory clicks than subjects experiencing greater boredom and less alertness.

Nicotine and Boredom

Nicotine promotes alertness, as determined by objective EEG and subjective questionnaire results from Experiments 1 and 2. Alert individuals report less boredom (e.g., results from Experiment 2), and the experience of boredom has been theoretically linked to low alertness (Zuckerman 1969). Boredom is also highly correlated with nicotine use (e.g., (Tuakli, Smith et al. 1990; Sarramon, Verdoux et al. 1999)) and drug abuse (Samuels and Samuels 1974; Leong and Schneller 1993). Nicotine should reduce boredom.

PREDICTION #3, BOREDOM: Nicotine will reduce subjective assessment of boredom after non-smoking subjects complete a very long and boring task. Subjects asked to rate their level of boredom on a visual analog scale (VAS), by placing a mark on a continuous line marked at one end by the words "Not Bored" and at the other end by "Very Bored," will report less boredom on nicotine than on placebo. Reduction of boredom will be reflected in more exploratory eye movements to art images presented after the boring task, and by an increased tendency to examine novel items presented in images of novel/familiar item pairs. Nicotine reduction of boredom may also be reflected in more AEP habituation to the second of a pair of clicks.

Time Perception

We are all aware of the passage of time, a useful skill for anticipating predictable events and assessing the quality of a resource (Gibbon, Malapani et al. 1997). For example, we alter our behavior based on when or how often a favored fruit is found on a particular tree, or how quickly a web page downloads with a particular modem. Reinforcement schedules have their intended effects only in organisms capable of detecting the passage of time (Meck 1996). Consistent timing is also required for perceptual time-keeping operations, from keeping track of how many minutes have passed since one arrived in a doctor's waiting room, to the phenomenon of attentional blink, that period of time (about

400ms) after one engages a target stimulus when attention to other stimuli is blocked (Husain, Shapiro et al. 1997).

Because of the motor timing abnormalities associated with Parkinson's, the basal ganglia have long been implicated in timing processes (e.g., (O'Boyle, Freeman et al. 1996; Harrington, Haaland et al. 1998; Harrington, Haaland et al. 1998); (Gibbon, Malapani et al. 1997)), and timing deficits associated with cerebellar damage have suggested involvement of the cerebellum as well (e.g., (Ivry and Keele 1989)). One study (Harrington, Haaland et al. 1998) found that patients with right hemisphere cortical damage, but not left hemisphere damage, had selective impairment in time perception. The authors used a duration perception task, presenting two tone pairs, with subjects required to determine whether the interval between the second pair was longer or shorter than the first. Those with left hemisphere damage performed this task without difficulty, while those with damage to prefrontal cortex and/or inferior parietal cortex on the right made significantly more errors. These areas, aside from having direct reciprocal projections to the basal ganglia, are also regions associated with network models of spatial attention (e.g., (Mesulam 1981; Mesulam 1990; Posner and Petersen 1990)). The authors therefore suggested that time-dependent mechanisms of attention might play a role in the perception of time.

Drug effects on time perception in the rat have been experimentally examined by W. H. Meck (e.g., (Meck 1983; Meck and Church 1987; Meck 1996)). Meck trained rats to discriminate two auditory cues by providing reinforcement for one behavior following a short, two-second tone, and a different behavior following a long, eight-second tone. Unreinforced signals of intermediate duration were also presented, and the proportion of "long" behavioral responses increased as their duration increased. Drugs that increased synaptic DA (e.g., methamphetamine) increased the "speed" of the rat's internal clock (i.e., speeded up its perception of time passage), as inferred from the change in the point of subjective equality between these two behavioral responses. Drugs that blocked DA receptors (e.g., haloperidol) decreased the speed (Meck 1983). In another study (Meck and Church 1987), physostigmine (an cholinesterase inhibitor) was found to increase clock speed (and decrease the variability of the temporal discrimination), while atropine (a muscarinic antagonist) decreased clock speed (and increased the variability).

Finally, boredom has been directly correlated with the perception that time is passing more slowly (Watt 1991). Anyone sitting through a long, boring lecture knows this to be true! Watt compared the BPS scores of 110 undergraduates at the University of West Florida with their responses on a 7-point Likert scale that asked for their subjective perception of time passage before and after performance of a long, tedious, number circling task. He also asked participants to record (in minutes) the amount of time they thought they had spent engaged in the experimental task. Watt found that subjects with higher BPS scores (those who were generally bored in most situations) reported a subjective slowing of time after the task was complete. However, both boredom prone subjects and subjects not prone to boredom as measured by the BPS made similar objective assessments of the amount of chronometric time that had passed. Watt noted that other studies have shown that depressed affect also produces a subjective slowing of time passage, but does not alter the objective assessment (e.g., (Hawkins, French et al. 1988)).

Nicotine and Time Perception

Nicotine promotes alertness, and appears to decrease boredom (based on questionnaire results from Experiment 2), which is correlated with the subjective sense that time is passing faster (Watt 1991). An increased level of alertness can non-specifically improve cognitive function as measured by task performance, including the decreased RTs observed on the covert orienting task in Experiment 1, and attention mechanisms and cortical substrates have been implicated in a network model of time perception (Harrington, Haaland et al. 1998). Nicotine promotes the release of ACh and DA, and drug studies (e.g., (Meck and Church 1987)) have suggested that increased cholinergic and dopaminergic activity each independently speed the perception of time passage in rats. Nicotine may have similar effects on time perception in human non-smokers as well.

PREDICTION #4, TIME PERCEPTION: Drug studies in animals (e.g., (Meck and Church 1987)) suggest that an internal clock involved in keeping track of short time intervals (seconds to minutes) is speeded by ACh and DA, while at longer time intervals (minutes to hours) in humans, subjective perception of time passage is affected by boredom, while objective assessment is not. Therefore, it is predicted that subjects asked to estimate time passage of shorter duration (5, 10, 30 and 60 seconds) will estimate shorter lengths of time when on nicotine. In addition, subjective perception of time passage will be speeded up by nicotine during a long, explicitly boring task. Subjects asked how long the task felt (using a visual analog scale) will report that it took less time when exposed to nicotine. Yet subjects asked to objectively report the number of minutes the long task required will not significantly alter their responses based on drug condition.

EXPERIMENT #3: NICOTINE EFFECTS ON BOREDOM AND TIME PERCEPTION

Introduction: Experiment #3

To examine nicotine effects on boredom, twelve non-smoking subjects were asked to complete a long, boring task (a 35-minute version of Posner's covert orienting task with endogenous cues). Subjects were asked to rate how bored they felt, using a visual analog scale. It was hypothesized that subjects on nicotine would rate themselves less bored than those on placebo. Finally, subjects were asked to grip a "gripometer," a device that measures the strength of a person's grip in terms of pounds/square inch. This device has not been used previously in studies of effort; however, it was hypothesized that bored subjects who might be generally less inclined to expend effort in this experiment might also grip with less strength.

To examine nicotine effects on time perception, subjects were asked to rate how long they thought the boring task took, both chronometrically, in minutes, and subjectively, using a visual analog scale. It was hypothesized that subjects on nicotine would rate the task as passing faster on the subjective VAS than those on placebo, but that neither group would report any difference in their objective, chronometric estimates. In addition, subjects were asked to estimate short lengths of time, by pushing a key twice; once to start their internal clock, and another when they believed either five or ten seconds had elapsed. It was hypothesized that subjects on nicotine would record shorter times.

Methods: Experiment #3

Participants. Subjects were 19 non-smokers (9 female, 10 male) from OHSU, Portland State University, and the general public. No subject had any history of regular tobacco use. Subjects were age 20 - 38 (average age of 27), and had, on average, 17 years of education. All subjects were right-handed. Each subject experienced both test conditions: nicotine and placebo control. Subjects were asked to avoid alcohol for 24 hours before each session, and caffeine for at least three hours prior to each session.

Drug. Nicotine was delivered by a 7mg transdermal patch (Nicoderm CQ, SmithKline Beecham) as described for Experiments 1 and 2.

Procedure. Subjects completed one practice and two experimental sessions at the same time of day. Experimental sessions were separated by at least two days, in order to assure complete nicotine elimination between sessions. In the practice session, subjects were asked to answer the 28 true/false questions on the Boredom Proneness Scale ((Farmer and Sundberg 1986)). Subjects also performed a short version of the same boring task (15 versus 35 minutes long), and the exact same 5/10/30/60 second time estimation task that they performed during each experimental session. The two experimental sessions were identical except for the administered nicotine dose. A nicotine session involved application of one 7mg nicotine patch to the underside of the subject's upper arm (on the non-dominant side). One placebo patch (a square Band-Aid) was applied at the placebo control session. Drug condition was counterbalanced, and each subject experienced the same task order in all sessions. Both subject and principal investigator were blind to the administered nicotine dose. Patches were applied and removed by a third person not directly involved in the study, and covered by a colorful sticker.

The two experimental sessions proceeded as follows:

- 0:00 Nicotine patch application
- 0:05 Stanford sleepiness scale (SSS), Profile of Mood States (POMS)
- 0:20 Boring task practice
- 0:30 The boring task
- 1:05 Visual analog scales (boredom, time passage)
- 1:10 Time estimation task (5/10/30/60 seconds)
- 1:50 Grip strength effort task
- 2:00 SSS, POMS

The Boring Task. The Boring task was an extended version of the endogenous orienting task used in Experiment 1. Subjects sat 70cm in front of a color monitor in a dimly lit room, and maintained fixation at the center of the screen. A series of 450 images (400 circles, 50 squares) was presented with equal frequency 7 degrees to the left and right of fixation in five, 6.2-minute blocks, each block followed by a 1-minute rest. The entire task took 35 minutes to complete. Both cues and targets were black on a white background. Cues subtended a visual angle of 1 degree, while the target circles and non-target squares subtended an angle of 1.8 degrees. Subjects pressed a button with their dominant hand whenever a circle appeared. Subjects were asked to respond as rapidly as possible without sacrificing accuracy. Stimulus sequence was randomized so that subjects could not predict the order of stimuli from one experimental session to the next. In no case were more than two invalid stimuli presented in a row. In the majority of trials, images were preceded by a predictive, centrally presented cue stimulus (~ 86% validity). Cues consisted of a left arrow, and a right arrow. The inter-stimulus interval was varied to prevent subjects from anticipating stimulus onset. The interval from cue onset to stimulus onset was 800ms, and each stimulus was on-screen for 100ms. Of the 450 stimuli presented, 300 were validly cued circles, 50 were invalidly cued circles, 50 were validly cued squares, and 50 were circles not preceded by any cue. In the practice version of the boring task (administered during the one practice session), subjects completed three blocks of ninety stimuli, with two, 1-minute breaks between them. Of the 270 stimuli presented during the practice task, 180 were validly cued circles, 30 were invalidly cued circles, 30 were validly cued squares, and 30 were circles not preceded by any cue.

Visual Analog Scales. Both before and after completion of the boring task during experimental sessions, each subject was presented with a page titled "Boredom Level," which included a line 20 centimeters long, marked by "Not Bored" at the left end, and

"Very Bored" at the right. A second page titled "Energy Level" was also presented twice (both before and after the boring task), with another 20cm line marked with "No Energy" on the left side, and "Energetic" on the right. A final page, presented only once, after completion of the boring task, was titled "How long did this task seem to you?", and included a third 20cm line, with "Very Short" at the left end, "Long" at the precise midpoint, and "Extremely Long" at the right end. Subjects were instructed to "Please make a single mark on the following scale," indicating how bored and how energetic they felt in the first two cases, and how long the task felt in the third.

Time Estimation Tasks. After completing the boring task (70 minutes after patch application), subjects were presented with a standard computer keyboard. They were asked to press the space bar once, and then wait until they believed that five seconds had passed before pressing the space bar a second time. Subjects repeated this exercise with five seconds between bar presses, and then made two more estimates of ten seconds each. Subjects then made two estimates of 30 seconds each, and ended the task by making two additional estimates of 60 seconds each. No clock or watch or any other time keeping device was visible in the room. Subjects were not given any explicit instruction as to how they should estimate the passage of time, and were not prevented from silently counting.

Subjective Mood Measures. The Stanford Sleepiness Scale (SSS, (Hoddes, Zarcone et al. 1973)) and the vigor-activity, tension-anxiety, and anger-hostility subscales of the Profile of Mood States (POMS, (McNair, Lorr et al. 1992)) were administered to subjects upon arrival at each experimental session (prior to nicotine patch attachment), and again after performance of all tasks. Three additional POMS-like subscales were also administered, each one scored by the subject on the same POMS scale (a five-point scale ranging from "not at all" to "extremely"). These new subscales included terms representing Boredom (bored, disinterested, apathetic), Engagement (interested, curious, engrossed), and Autonomic Response (nauseous, dizzy, sweaty). All scales were administered in order to examine (and in some cases confirm) nicotine effects on subjective levels of alertness, boredom, and autonomic responsiveness. Subjects were also asked at the end of each test session whether they believed they had received nicotine.

Grip Strength. After completing all other tasks, subjects were asked to squeeze a "gripometer" as hard as they could. They repeated this exercise five times, and each time their maximum grip strength was recorded.

Analysis. In all cases, ANOVA with repeated measures was performed, after determining that all assumptions of ANOVA were met. To address nicotine's behavioral effects on alertness, a repeated measures ANOVA was performed on RTs across drug condition (0, 7mg), and trial type (valid, invalid) in the boring task, looking for evidence of faster RTs without specific effects on validity (since this task was administered only 30 minutes after patch attachment, it wasn't clear that subjects would have enough circulating nicotine to produce any effect). To examine nicotine effects on boredom and subjective perception of how long the boring task took, the mark on each visual analog scale (VAS) was converted to the number of centimeters along the 20cm line length (with 0 at the left end), and a repeated measures ANOVA on the change in line length across drug condition was performed. To examine nicotine effects on subject assessment of chronometric time passage after the boring task, a repeated measures ANOVA on subject estimates (in minutes) across drug condition was performed. To determine whether nicotine changed subject assessment of short periods of time passage, a repeated measures ANOVA on subject estimates of 5 and 10 seconds across drug condition was performed. To examine nicotine effects on effort (also as a measure of boredom versus engagement), an ANOVA with repeated measures on grip strength results across drug condition was performed. To address nicotine's effects on subjective measures of alertness, a within subjects ANOVA on SSS scores and the vigor-anxiety subscale of the POMS across drug condition was performed. In order to assess nicotine effects on other POMS subscales, as well as new subscales representing boredom, engagement and autonomic response, an ANOVA with repeated measures was performed on these scale scores across drug condition. In addition, the Mann-Whitney U Test was used to determine whether drug condition affected subject responses about whether or not they received drug.

Results: Experiment #3

Participants. Of the 19 subjects tested in Experiment 3, four were dropped from the study after experiencing extreme nausea during performance of the boring task, which left them unable to complete the experiment. Three additional subjects were dropped from the study, one because of incomplete data (she never returned after the practice session), and two because of errors in drug regimen (one subject accidentally received nicotine on both test days, the other received placebo on both test days). Of the twelve subjects whose results are reported here, three experienced significant nausea during performance of the boring task, but nevertheless completed the experiment (all three refrained from reporting any nausea until after all experimental sessions were complete). One additional subject experienced nausea, but not until after finishing all experimental tasks (i.e., he did not experience nausea at any time during the experiment). The eight remaining subjects completed all sessions without reporting any nausea at all.

Boredom Proneness, Boredom, and Nausea. BPS scores were related to subjective estimates of boredom on the visual analog scale. Subjects with low BPS scores (BPS less than 6) reported no boredom on the VAS on the placebo day before beginning the Boring Task, while subjects with high BPS scores (6 and above) did report some boredom. A between subjects ANOVA finds this relationship to be highly significant ($F(1,11) = 22.756$, $p = 0.001$). In contrast, BPS scores were not correlated with VAS responses concerning initial energy level on placebo days, nor with the difference between either boredom or energy level responses before and after completion of the Boring Task. In addition, BPS scores were not correlated with the difference in SSS results from the placebo day. However, there appeared to be a curious correlation between scores on the BPS and the experience of nausea in response to nicotine. Low BPS scores (indicating low boredom proneness) were associated with a high incidence of nausea, while higher BPS scores (indicating more boredom proneness) were associated with a lack of nausea following nicotine exposure. The correlation was highly significant (0.86), with subjects who felt nausea having an average BPS score of 2.875 (SD = 0.52), and subjects without nausea reporting an average score of 8.4 (SD = 0.6). Results are presented in Figure 11.

The Boring Task. In the nine subjects who did not experience any nausea during performance of the Boring Task, there was a significant within subjects effect of validity (F(1,8) = 66.07, p = 0.000), with subjects exhibiting faster RTs to valid targets than to those invalidly cued. There was also a significant effect of drug condition (F(1,8) = 5.62, p = 0.045), with nicotine decreasing RTs to both valid and invalid targets. There was again no significant drug effect on the validity effect, the RT difference between validly and invalidly cued targets (F(1,8) = 0.37, p = 0.561). Results are in Figure 12.

Visual Analog Scale: Self-Reported Boredom. Subject marks on the 20cm VAS were converted to scores representing distance in centimeters, starting with 0 on the left ("Not Bored") end of the line. Scores from the VAS administered before beginning the boring task (when subjects tended to be less bored) were subtracted from scores derived from the VAS administered after the boring task was complete. A within subjects ANOVA of the difference scores was significant (F(1,8) = 14.97, p = 0.005), with nicotine consistently reducing or preventing subjective reports of boredom. Results are presented in Figure 13. The three subjects who experienced nausea, in contrast, reported less consistent effects of nicotine; two reported more boredom on drug, while one reported less.

Visual Analog Scale: Self-Reported Energy Level. Difference scores were computed as for boredom above. A within subjects ANOVA of the difference scores across drug condition found no significant effect of nicotine (F(1,8) = 3.64, p = 0.093), although eight of the nine subjects who completed the task without reporting nausea reported increased energy on nicotine than on placebo. In addition, a t-test comparing difference scores across drug condition was significant (p = 0.045), with subjects on drug reporting more energy. Results are presented in Figure 14. In contrast, all three subjects experiencing nausea reported less energy on nicotine than on placebo.

Visual Analog Scale and Chronometric Assessment: Boring Task Length. Subjects asked to subjectively describe the length of the boring task consistently rated it faster when receiving nicotine than when given a placebo patch. A within subjects ANOVA of task length response across drug condition was significant (F(1,8) = 35.87, p =0.000). Results are presented in Figure 15. Subjects experiencing nausea reported the opposite; i.e., the task seemed to take longer on nicotine than on placebo. There was no drug effect on subject estimates of chronometric time passage; subjects consistently reported that the same amount of time (in minutes) had elapsed in each session.

Time Estimation. Subjects were remarkably consistent in their estimates of short periods of time passage (5/10/30/60 seconds). The first estimate of 5/10/30 or 60 seconds was often remarkably close to the second. There was no significant effect of nicotine at five and ten seconds in the nine subjects reporting no nausea; however, there was a trend towards shorter 30 second estimates with nicotine in this group (F(1,8) = 4.21, p = 0.074). In addition, the estimates were more consistently accurate (i.e., closer to the actual passage of time) at the two longer time periods (30 and 60 seconds) when subjects were given nicotine than when they received a placebo patch. Results are in Figure 16.

Subjective Questionnaires. A within subjects ANOVA of Stanford Sleepiness Scale scores from the nine subjects who did not experience nausea with two factors (drug condition, and pre-drug versus post-drug administration), revealed no significant effect of drug condition (F(1,8) = 1.7, p = 0.228). However, there was a significant effect of pre-drug versus-post drug testing (F(1,8) = 7.93, p = 0.023), plus a significant drug condition by pre/post-drug interaction (F(1,8) = 7.84, p = 0.023). Post-drug SSS scores did not significantly change from baseline (indicating maintained alertness) when subjects were given nicotine, while SSS scores increased from baseline (indicating decreasing alertness) when subjects did not receive drug.

There was no significant difference between POMS subscales scores (including vigor-activity, tension-anxiety, anger-hostility) or POMS-like subscale scores (boredom, engagement, autonomic response) prior to task performance on each test day based on drug condition; everyone arrived at each session reporting similar scores. However, a comparison of pre-drug and post drug scores on the vigor-activity subscale showed a trend towards decline (indicating less vigor and activity) after all tasks were completed for the nine, "non-nauseous" subjects on placebo (F(1,8) = 4.36, p = 0.07), while these same subjects on nicotine reported similar (i.e., no decline) vigor-activity scores both pre and post-session (F(1,8) = 1.78, p = 0.219). There were no significant changes in either drug condition for scores on the anger-hostility or tension-anxiety subscales. For the boredom subscale, subjects on placebo reported significantly more boredom at the end of each session than at the beginning (F(1,8) = 5.76, p = 0.043), while not one of these nine subjects reported any boredom at the session end when they were given nicotine. These results were mirrored by subject responses on the engagement subscale; subjects on placebo reported significantly less engagement after completing all tasks (F(1,8) = 5.84, p = 0.042), while those on nicotine reported a trend towards more engagement (F(1,8) = 3.82, p = 0.086). In terms of autonomic response, neither subjects on placebo (F(1,8) = 0.13, p = 0.729) nor nicotine (F(1,8) = 3.20, p = 0.111) reported significant increases in dizziness, sweatiness or nausea. Results are in Figure 17.

Unlike results from Experiment #2, most subjects in Experiment #3 were well aware of when they received drug. Ten out of twelve subjects on nicotine knew that they were on nicotine (eight out of the nine subjects who did not report nausea), while ten of twelve subjects on placebo (seven of the nine non-nauseous subjects) correctly guessed that they had not received any nicotine on that test day. Results are presented in Figure 18.

Grip Strength. There was no significant within subject difference between gripometer readings from subjects on nicotine test days and placebo days.

Discussion: Experiment #3

As in Experiment 1 and 2, a group of non-smoking subjects performing a covert orienting of attention task using purely endogenous cues responded faster after receiving a nicotine patch than after receiving a placebo patch. In addition, there were again no drug effects on validity; i.e., these subjects did not selectively reduce RTs to invalidly cued targets with nicotine as if they were better able to shift attention to a new location in space. Therefore, once again, nicotine appears to have non-specifically improved cognitive performance, without any selective effect on the endogenous orienting of spatial attention.

This may be the result of nicotine ability to increase alertness, as performance improvements were non-specific, and as nicotine is known to promote the release of multiple neurotransmitters associated with non-specific brainstem projection systems directly related to a subject's level of alertness. In addition, attentional networks associated with endogenous orienting of spatial attention consist of brain regions with only a moderate density of nAChR's (Clarke, Schwartz et al. 1985), and a majority of these appear to be the cholinergic subtype least responsive to nicotine (Decker, Brioni et al. 1995). In contrast, it remains to be seen whether non-smokers performing a covert orienting task that selectively engages the proposed "posterior" attentional network (Posner and Petersen 1990), with its higher density of nicotinic receptors more responsive to nicotine (Clarke, Schwartz et al. 1985; Decker, Brioni et al. 1995), would show any attentional improvements when given drug (this was tested in Experiment #4).

This improvement in alertness is also indexed by the significant tendency for non-smokers on nicotine to maintain their reported level of alertness as measured by the Stanford Sleepiness Scale (SSS), while indicating a drop-off in alertness after receiving the placebo patch. This is another finding replicated in all three experiments thus far.

Results from the POMS also support nicotine facilitation of alertness, with subjects on placebo reporting a near-significant decline in vigor-anxiety, while those on nicotine showed no change in vigor-activity after completion of all session tasks.

As mentioned previously, alertness has been theoretically linked to the experience of boredom (Zuckerman 1969; DeChenne 1988), with subjects below their "optimal" level of arousal or alertness thought to suffer greater degrees of tedium and ennui. In this experiment, non-nauseated subjects who placed marks along a VAS representing their current level of boredom following completion of a deliberately long and boring chore, consistently indicated that they felt more bored when they received placebo than when they received nicotine. In addition, most of these same subjects (eight out of nine) reported higher levels of energy on a second VAS when given nicotine than when exposed to a placebo patch. Nicotine also reduced the subjective assessment of boredom, and increased the assessment of engagement in results from the POMS-like subscales, with subjects reporting the opposite effects without drug. Nicotine appears, at least subjectively, to maintain alertness and energy, increase engagement and reduce the experience of boredom explicitly induced by a long, repetitive task.

Another hypothesis underlying this experiment was that nicotine might affect the subjective sense of time passage, while not impairing subject ability to estimate the more objective, chronometric passage of time. A similar dichotomous result has been reported for subjects who differed in terms of their boredom proneness (Watt 1991). Since nicotine apparently relieves boredom in non-nauseous non-smokers, it was predicted that this would translate into a faster subjective appraisal of the time it took to complete the boring task. This is exactly what was found in Experiment #3. Subjects asked to rate their subjective sense of how long the boring task took consistently estimated a faster experience after receiving nicotine than after receiving a placebo patch. In contrast, there was no significant difference between estimates of the number of minutes this task took dependent on drug condition. However, this may be due to the design of the experiment, which used the same task (with different stimulus order, but identical length) on each test day. Many subjects recognized that the task took the same amount of time each day, but specifically indicated that nicotine made the task pass at a subjectively faster rate.

Subject estimates of short periods of time passage (5/10/30/60 seconds) were hypothesized to get shorter with nicotine, since both cholinergic and dopaminergic drugs apparently speed up some version of an "internal clock" in animal studies (Meck and Church 1987); (Meck 1983; Meck 1996). Rats trained to respond to tone cues with two distinct behaviors, depending the length of the tone, generally execute the "short" response at longer intermediate tone lengths after injection with physostigmine (a cholinesterase inhibitor) or amphetamine. Nicotine promotes the release of both ACh and DA (Wonnacott 1997). Subjects in Experiment #3 showed no drug effect on estimates of five or ten seconds. However, at longer time estimates (30 and 60 seconds), subjects on nicotine tended to make estimates closer to the actual time that had passed, and shorter estimates than when they had received placebo. This approached significance for estimates of 30 seconds. Perhaps subjective estimates were more accurate following nicotine because the drug prevented boredom and maintained alertness. Boredom has been linked to a slowed sense of time passage (Watt 1991), so perhaps the increased boredom following performance of the boring task on placebo contributed to the subject's sense that time was passing more slowly.

A significant influence on these outcomes is the particularly large autonomic reaction to nicotine in Experiment #3, in contrast to the almost non-existent reports of dizziness or nausea in Experiment #2. While recruiting subjects without previous history of nicotine use appeared to eliminate severe nausea in subjects naïve to drug in the last experiment (few subjects were even cognizant of their drug state), unpleasant side effects were far more common in Experiment #3. Eight of 19 subjects experienced nausea at some point in response to nicotine; four had to be dropped from the study. Three more who experienced nausea during testing reported more boredom (two of three), less energy (three of three) and a longer task experience (three of three) while on drug.

Perhaps this increased incidence of unpleasant autonomic excitability has to do with when the tasks were administered. In Experiment #2, subjects performed the first of two 25-minute orienting tasks at 75 minutes following patch attachment, possibly after the initial autonomic effects, such as brief nausea, or increased heart rate, had subsided. During the first hour of Experiment #2, subjects were often distracted by conversation and interaction with the experimenter, as electrodes were attached to the scalp. In contrast, the naïve non-smokers in Experiment #3 were required to begin an even longer, 35-minute orienting task only 30 minutes after patch attachment, with nothing but task demands to distract them from any unsettling autonomic side effects of nicotine. This may partly explain the much higher incidence of nausea in Experiment #3, as well as the tendency for subjects to guess correctly when they were and were not on drug.

Subjects with higher BPS scores (6 and above) did report significantly more boredom on a visual analog scale administered before the beginning of the Boring Task than did those with lower scores. Curiously, those subjects reporting lower BPS scores (indicating that they were rarely bored) were also subjects most likely to experience nausea in response to nicotine. Perhaps individuals who consider themselves to be always involved, engaged and interested in their surroundings are also more autonomically reactive in general, and therefore more sensitive to the PNS side effects of nicotine.

It should also be noted that many of these results (including VAS responses concerning boredom and time perception) may be directly related to subject awareness of drug exposure. In other words, "something" was happening to these subjects, and they apparently knew it; this may have been intrinsically less boring than having nothing unusual to experience at all. However, the nine subjects who did not report significant nausea also failed to report significant autonomic changes on the POMS-like "autonomic response" subscale administered before and after each test session. In addition, subjects in Experiment #2, who were unable to accurately detect the presence or absence of drug, also reported significantly reduced boredom when given nicotine.

EXPERIMENT #4: NICOTINE EFFECTS ON MOTOR SEQUENCING AND THE EXOGENOUS ORIENTING OF ATTENTION

Introduction: Experiment #4

Experiment #4 was run concurrently with Experiment #3, and both were completed and analyzed in tandem. There were several findings from Experiment #3 that could have informed the design of Experiment #4 (including the use of more visual analog scales, and additional tasks examining boredom and time perception, especially the subjective estimates of 30 and 60 seconds). However, the focus of Experiment #4 was on three different predictions: one concerning the exogenous orienting of spatial attention, the second the effect of nicotine on DA-influenced motor task speed, and the last an examination of nicotine effects on auditory evoked potentials (AEPs).

The first prediction was referred to earlier as Prediction #2, and was tested in both Experiments 1 and 2. It suggested that nicotine, while failing to selectively enhance the top-down or endogenous orienting of spatial attention, would improve the bottom up or exogenous orienting of spatial attention driven by unpredictable, peripheral visual cues. This latter ability has been theoretically (Posner and Petersen 1990) and experimentally (e.g., (Rafal, Posner et al. 1988; Rafal and Robertson 1998)) linked to a posterior network of brain regions including the superior colliculus and the pulvinar nucleus of the thalamus, evolutionarily older structures containing a high density of nAChR's that exhibit maximal response to nicotine (Clarke, Schwartz et al. 1985; Decker, Brioni et al. 1995).

In Experiments #1 and #2, as predicted, subjects performing a covert orienting task using top down, endogenous cues failed to show any specific attentional improvement. There was no change in the validity effect (the RT difference between validly and invalidly cued targets), although subjects did respond more quickly (Experiment #1 and #2) or more accurately (Experiment #2) on nicotine than on placebo. Yet in Experiment #2, a covert orienting task with bottom up, exogenous cues failed to produce any validity effect in subjects, which made it impossible to examine drug influence over this particular measure of attentional performance.

The task involved in Experiment #2 was an adapted version of a letter discrimination task used by Parasuraman (1992) in a study of patients with Alzheimer's disease, and age-matched healthy controls. The automatic attentional process provoked by exogenous cues is thought to be fast-acting (Muller and Rabbitt 1989), so a short stimulus onset asynchrony (SOA, the time between cue and target appearance) is considered necessary to trigger a robust orienting response, and therefore a faster RT when the cue is valid (the validity effect). In contrast, longer SOAs are believed to induce a phenomenon known as "inhibition of return" (IOR), with paradoxically slower responses on valid trials versus invalid trials indicating a disinclination to return spatial attention to a recently attended site (e.g., (Posner, Cohen et al. 1982)). Neither a validity effect at the short SOA, nor an IOR at the long SOA, was evident in the data collected from the exogenous task used in Experiment #2.

Both validity at short SOAs and IOR at long SOAs have been demonstrated in previous studies (Posner, Cohen et al. 1982; Henderson 1991; Parasuraman, Greenwood et al. 1992); (Posner, Rafal et al. 1985), although not all (including (Berlucchi, Tassinari et al. 1989); (Tassinari and Berlucchi 1996); (Tanaka and Shimojo 1996); (Corbetta, Miezin et al. 1993); in addition, some labs have personally communicated difficulty in designing exogenous tasks capable of producing either validity or IOR). Yet their absence in Experiment #2 may have been due to a failure to include a fixation stimulus in the task, prior to the start of each trial, as a number of previous studies have done (e.g., (Henderson 1991; Parasuraman, Greenwood et al. 1992)). While eye movements were monitored throughout the experiment, and subjects did maintain fixation, their attention may have wandered around the monitor screen, and the time required to shift towards each peripheral cue may have varied accordingly. In addition, the absent fixation stimulus may have served a critical alerting role in these previous studies, providing a baseline level of cortical activation necessary for consistent exogenous orienting of attention on each trial during long cognitive tasks. Thus, in this experiment, the exogenous task used in Experiment #2 was adapted to include a fixation stimulus that remained on screen throughout each trial.

Experiment #4 was also used to test a preduction concerning the effect of nicotine on simple response speed. Nicotine promotes DA release (Wonnacott 1997), and DA release can affect the speed of movement (e.g., (Koob 1992)), so perhaps the RT improvements observed in the first three experiments are primarily due to a faster motor response on the button. Faster motor response could also be a consequence of generally increased alertness, or the increased effort expended on the tasks by less bored subjects taking nicotine. In Experiment #2, subjects were asked to tap back and forth on two response buttons as fast as they could, and no drug effect on their response speed was detected. Yet perhaps the tapping task used was too simple, and all subjects performed it at peak even on placebo days. In Experiment #4, a more complex finger tapping task was employed, in order to better challenge subjects, and perhaps reveal a nicotine effect on motor response speed.

One final prediction was tested in Experiment #4. When a series of paired auditory clicks are presented to normal subjects, auditory evoked potentials (AEPs) recorded after the second click often show habituation when compared to AEPs recorded in response to the first. This effect has been shown in both early AEP component waveforms (e.g., the P50, (Adler, Pachtman et al. 1982)), and in later, cognitive AEP waveforms known to be influenced by attention (e.g., (Lukas and Siegel 1977; Lutzenberger, Schandry et al. 1979; Wang, Timsit-Berthier et al. 1996)). In two studies involving rats (Acri, Grunberg et al. 1991; Acri, Morse et al. 1994), a low dose of nicotine increased both the acoustic startle response and pre-pulse inhibition of startle, indicating (according to the authors) an enhancement of pre-attentive auditory processing by the drug. Two other studies (Adler, Hoffer et al. 1992; Adler, Hoffer et al. 1993) have shown that nicotine normalizes deficient auditory gating, both in schizophrenics and in relatives of schizophrenics. The authors suggest that the nicotinic cholinergic system may contribute to the typically observed habituated response to repeated stimuli in normal subjects. If subjects are less bored, and more alert when given a nicotine patch, perhaps they are gating and responding cognitively to auditory stimuli more effectively, and will thus show greater habituation to the second of two paired auditory clicks than when bored and less alert after completing multiple cognitive tasks with only a placebo patch attached.

In order to reduce the occurrence of significant nausea in subjects, tasks were made shorter than in previous experiments, and the first task (a short, eight-minute, "practice" version of the exogenous orienting task) was delayed until 45 minutes after patch attachment, hopefully past any initially unpleasant autonomic reactions to the nicotine patch. In addition, EKG was recorded to monitor subject heart rate, to serve as a marker for nicotine exposure and as an early warning signal that might indicate when a subject was beginning to experience disagreeable side effects of the drug.

Methods: Experiment #4

Participants. Subjects were 13 non-smokers (8 female, 5 male) from OHSU and the general public. No subject had any history of regular tobacco use. Subjects were age 23 - 35 (average age of 28), and had, on average, 16 years of education. All subjects were right-handed. Each subject experienced both test conditions: nicotine and placebo control. Subjects were asked to avoid alcohol for 24 hours before each session, and caffeine for at least three hours prior to each session.

Drug. Nicotine was delivered by a 7mg transdermal patch (Nicoderm CQ, SmithKline Beecham) as described for Experiments 2 and 3.

Procedure. Subjects completed one practice and two experimental sessions at the same time of day. Experimental sessions were separated by at least two days, in order to assure complete nicotine elimination between sessions. In the practice session, subjects were asked to answer the 28 true/false questions on the Boredom Proneness Scale ((Farmer and Sundberg 1986)). They also practiced the same, fifteen-minute orienting of attention task using exogenous cues, and the same motor sequencing task that they subsequently performed on each test day. The two experimental sessions were identical except for the administered nicotine dose. A nicotine session involved application of one 7mg nicotine patch to the underside of the subject's upper arm (on the non-dominant side). One placebo patch (a square Band-Aid) was applied at the placebo control session. Drug condition was counterbalanced. Both subject and principal investigator were blind to the administered nicotine dose. Patches were applied and removed by a third person not directly involved in the study, and were covered by a colorful sticker.

The two experimental sessions proceeded as follows:

- 0:00 Nicotine patch application
- 0:05 Stanford sleepiness scale (SSS)
- 0:20 Attach EEG/EKG electrodes
- 0:45 Practice Exogenous Task
- 1:00 Motor sequencing task
- 1:20 Exogenous cueing task
- 1:40 Auditory evoked potential task
- 2:00 SSS

Exogenous Task. Forty five minutes after patch attachment, subjects practiced a short version of the orienting task with exogenous cues. At one hour and twenty minutes after patch attachment, they performed the full-length version of the task. Subjects sat 70cm in front of a color monitor in a dimly lit room, and maintained fixation at the center of the screen. A series of 192 target images (96 for the practice task) was presented with equal frequency 7 degrees to the left and right of fixation in three, approximately four-minute blocks, each period followed by a 1-minute rest. Each block contained 64 trials (32 trials for the practice task). Each trial began with the appearance of a fixation stimulus (a small plus sign) which remained on-screen by itself for 641ms before the appearance of the cue. Cue stimuli were on-screen for 85.5ms, target stimuli were on-screen for 114.25ms, and the cue-target interval (or stimulus onset asynchrony (SOA)) was either 128.52ms or 671.16ms, each 50% of the time. Following target presentation, the fixation stimulus remained onscreen for an additional 883.5ms, before vanishing for 1500ms until the next trial began. Stimulus sequence was randomized so that subjects could not predict the order from one experimental session to the next. Subjects pressed one of two buttons on a computer mouse in response to the presentation of a target letter; the left button in response to an "N," and the right button in response to an "A." Subjects were asked to respond as rapidly as possible without sacrificing accuracy. The cue was always an upward pointing arrow presented 7 degrees to the right or left of fixation (50% of the time in each direction). Exogenous cues did not predict the subsequent target location; 50% of the time they were correct, 50% of the time they were incorrect. Both cues and targets were black on a white background. Target letters subtended a visual angle of 1 degree, while the exogenous cue subtended an angle of 0.3 degrees. The exogenous cue was smaller because a previous study suggested that smaller cue stimuli draw attention to more circumscribed spatial locations, instead of attracting attention to a wider region that could include both target locations (Henderson 1991).

EEG/EKG Recording. In order to record auditory evoked potentials, five gold EEG electrodes were attached to each subject, according to the International 10 - 20 System (Daly and Pedley 1990), at the following scalp sites: Cz, Pz, Oz, and linked mastoids. All sites were referenced to linked mastoids. Four additional electrodes were attached above and below one eye and over each lateral canthus to record EOG, in order to exclude artifact in EEG acquisition. To monitor heart rate during the experiment, EKG electrodes were also attached. Heart rate was recorded during subject performance of the main exogenous task, at 80 minutes after application of the patch. Electrode impedance was kept below 3000 ohms, and calibration was performed using 100μV sine waves. The analog filter range was 0.3 to 70 Hz, amplitude step size for digitization was 0.1μV, and the digital sampling rate was 256 per second.

Motor Sequencing Task. One hour after patch attachment, subjects were presented with an Apple keyboard, and asked to make one of two key press responses depending on which of two letters appeared on a computer monitor screen. The task was one used in a previous study of estrogen effects on motor sequencing (Jennings, Janowsky et al. 1998). When subjects saw the letter “H,” they were asked to press the following keys in order: “312”; when they saw the letter “T,” they pressed “132.” Subjects were asked to respond as rapidly as possible without sacrificing accuracy. The task consisted of ten blocks of 18 trials each, with one additional 18-item practice block at the beginning (responses from the practice block were discarded). The order of letter presentation was randomized, and there were an equal number of H's and T's. Subjects received feedback ("Correct" or "Incorrect") after each trial, and again after each block (% correct). The reaction time for each key press was recorded.

Auditory Evoked Potential Task. Two hours after patch attachment, each subject was seated comfortably in a reclining chair with their eyes closed, and headphones were placed over their ears. The auditory threshold for each ear was determined by stepping up the decibel level of a square wave click in 5dB increments, and subsequent stimuli were presented at 40dB above threshold for each ear. Each subject was then asked to relax while approximately 50 click pairs were delivered binaurally through the headphones. Each click was presented for 20ms (click bandwidth was 20-12,000Hz), with a 500ms interstimulus interval between clicks, while 3.5 seconds separated each click pair. EEG was recorded from Fz, Cz and Pz with a linked mastoids reference, and EOG was monitored to exclude movement artifact (recordings with excessive artifact were discarded during the task). After 50 artifact-free recordings were obtained, subjects were exposed to a second series of 50 click pairs, and EEG was again recorded.

Subjective Mood Measures. The Stanford Sleepiness Scale (SSS) (Hoddes, Zarcone et al. 1973) was administered to subjects upon arrival at each experimental session (prior to nicotine patch attachment), and after performance of all tasks. This task was used in order to examine and confirm nicotine effects on subjective levels of alertness. Subjects were also asked at the end of each test session whether they believed they had received nicotine.

Analysis. In all cases, ANOVA with repeated measures was performed, after determining that all assumptions of ANOVA were met. To address nicotine's behavioral effects on automatic orienting of attention, a repeated measures ANOVA was performed on RTs across drug condition (0, 7mg), and trial type (valid, invalid) in the exogenous task, looking for evidence of faster RTs with specific effects on validity in both the practice and experimental versions of the task . To examine nicotine effects on motor sequencing, a repeated measures ANOVA on keypress RTs across drug condition was performed. To address nicotine's effects on subjective measures of alertness, an ANOVA on SSS scores across drug condition was performed. In addition, the Mann-Whitney U Test was used to determine whether drug condition affected subject responses about boredom, euphoria, difficulty with task, increased or decreased heart rate, nausea, dizziness, physical illness, ability to concentrate, and whether or not they received drug.

Results: Experiment #4

Participants. Of the 13 subjects tested in Experiment 3, only one was dropped from the study after experiencing some nausea and dizziness during recording of auditory evoked potentials on their first test day. No other subject experienced nausea, or was dropped from the study for any other reason. The one subject who experienced nausea had a low boredom proneness scale score (3); however, two subjects who did not report any nausea had the same or a lower score (2) on the BPS.

Exogenous Task. Unlike the exogenous task used in Experiment #2, this task did produce a within subjects validity effect, but only for subjects responding to valid and invalid cues during the short practice task (45 minutes post-patch), and only when those same subjects received nicotine. RTs were faster on valid rather than invalid trials at the fast SOA in the practice task on the nicotine day only (F(1,11) = 6.99, p = 0.023). There was no significant effect of validity at the longer SOA in either task. Results are presented in Figure 19.

In terms of drug effects on task error rate, there was a within subjects trend towards reduced errors with nicotine in the practice task at 45 minutes post-patch (F(1,11) = 4.63, p = 0.054). However, nicotine significantly reduced the number of errors within subjects in the main exogenous task at 80 minutes after patching (F(1,11) = 25, p = 0.000). Results are presented in Figure 20.

Heart Rate. Nicotine significantly increased heart rate, recorded while subjects performed the main exogenous task (80 minutes post-patch, F(1,11) = 63.69, p = 0.000).

Motor Sequencing Task. There were no significant drug effects on motor RTs or error rates in the complex motor sequencing task.

Auditory Evoked Potentials. To examine drug effects on AEPs, the P1 (the highest positive peak at approximately 80 – 110ms after click presentation) and the N1 (the highest negative peak at 125 – 150ms post-click) were cursored using a Cadwell EP recording machine. EPs were cursored after both the first and second click on the average of both the first and second series of fifty click pairs. Seven of the twelve AEP waveform pairs (from placebo and nicotine test days) included too much noise to be accurately read; in three cases there were no discernable waveforms on at least one of the two recordings. However, AEPs from the remaining five subjects were clear and detectable. A three way within subjects ANOVA across drug condition, series (first versus second), and order (first versus second click in each click pair) revealed a significant main effect of order ($F(1,4) = 9.33$, $p = 0.038$), with the amplitude of the first P1/N1 response decreasing to the second click in the pair. There was no significant drug by order interaction ($F(1,4) = 2.74$, $p = 0.173$), or drug by series interaction ($F(1,4) = 1.2$, $p = 0.334$) in this small group of five subjects; however there was a significant series by order interaction, with the P1/N1 response to the first click declining from the first to the second series of 50 click pairs ($F(1,4) = 8.01$, $p = 0.047$).

Further posthoc analyses separately examined AEPs from placebo and nicotine test days. On placebo days, the difference between P1 and N1 amplitudes recorded in response to the first click in the first series of 50 click pairs (mean of 16.916 millivolts (mv), SD = 7.931) was significantly higher than the P1/N1 difference recorded in response to the second click (mean of 7.818mv, SD = 2.882) (within subjects, $F(1,4) = 13.53$, $p = 0.021$). This was also true for the P1/N1 difference derived from AEP responses to the second series of 50 click pairs (first click mean of 14.282mv, SD = 9.289; second click mean of 9.096, SD = 6.035) (F(1,4) = 11.62, p = 0.027). In addition, there was a near significant within subjects decline in the P1/N1 difference from the first click in the first series to the first click in the second series, also on placebo days (F(1,4) = 7.32, p = 0.054). However, there was no significant difference between the P1/N1 response to the second click in the first series and the second click in the second series (F(1,4) = 0.73, p = 0.441).

On nicotine test days, in contrast, there was a different pattern of response. The difference between P1 and N1 amplitudes recorded in response to the first click in the first series of 50 click pairs (mean of 13.032mv, SD = 5.791) was almost significantly higher than the P1/N1 difference recorded in response to the second click (mean of 8.232mv, SD = 3.159) (F(1,4) = 6.79, p = 0.06), although (unlike placebo day results) the response to the first click (mean of 13.104, SD = 7.041) was not significantly higher than the response to the second click (mean of 9.092, SD = 2.33) in the second series of click pairs (F(1,4) = 2.38, p = 0.198). Also unlike results from placebo days, there was no near significant within subjects decline in the P1/N1 difference from the first click in the first series (13.032, SD = 5.791) to the first click in the second series (13.104, SD = 7.041); in fact they were nearly identical (F(1,4) = 0.01, p = 0.919). Yet mirroring results from placebo, there was no significant difference between the response to the second click in the first series and the second click in the second series (F(1,4) = 0.76, p = 0.433).

Subjective Mood Measures. A within subjects ANOVA of SSS scores with two factors (drug condition, and pre- versus post-drug administration) revealed no significant effect of drug condition (F(1,11) = 4.07, p = 0.069). However, there was a significant effect of pre-drug versus post-drug testing (F(1,11) = 12.67, p = 0.004), and a significant drug condition by pre/post interaction (F(1,11) = 9.27, p = 0.011). A within subjects ANOVA of baseline pre-drug SSS scores (from tests administered before cognitive testing) revealed no differences among subjects regardless of drug condition (F(1,11) = 0.8, p = 0.389). However, post-session SSS scores were significantly higher (indicating less alertness) when subjects received a placebo patch (F(1,11) = 12.57, p = 0.005). In contrast, subjects on nicotine showed no decline in alertness as reflected by no change in response on the SSS (F(1,11) = 0.31, p = 0.586). In addition, a within subjects ANOVA analyzing the difference scores (post-drug minus pre-drug) across drug condition also revealed a significant effect of nicotine (F(1,11) = 9.27, p = 0.011).

Discussion: Experiment #4

Once again, nicotine produced an improvement in subjective measures of alertness compared with the effects of placebo. This is the fourth experiment in which Stanford Sleepiness Scale results reflected either maintenance or improvement in alertness with nicotine, as opposed to a reduction in alertness with placebo. Combined with similar indications of enhanced alertness from earlier experiments (including POMS results from Experiments #2 and #3, and EEG results from Experiment #1), this appears to be a consistent effect of the drug, at least in non-smoking subjects not suffering from adverse autonomic side effects such as nausea. Perhaps alertness is enhanced because of nicotine action at nAChR's found on largely non-specific projections from nuclei in the brainstem and basal forebrain, whose activity is linked to alertness level.

Once again, nicotine produced within subject performance improvements in a covert orienting task, this time reflected by a significantly reduced error rate on drug compared to placebo. Improvements in past experiments have included both reduced error rates and faster RTs. These improvement (particularly the RT improvements) do not appear to be a result of faster motor response with drug, since there were no significant nicotine effects on performance of a motor sequencing task in this experiment, or in a simple finger tapping task administered in Experiment #2.

The covert orienting task used in this experiment, which involved peripheral, non-predictive exogenous cue stimuli, was unlike the task used in Experiment #2, as it did produce a significant validity effect at the fast (128ms) SOA. Yet this effect was only observed when smokers given nicotine engaged in the practice task at 45 minutes post-patch. In stark contrast, no validity effect was observed in either the longer main task given at 80 minutes post-patch, nor in the practice task when the subjects did not receive drug. A closer examination of the data reveals that eight out of twelve subjects who performed the practice task on the nicotine test day showed a validity effect ranging from 5 to 37ms; the remaining four had faster responses on the invalid trials (inhibition, rather than facilitation, by the valid cue) which ranged from –7 to –37ms. Given the complete lack of validity in three other performances of this same task, and the fact that validity results from four subjects range as high in the negative direction (-37ms) as results from the other eight subjects range in the positive direction (37ms), perhaps this one significant example of validity is an anomalous result.

A fixation stimulus, which was hypothesized to perhaps prevent attention from wandering at the start of each trial, or to stimulate a brief but necessary "alerting" effect on cortical orienting networks before cue and target presentation, has been used in studies reporting successful exogenous task validity effects in the past (including (Henderson 1991; Parasuraman, Greenwood et al. 1992)). However, the use of a fixation stimulus did not provoke a consistent validity effect in this experiment.

In addition, as in Experiment #2, the task used in this experiment did not produce a significant inhibition of return (IOR), the tendency for RTs to validly cued targets to be longer than RTs to invalidly cued targets at longer SOAs. The phenomenon of IOR was first proposed by Posner and Cohen (Posner and Cohen 1984), and is thought to reflect the active inhibition of attention to a spatial location recently indicated by an exogenous cue. At short SOAs, spatial attention remains focused on a validly cued site when the target appears, so responses are facilitated and a validity effect results. However, at longer SOAs, attention is believed to have left the cued location by the time the target appears, and an innate inhibition of return to a recently examined site then slows down responses to valid versus invalid targets. The behavioral function of IOR is hypothesized as a bias towards novel stimuli (Posner, Rafal et al. 1985). The "crossover" point from cue facilitation (the validity effect) to inhibition (IOR) appeared to occur around 225ms in the Posner & Cohen study (reviewed in (Klein 2000)). Studies examining effects of task difficulty on the point where IOR appears (including (Lupianez and al 1997; Briand and al 1998)), indicate that increasing attentional demands increase the length of SOA needed to show IOR, with some particularly difficult discrimination tasks lengthening the required SOA to 600ms. In this experiment, there was no IOR exhibited by subjects performing a letter discrimination task at the long SOA of 671ms. Perhaps this SOA was not long enough to produce a significant IOR in Experiment #2 and #4. Yet the task was not exceedingly difficult (RTs were in the 320 – 500ms range), and several other researchers have failed to report IOR, both in the literature (e.g., (Berlucchi, Tassinari et al. 1989); (Tassinari and Berlucchi 1996); (Tanaka and Shimojo 1996); (Corbetta, Miezin et al. 1993)), and in unpublished personal communication.

A recent study (Maruff, Yucel et al. 1999) suggested that facilitation of exogenous orienting by valid exogenous cues at short SOAs (a validity effect) only occurs when the cue and target temporally overlap; that is, when the cue remains on-screen until after the target has been present for at least 75ms. The authors found this to be the case in several studies of exogenous cueing that reported facilitation (including Posner (1984), Maylor and Hockey (1987)). (The authors also found that the presence of IOR at longer SOAs depended on cues and targets that did *not* temporally overlap). If these rather specific conditions for producing validity in exogenous tasks were not established in some earlier studies of exogenous orienting (including (Berlucchi, Tassinari et al. 1989; Tanaka and Shimojo 1996; Tassinari and Berlucchi 1996); this experiment and Experiment #2), facilitation was not observed; in fact, an IOR was often reported at these shorter SOAs.

In this experiment and in Experiment #2, cues were visible for 85ms, and then vanished for 42ms before the target appeared, for a total SOA of 128ms. Thus, cue offset before target presentation may have prevented facilitation of target detection by valid cues, as no difference between valid and invalid trials was observed at the short SOA in either experiment. The offset was included in Experiment #2 in order to match the parameters of the endogenous cueing task, and many successful endogenous cueing tasks (including the task used in Experiment #1) incorporate a break between cue and target. There was no a priori reason to remove this break for the exogenous cueing task, as no hypothesis in the relevant literature suggests that attention drawn by non-predictive, peripheral cues will be inhibited by a brief interval between cue and target. However, in light of these results and the recent paper by (Maruff, Yucel et al. 1999), the removal of a cue before target presentation, even for a brief period, apparently influences exogenous orienting to targets, abolishing any validity effect (or, in some cases, provoking an IOR) at short SOAs. Why this would occur is unclear, and likely requires further study.

One hypothesis in this study was that nicotine would enhance covert orienting in a task that used purely exogenous (non-predictive, peripherally presented) visual cues, because of the greater density of high affinity nAChR's in brain regions thought to compose the relevant attention network, including superior colliculus and thalamus (e.g., (Posner 1980; Clarke, Schwartz et al. 1985; Posner and Petersen 1990)). The failure to show consistent validity effects at the fast SOA, or IOR at the long SOA, makes it impossible, as with results from the task used in Experiment #2, to examine drug effects on this particular measure of attentional orienting. Whether reported nicotine facilitation of performance on tasks combining elements of endogenous and exogenous orienting is specifically due to the exogenous components is not a question that can be answered given the absence of an attentional measure in this task.

While there was no significant drug effect on AEP amplitudes in response to two consecutive series of 50 click pairs each, the number of waveforms available for analysis was limited, as only five subjects produced consistently clean recordings on both placebo and nicotine test days. This undoubtedly limited the power of the analysis. Nevertheless, the paradigm did provoke a significant decrement in averaged P1/N1 difference from the first click to the second in a click pair. This is the first demonstration of a P1/N1 amplitude decrement with a 3.5 second interval between click pair presentations; previous studies examining auditory habituation have used inter-trial intervals of at least ten seconds (e.g., (Adler, Hoffer et al. 1992)). Interestingly, there was a significant order (within a click pair) by series (first versus second series of 50 click pairs) interaction, apparently due to a decline in the amplitude of response to the first click in the second series when compared to the first click in the first series. However, post-hoc analyses indicated that subjects on nicotine did not show this habituation; the effect appears limited to amplitudes recorded on placebo days.

It is tempting to suggest that nicotine might prevent amplitude habituation from the first to the second series of click pairs, because engagement in the task is maintained with drug. Yet this particular AEP paradigm (specifically, two sets of 50 click pairs with only 3.5 seconds between each pair) has not been used experimentally before, and it is difficult to interpret data from only five subjects. One previous study (Polich, Aung et al. 1988) reported no change in P1 or N1 amplitude with presentations of 50dB SPL 1000Hz tones three seconds apart. However, as noted, that study did not use the same click pair protocol as in Experiment #4, and changes in the number and character of stimuli can influence the amplitude of various AEP components (Polich, Aung et al. 1988), and perhaps their tendency to habituate (e.g., Experiment #4 used clicks, not tones, presented at 40 dB SPL above threshold, much louder than the 50 dB SPL used in Polich (1988)). More study is probably warranted, using a larger sample size.

CONCLUSIONS

Randy Wykoff, a member of the US Food & Drug Administration committee organized to attempt the government regulation of nicotine as a controlled substance, has explained why this drug is considered by most scientists to be powerfully addictive. David Kessler, the former FDA Commissioner, writes in his book, A Question of Intent, that Wykoff rattled off the following statistics at a "tobacco team" meeting in 1994: "There are forty nine million smokers in the United States…Three fourths of them say they are addicted and two thirds of them say they want to quit. Seventeen million smokers try to quit every year but more than ninety percent of them fail." Wykoff went on to note, according to Kessler, that "after surgery for lung cancer, nearly fifty percent of those who survive resume smoking. Even when a smoker's larynx is removed, forty percent start smoking again" ((Kessler 2001), p. 120). Without question, and despite infamous tobacco industry claims to the contrary, nicotine is a strongly addictive compound. Something, perhaps several things, relating to how this drug affects the brain, encourages its continued use despite potent arguments and efforts to give it up.

One of these effects is undoubtedly nicotine-provoked release of DA. Nicotine can produce a euphoria similar to that engendered by other addictive drugs, including cocaine and d-amphetamine (Henningfield, Miyasato et al. 1985), which also increase DA concentrations in the nucleus accumbens and other targets of the medial forebrain bundle (Dani and Heinemann 1996); (Koob 1992). However, it has been argued that this euphoria may not be sufficient for maintaining addiction in human smokers, but that nicotine may improve certain cognitive functions, and that these improvements may also contribute to its continued use (Stolerman 1991). Some researchers, for example, (e.g., (Witte, Davidson et al. 1997; Phillips, McAlonan et al. 2000)) have suggested that nicotine selectively enhances the covert orienting of visuospatial attention. In addition, nicotine causes the release of modulatory neurotransmitters, including ACh and NE (Clarke and Pert 1985; Clarke, Schwartz et al. 1985; Wonnacott 1997), and thus potentially promotes alertness. It may also alter subjective experiences theoretically associated with alertness, including boredom and the perception of time passage. Nicotine effects on these "other" cognitive functions (i.e., those distinct from DA-linked euphoria), including alertness, attention, boredom and time perception, were examined during the course of this work. Four conclusions are summarized below:

1. Nicotine improves or maintains alertness in non-smokers.

"Alertness" is the sustained activation of cerebral cortex that non-specifically influences cognitive performance, and it typically ranges from full wakefulness to deep, slow-wave stages of sleep (Oken and Salinsky 1992). Alertness in both animals and humans is related to the activity of neuronal pathways originating in the brainstem, hypothalamus and basal forebrain that each primarily release one "classical" neurotransmitter in thalamus and/or cortex in a largely non-specific manner (Clark, Geffen et al. 1987; Foote 1987; McCormick 1989; Oken and Salinsky 1992). Since presynaptic nicotinic receptors are present on these ascending neurotransmitter-specific pathways to thalamus and cortex, and since nicotine action at these receptors promotes the release of RAS modulatory neurotransmitters (Clarke and Pert 1985; Clarke, Schwartz et al. 1985; Wonnacott 1997), it was hypothesized that nicotine has a general "alerting" effect in non-smokers.

In these four experiments, there was consistently strong evidence that nicotine improved or maintained subject alertness, while the same subjects were always comparatively less alert without drug. Subjects on nicotine in Experiment #1 exhibited greater median power frequency and peak alpha power in their EEG when compared to their own results on placebo, and a declining number of sleep epochs with increasing doses of drug. In addition, in all four experiments, Stanford Sleepiness Scale results reflected either maintenance (Experiments #2, #3, #4) or improvement (Experiment #1) in alertness with nicotine, as opposed to a consistent reduction in alertness with placebo. In Experiments #2 and #3, subjects on nicotine exhibited selectively increased vigor on the Profile of Mood States questionnaire (i.e., with no increase in other POMS measures), as was previously reported by (Levin, Conners et al. 1998). In Experiment #3, eight out of nine subjects not experiencing nausea who marked a visual analog scale after completing a long, boring task indicated that they had a higher "energy level" when they were given a nicotine patch, rather than a patch without drug.

In addition, subjects on nicotine demonstrated non-specific improvement in a number of cognitive tasks. As increasing alertness is known to produce non-specific enhancement of cognitive function (e.g., (Oken and Salinsky 1992)), these improvements are also probably related to the greater alertness of subjects on drug. In Experiments #1, #2, and #3, subjects performing a covert orienting task using endogenous cue stimuli were significantly faster when on nicotine than on placebo. In Experiments #2 and #4, subjects performed orienting tasks with fewer errors when taking nicotine than when taking placebo. In no case did these subjects exhibit a selective enhancement of visuospatial attention; only non-specific improvement most likely related to their higher level of alertness on drug.

Subjectively (SSS, POMS, VAS), and objectively (EEG, task performance), non-smoking subjects were more alert on nicotine than on placebo. Taken together, nicotine does appear to consistently promote alertness in non-smokers.

2. Nicotine has no specific effect on the endogenous covert orienting of spatial attention in non-smokers.

Covert orienting of spatial attention is the ability to concentrate visual attention on a particular spatial location, without moving the eyes, thus enhancing stimulus processing in that spatial location relative to others. In a covert orienting task, visual attention may be shifted in a "top down" or endogenous fashion if the cue used is meaningful, and provides predictive information about where a target stimulus will later appear. In contrast, attention shifted in an exogenous or "bottom up" fashion involves the appearance of a cue stimulus in the periphery, one that does not predict subsequent target appearance yet draws attention because its sudden emergence provokes an orienting response (e.g., (Posner and Petersen 1990; Oken and Salinsky 1992)). Michael Posner has argued (1980, 1990, 1998) that these two functionally distinct aspects of visuospatial attention can be attributed to two anatomically distinct attentional networks.

Attentional improvement in covert orienting tasks is often indexed by a reduction in the validity effect (RTs to invalidly cued targets - RTs to valid targets). Nicotine influence on covert orienting has been assessed in three recent studies, two involving humans and/or primates (Witte, Davidson et al. 1997; Murphy and Klein 1998), and one involving rats (Phillips, McAlonan et al. 2000). In all cases, nicotine reduced the validity effect, selectively decreasing RTs to invalidly cued targets, indicating a specific drug action on the ability to shift attention from an incorrectly cued location to the actual target location. However, only one experiment (Phillips, McAlonan et al. 2000), used cues that were purely exogenous (both non-predictive and peripheral), while others had task elements that potentially engaged both exogenous and endogenous attentional systems (i.e., the use of peripheral, exogenous cues that were also endogenously predictive). Therefore, it was hypothesized that nicotine would selectively enhance the covert orienting of spatial attention in non-smokers in a purely exogenous, but not in a purely endogenous, cueing task, due to the greater density of nAChR's with high affinity for nicotine in brain regions associated with the exogenous attentional network (e.g., (Clarke, Schwartz et al. 1985; Posner and Petersen 1990); (Posner and Petersen 1990)).

These experiments found, as predicted, no support for a selective nicotine effect on the endogenous orienting of spatial attention. In Experiments #1, #2, and #3, subjects performing three separate orienting tasks with endogenous cues showed no reduction in the validity effect, although they did respond more quickly (Experiment #1, #2, and #3) and/or more accurately (Experiment #2) with nicotine than with placebo. However, these non-specific performance improvements, likely related to drug enhancement of alertness, did reveal a dependency on time. Subjects with faster RTs on nicotine in Experiment #2 performed the endogenous task at 75 minutes after patching. In Experiment #1, subjects began the endogenous task at 90 minutes after receiving the patch, and also exhibited faster RTs. In Experiment #3, subjects showed faster RTs on an endogenous task begun at 30 minutes post-patch. Yet subjects who began a similar task at 115 minutes after patching (in Experiment #2) did not show nicotine facilitation of RT. These subjects also performed that task after completing an exogenously cued task, and perhaps the differing cue validities (chance in exogenous task, 80% in the endogenous) affected performance, by altering subject expectancy concerning the usefulness of the valid cue. Notably, Levin (1998) reported increased performance in non-smokers on Conner's Continuous Performance Task (CPT), a task requiring subjects to press a button when they see a target stimulus and withhold a response when they see a non-target stimulus, at a full three hours and ten minutes after an identical 7mg nicotine patch was attached. Yet the CPT does not require spatial attention, as all stimuli are presented in the same location. Perhaps nicotine loses its ability to enhance spatial attention tasks earlier (between 90 and 115 minutes), or perhaps subjects on placebo are less alert at three hours after patching compared to those on nicotine, and this lack of alertness, not reduced attentional performance, is responsible for the results on the CPT.

In contrast to results from the endogenous orienting tasks, two attempts to design an effective exogenous orienting task failed to produce either a validity effect, or an inhibition of return (IOR), two cardinal measures of attention previously examined in such tasks. In both Experiment #2 and Experiment #4, no consistent attentional effects were observed, although subjects did show non-specific improvement on the task in Experiment #4 with nicotine (a reduced number of errors, once again likely related to an increase in alertness with drug). However, a recent study (Maruff, Yucel et al. 1999) suggests that facilitation of exogenous orienting by valid cues at short SOAs (the validity effect) only occurs under rather specific conditions. Studies that followed these conditions (in particular, the temporal overlap of cue and target stimuli) (e.g., (Posner and Cohen 1984; Maylor and Hockey 1987)) reported validity, while those that did not (e.g., these experiments, (Berlucchi, Tassinari et al. 1989; Tanaka and Shimojo 1996; Tassinari and Berlucchi 1996)), failed to provoke it. Yet there is no clear theoretical reason why temporal overlap of cue and target stimuli, for example, is required to show validity, given that the exogenous attentional network is thought to respond to sudden, non-predictive peripheral stimuli with a shifting of spatial attention (and subsequent better processing of targets) to the cued location. Further research on why cue offset prevents a validity effect is probably in order.

Nevertheless, the lack of consistent validity renders analysis of drug effects on this important attentional measure in these particular exogenous tasks impossible. While nicotine has no apparent effect on the endogenous orienting of spatial attention (other than a general, non-specific enhancement of task performance), it is not clear whether the drug will selectively enhance orienting in a task with purely exogenous cues.

3. Nicotine reduces the subjective experience of boredom in non-smokers, and makes boring tasks seem to go faster.

In "Traffic," Steven Soderbergh's 2000 movie about the United States' "war" on drugs, the man just appointed the national drug czar, played by the actor Michael Douglas, tries to explain his regular consumption of alcohol. Writes Stephen Holden in a review of the movie in *The New York Times* (Wednesday, 12/27/00), "Waging a war against drugs isn't just a matter of combating corruption but of eradicating the basic human desire to 'take the edge off,' Mr. Douglas' character, Robert Wakefield, says in defense of his nightly drink of Scotch. 'Otherwise I'd be dying of boredom.'"

Boredom, a disagreeable, but usually temporary loss of interest or engagement in one's surroundings, is a significant risk factor for drug abuse (Samuels and Samuels 1974;

Leong and Schneller 1993), including the abuse of cigarettes (e.g., (Tuakli, Smith et al. 1990; Sarramon, Verdoux et al. 1999)). Nicotine has previously been alleged to relieve boredom, but primarily through literary or other artistic endeavors. For example, Jules LaForgue, a French poet credited with creating free verse (Benet 1996), actually wrote an ode to cigarettes in 1861, that begins with the words, "Yes, this world is flat and boring: as for the other, bullshit! I myself go resigned to my fate, without hope, And to kill time while awaiting death, I smoke slender cigarettes, thumbing my nose at the gods" ("La Cigarette," reprinted in (Klein 1993)). However, the ability of nicotine to alleviate the flatness and boredom of this world (or its potential to kill or at least quicken the perception of time passage) has not been systematically investigated in non-smoking subjects before.

In Experiment #2, subjects given an opportunity to "rate" their level of boredom on a five point scale reported significantly more boredom with the experimental tasks when on a placebo patch than when on a nicotine patch. These same subjects were unable to correctly report whether they'd been exposed to a nicotine or placebo patch, so these results were not directly related to conscious awareness of drug exposure. In Experiment #3, non-nauseated subjects who placed marks along a visual analog scale (VAS) representing their current level of boredom following completion of a deliberately long and boring chore, consistently indicated that they felt more bored when they received placebo than when they received nicotine. In addition, most of these same subjects (eight out of nine) reported higher levels of energy on a second VAS when given nicotine than when exposed to a placebo patch. Nicotine also reduced the subjective assessment of boredom, and increased the assessment of engagement in results from POMS-like subscales administered in Experiment #3, with subjects reporting the opposite effects without drug. And finally, the non-specific improvements in performance on a number of orienting tasks (including faster RTs and reduced error rates) may have been related to less bored, more engaged subjects expending somewhat greater effort on the tasks.

A previous study (Watt 1991) found that subjects who were highly boredom prone (i.e., had high BPS scores) tended to subjectively report a slowed passage of time, while those with less boredom proneness though that time passed faster. However, all subjects were able to accurately report the more objective, chronometric passage of time. Since nicotine relieves boredom in non-smokers (at least those who don't feel nausea), it was predicted that this would translate into a faster subjective appraisal of the time it took to complete the boring task, and this is exactly what was found in Experiment #3. Subjects asked to rate their subjective sense of how long the boring task took estimated a faster experience after receiving nicotine than after a placebo patch. In contrast, there was no significant difference between estimates of the number of minutes this task took dependent on drug condition. However, this may be due to the design of the experiment, which used the same task (with different stimulus order, but identical length) on each test day. Many subjects recognized that the task took the same amount of time each day, but specifically indicated that nicotine made the task pass at a subjectively faster rate.

The experience of boredom has been theoretically linked to low alertness (Zuckerman 1969; DeChenne 1988), with subjects below their "optimal" level of arousal or alertness thought to suffer greater degrees of tedium and ennui. Nicotine appears, at least subjectively, and in non-smokers who do not develop nausea, to maintain both alertness and energy, increase engagement, make uninteresting, repetitive tasks go faster, and generally reduce the experience of boredom explicitly induced by a long, monotonous task.

4. Nicotine can improve alertness and relieve boredom in non-smokers, but only if the autonomic effects are small. Nausea is a particular concern.

Despite a clear withdrawal syndrome (Stolerman and Jarvis 1995), many human studies of nicotine effects on cognition have examined smokers who had abstained from cigarettes for anywhere from 12 to 24 hours before each experiment (including (Peeke and Peeke 1984; Warburton, Wesnes et al. 1986; Hasenfratz, Michel et al. 1989; Warburton, Rusted et al. 1992; Witte, Davidson et al. 1997)), and in whom withdrawal relief might underlie their apparently enhanced cognitive performance (West 1993). However, by working with subjects tolerant to the autonomic side effects of nicotine, these researchers certainly avoided the confound of unpleasant experiences like nausea interfering with task performance and subjective assessment of drug effects. In addition to its actions at CNS receptors, nicotine is also a ganglionic nicotinic cholinergic agonist in the peripheral nervous system. Stimulation of both sympathetic ganglia and the adrenal medulla increases heart rate, blood pressure, stroke volume and cardiac output (LeHouezec and Benowitz 1991), and nicotine also increases the tone and motility of the gastrointestinal tract (1997). This latter effect, in combination with direct nicotine stimulation of the medullary chemoreceptor region in the brainstem, and GI afferent inputs in the vagus nerve, can produce significant nausea in naïve subjects (1997). As noted earlier, a common "rite of passage" for new smokers is apparently overcoming the queasiness and dizziness associated with those first few cigarettes (Kluger 1996).

Nausea was a constant concern in these investigations. In Experiment #1, seven out of 17 subjects experienced significant nausea (although two completed all experimental tasks before reporting any ill effects), and five were dropped from the study. In Experiment #3, eight of 19 subjects experienced nausea at some point in response to nicotine; four were dropped from that study. Three more who experienced nausea during testing in Experiment #3 reported more boredom (two of three), less energy (three of three) and a longer task experience (three of three) while on drug - the opposite of what subjects who did not experience noticeable autonomic side effects reported with nicotine.

However, not every experiment provoked nausea, and a number of factors appear to influence whether unpleasant autonomic side effects occur in response to a nicotine patch. In Experiment #1, four of the five subjects who experienced nausea severe enough to exclude their further participation reported having smoked regularly in the past, all more than three years prior to this study. Perhaps some compensatory recovery from the tolerance they had presumably established to the autonomic side effects of nicotine during their earlier years of smoking led to a much more extreme autonomic response when nicotine exposure was resumed. This is similar to the classical conditioning phenomenon of reinstatement, in which habituation to a previously common stimulus suddenly reverses with new presentation of the stimulus at a later point in time. Dose also likely plays a role in this phenomenon, since subjects given the high dose, 14mg patch in Experiment #1 were all aware of various autonomic side effects of the drug, including dizziness and rapid heart rate. However, due to the procedural design of that experiment, subjects were always given the lower, 7mg dose before the high dose. Four of the five who experienced nausea did so with the 7mg patch, and thus were never exposed to the higher dose nicotine patch.

An attempt to reduce the occurrence of nausea in Experiment #2 by recruiting subjects without any history of smoking was apparently successful in that all twelve participants completed the study, with only one reporting the onset of nausea after all experimental data had been collected. However, despite similar recruitment criteria in Experiment #3, eight of 19 subjects experienced nausea. Perhaps this increased incidence of unpleasant autonomic excitability has to do with when the tasks were administered. In Experiment #2, subjects performed the first of two, 25-minute orienting tasks at 75 minutes following patch attachment, possibly after the initial autonomic effects (brief nausea, increased heart rate, etcetera) had subsided. During the first hour of Experiment #2, subjects were often distracted by conversation and interaction with the experimenter, as electrodes were attached to the scalp. In contrast, the naïve non-smokers in Experiment #3 were required to begin an even longer, 35-minute orienting task only 30 minutes after patch attachment, with nothing but task demands to distract them from any unsettling autonomic effects of nicotine. This may partly explain the much higher incidence of nausea in Experiment #3, as well as the tendency for subjects to guess correctly when they were on drug.

Curiously, those subjects reporting lower BPS scores (indicating that they were rarely bored) were the subjects most likely to experience nausea in response to nicotine. The average BPS score for subjects who developed nausea was 2.875 (SD = 1.89), while subjects who did not feel nauseous reported an average score of 8.4 (SD = 1.45), and the difference was statistically significant. Perhaps those individuals who think of themselves as (or who are) always involved, engaged and alert to their surroundings are more autonomically reactive in general. In addition, the population of non-smokers studied in Experiment #3 had an average BPS score significantly lower (5.9, SD = 3.28) than the sample of 154 undergraduates surveyed at Laurentian University by (Ahmed 1990). For the Laurentian undergraduates, the mean BPS score was 11.01 for men (SD = 4.21), and 10.91 for women (SD = 4.21). Perhaps smokers, who were excluded from this study, tend to have higher BPS scores in general, indicating a greater tendency to experience boredom, and their absence from this subject pool skewed BPS results lower. Notably, boredom is a risk factor for drug abuse (Samuels and Samuels 1974; Leong and Schneller 1993), including the abuse of cigarettes (e.g., (Tuakli, Smith et al. 1990; Sarramon, Verdoux et al. 1999)).

In pilot testing for Experiment #1 (results not reported in this work), several of the subjects who experienced nausea registered high “mood disturbance scores” on a POMS questionnaire administered before patching or testing began. Subjects reporting nausea in pilot tests were also more likely to have high scores on the SSS, indicating less alertness (and probably some recent lack of sleep). It is possible that individuals under stress, or who are suffering from low alertness or sleeplessness, are more susceptible to the unpleasant side effects of this drug.

Nausea is likely to alter both subject responses to questionnaires and performance on cognitive instruments, as it clearly did in Experiment #3. Thus, it appears important to control for a number of these factors when designing studies on the cognitive effects of nicotine in healthy non-smokers, in order to avoid the potentially confounding influence of the drug's more objectionable side effects in those exposed for the first time. Subjects should be truly naïve to nicotine, and not have a history of regular tobacco use. Subjects should also be well-rested and not under much stress, which should be measured using instruments such as the POMS and SSS. Individual tasks should be relatively short, or at least delayed until 45 minutes or longer after attachment of the nicotine patch, while subjects should be engaged and diverted during those 45 minutes to distract them from any noticeable autonomic effects. Finally, subjects with low scores on the BPS are potentially more apt to experience nausea, at least if these other suggestions are not followed. Yet if these suggestions are followed, and one recruits healthy, unstressed, well-rested subjects without prior smoking experience, who are even a little bored (!), perhaps the risk of difficult and confounding side effects like nausea will be reduced.

Regardless, a relatively low dose of nicotine, the highly addictive compound in tobacco, appears to increase alertness, reduce boredom, and speed up subjective perception of the passage of time in healthy, unstressed, un-nauseated non-smokers, without producing any specific effect on the covert orienting of spatial attention to endogenous cues.

References

(1997). Miscellaneous Autonomic Drugs: Nicotine. AHFS Drug Information 1997**:** 1049-1052.

Acri, J. B., N. E. Grunberg, et al. (1991). "Nicotine increases acoustic startle reflex amplitude in rats." Psychopharmacology **104**: 244-248.

Acri, J. B., D. E. Morse, et al. (1994). "Nicotine increases sensory gating measured as inhibition of the acoustic startle reflex in rats." Psychopharmacology **114**: 369 - 374.

Adler, L. E., L. D. Hoffer, et al. (1993). "Normalization of auditory physiology by cigarette smoking in schizophrenic patients." American Journal of Psychiatry **150**: 1856 - 1861.

Adler, L. E., L. J. Hoffer, et al. (1992). "Normalization by nicotine of deficient auditory sensory gating in the relatives of schizophrenics." Biological Psychiatry **32**: 607-616.

Adler, L. E., E. Pachtman, et al. (1982). "Neurophysiological evidence for a defect in neuronal mechanisms involved in sensory gating in schizophrenia." Biological Psychiatry **17**: 639-654.

Ahmed, S. M. S. (1990). "Psychometric properties of the boredom proneness scale." Perceptual and Motor Skills **71**: 963 - 966.

Antes, J. R. (1974). "The time course of picture viewing." Journal of Experimental Psychology **103**: 62 - 70.

Aston-Jones, G. and F. E. Bloom (1981). "Activity of norepinephrine-containing locus coeruleus neurons in behaving rats anticipates fluctuations in the sleep-wake cycle." Journal of Neuroscience **1**: 876 - 886.

Aston-Jones, G., S. L. Foote, et al. (1984). Anatomy and physiology of locus coeruleus neurons: functional implications. Frontiers of Clinical Neurology. M. G. Ziegler. Baltimore, Williams and Wilkins.

Bates, T., G. Mangan, et al. (1995). "Smoking, processing speed and attention in a choice reaction time task." Psychopharmacology **120**: 209 - 212.

Bates, T., O. Pellett, et al. (1994). "Effects of smoking on simple and choice reaction time." Psychopharmacology **114**: 365 - 368.

Benet, W. R. (1996). Benet's Reader's Encyclopedia. New York, HarperCollins.

Benowitz, N. L. (1993). "Nicotine replacement therapy: What has ben accomplished - Can we do better?" Drugs **45**(2): 157-170.

Benowitz, N. L., P. J. III, et al. (1986). "Reduced tar, nicotine and carbon monoxide exposure while smoking ultralow - but not low-yield cigarettes." Journal of the American Medical Association **256**: 241 - 246.

Benwell, M. E. M., D. J. K. Balfour, et al. (1995). "Evidence that tobacco smoking increases the density of (-)-[3H]nicotine binding sites in human brain." Journal of Neurochemistry **50**: 1243 - 1247.

Berlucchi, G., G. Tassinari, et al. (1989). "Spatial distribution of the inhibitory effect of peripheral non-informative cues on simple reaction times to non-fixated visual targets." Neuropsychologia **27**: 201 - 221.

Berlyne, D. (1960). Conflict, Arousal and Curiosity. New York, NY, McGraw-Hill International Book Company.

Berlyne, D. E. (1960). Conflict, arousal and curiosity. New York, McGraw-Hill.

Bouyer, J. J., M. F. Montaron, et al. (1987). "Anatomical localization of cortical beta rhythms in cat." Neuroscience **22**: 863 - 869.

Briand, K. and e. al (1998). "Differences in the time course of inhibition of return using manual and saccadic responses." Investigative Opthalmological Visual Science **39**: S631.

Castellano, C. (1976). "Effects of nicotine on discrimination learning, consolidation and learned behavior in two inbred strains of mice." Psychopharmacology **48**: 37 - 43.

Clark, C. R., G. M. Geffen, et al. (1987). "Catecholamines and attention. II. Pharmacological studies in normal humans." Neuroscience and Biobehavioral Review **11**: 353 - 364.

Clark, V. P. and S. A. Hillyard (1996). "Spatial selective attention affects early extrastriate but not striate components of the visual evoked potential." Journal of Cognitive Neuroscience **8**(5): 387 - 402.

Clarke, P. B. S. and A. Pert (1985). "Autoradiographic evidence for nicotine receptors on nigrostriatal and mesolimbic dopaminergic neurons." Brain Research **348**: 355-358.

Clarke, P. B. S., R. D. Schwartz, et al. (1985). "Nicotinic binding in rat brain: Autoradiographic comparison of [3-H]acetylcholine, [3-H]nicotine and [125-I]alpha bungarotoxin." The Journal of Neuroscience **5**(5): 1307-1315.

Corbetta, M., F. M. Miezin, et al. (1991). "Selective and divided attention during visual discriminations of shape, color and speed: Functional anatomy by positron emission tomography." The Journal of Neuroscience **11**(8): 2383 - 2402.

Corbetta, M., F. M. Miezin, et al. (1993). "A PET study of visuospatial attention." The Journal of Neuroscience **13**(3): 1202 - 1226.

Corrigall, W. A. (1991). "Understanding brain mechanisms in nicotine reinforcement." British Journal of Addiction **86**: 507 - 510.

Coultas, D. B., C. A. Stidley, et al. (1993). "Cigarette yields of tar and nicotine and markers of exposure to tobacco smoke." American Review of Respiratory Disease **148**: 435 - 440.

Csikszentmihalyi, M. and I. S. Csikszentmihalyi (1988). Optimal experience: Studies of flow in consciousness. New York, Cambridge University Press.

Daffner, K. R., L. F. M. Scinto, et al. (1994). "The impact of aging on curiosity as measured by exploratory eye movements." Archives of Neurology **51**: 368 - 376.

Daffner, K. R., L. F. M. Scinto, et al. (1992). "Diminished curiosity in patients with probable Alzheimer's disease as measured by exploratory eye movements." Neurology **42**: 320 - 328.

Daly, D. D. and T. A. Pedley (1990). Current Practice of Clinical EEG. New York, Raven Press.

Dani, J. and S. Heinemann (1996). "Molecular and cellular aspects of nicotine abuse." Neuron **16**: 905-908.

Davies, A. H. (1926). "The physical and mental effects of monotony in modern industry." British Medical Journal **2**: 472 - 479.

DeChenne, T. K. (1988). "Boredom as a clinical issue." Psychotherapy **25**: 71 - 81.

Decker, M. W., J. D. Brioni, et al. (1995). “Minireview - Diversity of neuronal nicotinic acetylcholine receptors: lessons from behavior and implications for CNS therapeutics.” Life Sciences **56**(8): 545-570.

Everitt, B. J. and T. W. Robbins (1997). “Central cholinergic systems and cognition.” Annual Review of Psychology **48**: 649 - 684.

Farmer, R. F. and N. D. Sundberg (1986). “Boredom proneness - The developments and correlates of a new scale.” Journal of Personality Assessment **50**: 4 - 17.

Fernandez-Duque, D. and M. I. Posner (1997). “Relating the mechanisms of orienting and alerting.” Neuropsychologia **35**(4): 477 - 486.

Fibiger, H. C. (1991). “Cholinergic mechanisms in learning, memory and dementia: a review of recent evidence.” Trends in Neurosciences **14**: 220 - 223.

Flores, C. M., S. W. Rogers, et al. (1992). Molecular Pharmacology **41**: 31 - 37.

Foote, S. L. (1987). “Extrathalamic modulation of cortical function.” Annual Review of Neuroscience **10**: 67 - 95.

Geiwitz, P. J. (1966). “Structure of boredom.” Journal of personality and social psychology **3**: 592 - 600.

Gellhorn, M. E. (1979). Travels with Myself and Another.

Gibbon, J., C. Malapani, et al. (1997). “Toward a neurobiology of temporal cognition: Advances and challenges.” Current Opinion in Neurobiology **7**: 170 - 184.

Goldberg, G. (1981). “Medial frontal cortex infarction and the alien hand sign.” Neurology **38**: 683 - 686.

Goldberg, M. E. and M. A. Segraves (1987). “Visuospatial and motor attention in the monkey.” Neuropsychologia **25**: 107 - 118.

Goodglass, H. and E. Kaplan (1983). Boston Naming Test. Hillsdale, NJ, Lea & Febiger.

Gordon, A., R. Wilkinson, et al. (1997). "The psychometric properties of the boredom proneness scale: an examination of its validity." Psychological Studies **42**(2 & 3): 85 - 97.

Gotman, J. (1990). Current Practice of Clinical Electroencephalography. New York, Raven Press.

Gourlay, S. G., N. L. Benowitz, et al. (1997). "Determinants of plasma concentrations of nicotine and cotinine during cigarette smoking and transdermal nicotine treatment." European Journal of Clinical Pharmacology **51**: 407-414.

Gray, R., A. S. Rajan, et al. (1996). "Hippocampal synaptic transmission enhanced by low concentrations of nicotine." Nature **383**: 713-716.

Grenhoff, J., G. Aston-Jones, et al. (1986). "Nicotinic effects on the firing patterns of midbrain dopamine neurons." Acta Physiologica Scandinavia **128**: 351 - 358.

Grobe, J. E., K. A. Perkins, et al. (1998). "Importance of environmental distractors in the effects of nicotine on short term memory." Experimental Clinical Psychopharmacology **6**(2): 209 - 216.

Gupta, S. K., N. L. Benowitz, et al. (1993). "Bioavailability and absorption kinetics of nicotine following application of a transdermal system." British Journal of Clinical Pharmacology **36**: 221-227.

Hamilton, J. A., R. J. Haier, et al. (1984). "Intrinsic enjoyment and boredom coping: Validation with personality, evoked potential and attention measures." Personality and Individual Differences **5**: 183 - 193.

Harrington, D. L., K. Y. Haaland, et al. (1998). “Temporal processing in the basal ganglia.” Neuropsychology **12**: 1 - 10.

Harrington, D. L., K. Y. Haaland, et al. (1998). “Cortical networks underlying the mechanisms of time perception.” The Journal of Neuroscience **18**(3): 1085 - 1095.

Hasenfratz, M., C. Michel, et al. (1989). “Can smoking increase attention in rapid information processing during noise? Electrocortical, physiological and behavioral effects.” Psychopharmacology **98**: 75 - 80.

Hawkins, W. L., L. C. French, et al. (1988). “Depressed affect and time perception.” Journal of Abnormal Psychology **97**: 275 - 280.

Haxby, J. V., B. Horowitz, et al. (1994). “The functional organization of human extrastriate cortex: A PET-rCBF study of selctive attention to faces and locations.” The Journal of Neuroscience **14**(11): 6336-6353.

Health, O. o. S. a. (1988). The health consequences of smoking: Nicotine addiction. A report of the Surgeon General. Baltimore, Maryland, US Department of Health and Human Services.

Heinze, H. J., G. R. Mangun, et al. (1994). “Combined spatial and temporal imaging of brain activity during visual selective attention in humans.” Nature **372**: 543 - 546.

Heishman, S. J., F. R. Snyder, et al. (1993). “Performance, subjective and physiological effects of nicotine in non-smokers.” Drug and Alcohol Dependence **34**: 11 - 18.

Henderson, J. M. (1991). “Stimulus discrimination following covert attentional orienting to an exogenous cue.” Journal of Experimental Psychology: Human Perception and Performance **17**(1): 91 - 106.

Henningfield, J. E., K. Miyasato, et al. (1985). “Abuse liability and pharmacodynamic characteristics of intravenous and inhaled nicotine.” Journal of Pharmacology and Experimental Therapeutics **234**: 1 - 12.

Henningfield, J. E., J. M. Stapleton, et al. (1993). Drug and Alcohol Dependence **33**: 23 - 29.

Hindmarch, I., J. S. Kerr, et al. (1990). “Effects of nicotine gum on psychomotor performance in smokers and non-smokers.” Psychopharmacology **100**: 535 - 541.

Hoddes, E., V. Zarcone, et al. (1973). “Quantification of sleepiness: A new approach.” Psychophysiology **10**: 431 - 436.

Husain, M., K. Shapiro, et al. (1997). “Abnormal temporal dynamics of visual attention in spatial neglect patients.” Nature **385**: 154 - 156.

Imperato, A., M. A, et al. (1986). “Nicotine preferntially stimulates dopamine release in the limbic system of freely moving rats.” European Journal of Pharmacology **132**: 337 - 338.

Ivry, R. B. and S. W. Keele (1989). “Timing functions of the cerebellum.” Journal of Cognitive Neuroscience **1**: 136 - 152.

Jacob, P. (1981). “Improved gas chromatographic method for the determination of nicotine and cotinine in biological fluid.” Journal of Chromatography **232**: 61 - 70.

James, W. (1890). The Principles of Psychology. New York, Dover Publications.

Jarvik, M. E. (1991). “Beneficial effects of nicotine.” British Journal of Addiction **86**: 571 - 575.

Jennings, P., J. S. Janowsky, et al. (1998). “Estrogen and sequential movement.” Behavioral Neuroscience **112**(1): 154-159.

Jones, G. M. M., B. J. Sahakian, et al. (1992). "Effects of subcutaneous nicotine on attention, information processing and short-term memory in Alzheimer's disease." Psychopharmacology **108**: 485 - 494.

Jonides, J. (1981). Voluntary versus automatic control over the mind's eye's movement. Attention and Performance IX. J. Long and A. Baddeley. Hillsdale, NJ, Erlbaum: 187 - 204.

Kessler, D. (2001). A Question of Intent. New York, Public Affairs.

Klein, R. (1993). Cigarettes Are Sublime. Durham and London, Duke University Press.

Klein, R. (2000). "Inhibition of return." Trends in Cognitive Sciences **4**(4): 138 - 146.

Kluger, R. (1996). Ashes to Ashes: America's Hundred-Year Cigarette War, the Public Health, and the Unabashed Triumph of Philip Morris. New York, Vintage Books.

Knott, V. (1989). "Brain electrical imaging the dose-response effects of cigarette smoking." Neuropsychobiology **22**: 236 - 242.

Koob, G. F. (1992). "Drugs of abuse: Anatomy, pharmacology and function of reward pathways." Trends in Pharmacologic Sciences **13**: 177-183.

Ksir, C., R. L. Hakan, et al. (1987). "Chronic nicotine and locomotor activity: influences of exposure dose and test dose." Psychopharmacology **92**: 25 - 29.

Lawrence, A. D. and B. J. Sahakian (1995). "Alzheimer disease, attention and the cholinergic system." Alzheimer Disease Associated Disorders **9**: 43 - 49.

Leary, M. R., P. A. Rogers, et al. (1986). "Boredom in interpersonal encounters: Antecedents and social implications." Journal of Personality and Social Psychology **51**: 968 - 975.

LeHouezec, J. and N. L. Benowitz (1991). "Basic and clinical psychopharmacology of nicotine." Clinics in Chest Medicine **12**(4): 681-699.

Lena, C., J.-P. Changeux, et al. (1993). Journal of Neuroscience **13**: 2680 - 2688.

Leong, F. T. L. and G. R. Schneller (1993). "Boredom proneness: Temperamental and cognitive components." Personality and Individual Differences **14**(1): 233 - 239.

Levin, E. D. (1992). "Nicotinic systems and cognitive function." Psychopharmacology **108**: 417 - 431.

Levin, E. D., C. K. Conners, et al. (1998). "Transdermal nicotine effects on attention." Psychopharmacology **140**: 135 - 141.

Levin, E. D., C. K. Conners, et al. (1996). "Nicotine effects on adults with attention-deficit/hyperactivity disorder." Psychopharmacology **123**: 55 - 63.

Loftus, G. R. and N. H. Mackworth (1978). "Cognitive determinants of fixation location during picture viewing." Journal of Experimental Psychology: Human Perceptual Performance **4**: 565 - 572.

London, E. D., U. Scheffel, et al. (1995). "In vivo labeling of nicotinic acetylcholine receptors in brain with [3-H]epibatidine." European Journal of Pharmacology **278**: R1-R2.

Lopes-da-Silva, F. (1991). "Neural mechanisms underlying brain waves: from neural membranes to networks." EEG in Clinical Neurophysiology **79**: 81 - 93.

Luck, S. J. (1995). "Multiple mechanisms of visual-spatial attention: recent evidence from human electrophysiology." Behavioural Brain Research **71**: 113 - 123.

Luck, S. J., S. Fan, et al. (1993). "Attention-related modulation of sensory-evoked brain activity in a visual search task." Journal of Cognitive Neuroscience **5**: 188 - 195.

Luck, S. J., H. J. Heinze, et al. (1990). "Visual event-related potentials index focused attention within bilateral stimulus arrays. II. Functional dissociation of P1 and N1 components." Electroencephalography and Clinical Neurophysiology **75**: 528 - 542.

Lukas, J. H. and J. Siegel (1977). "Cortical mechanisms that augment or reduce evoked potentials in cats." Science **198**: 73-75.

Lupianez, J. and e. al (1997). "Does IOR occur in discrimination tasks? Yes, it does, but later." Perceptual Psychophysics **59**: 1241 - 1254.

Lutzenberger, W., R. Schandry, et al. (1979). Habituation of the components of the AEP to stimuli of different intensities. The Orienting Reflex in Humans. H. D. Kimmel, E. H. v. Olst and J. F. Orlebeke. Hillsdale, NJ, Lawrence Erlbaum Associates: 123-128.

Maggini, C. (2000). "Psychobiology of Boredom." CNS Spectrums **5**(8): 24 - 27.

Mangun, G. R. and S. A. Hillyard (1987). "The spatial allocation of attention as indexed by event-related brain potentials." Human Factors **29**: 195 - 211.

Marks, M. J., E. Romm, et al. (1989). "Variation of nicotinic binding sites among inbred strains." Pharmacology, Biochemistry and Behavior **33**: 679 - 689.

Maruff, P., M. Yucel, et al. (1999). "Facilitation and inhibition arising from the exogenous orienting of covert attention depends on the temporal propoerties of spatial cues and targets." Neuropsychologia **37**: 731 - 744.

Maylor, E. A. and R. Hockey (1987). "Effects of repetition on the facilitatory and inhibitory components of orienting in visual space." Neuropsychologia **25**: 41 - 54.

McCormick, D. A. (1989). "Cholinergic and noradrenergic modulation of thalamocortical processing." Trends in Neurosciences **12**: 215 - 221.

McCormick, D. A. (1992). “Neurotransmitter actions in the thalamus and cerebral cortex and their role in neuromodulation of thalamocortical activity.” Progress in Neurobiology **39**: 337 - 388.

McGehee, D. S. and e. al (1995). Science **269**: 1692 - 1696.

McGehee, D. S. and L. W. Role (1996). “Presynaptic ionotropic receptors.” Current Opinion in Neurobiology **6**: 342-349.

McGiboney, G. W. and C. Carter (1988). “Boredom proneness and adolescents' personalities.” Psychological Reports **63**: 741 - 742.

McNair, D. M., M. Lorr, et al. (1992). Manual for the Profile of Mood States. San Diego, CA, EdITS Educational and Testing Service.

Meck, W. H. (1983). “Selctive adjustment of the speed of internal clock and memory processes.” Journal of Experimental Psychology: Animal Behavior Processes **9**(2): 171 - 201.

Meck, W. H. (1996). “Neuropharmacology of timing and time perception.” Brain Research: Cognitive Brain Research **3**(3-4): 227 - 242.

Meck, W. H. and R. M. Church (1987). “Cholinergic modulation of the content of temporal memory.” Behavioral Neuroscience **101**(4): 457 - 464.

Mesulam, M.-M. (1981). “A cortical network for directed attention and unilateral neglect.” Annals of Neurology **10**: 309 - 325.

Mesulam, M.-M. (1990). “Large-scale neurocognitive networks and distributed processing for attention, language and memory.” Annals of Neurology **28**: 597 - 613.

Mesulam, M. M., E. J. Mufson, et al. (1983). “Cholinergic innervation of cortex by the basal forebrain: Cytochemistry and cortical connections of the septal area, diagonal band nuclei, nucleus basalis (substantia inominata), and hypothalamus in the rhesus monkey." The Journal of Comparative Neurology **214**: 170-197.

Mikulas, W. L. and S. J. Vodanovich (1993). "The essence of boredom." The Psychological Record **43**: 3 - 12.

Misfud, J. C., L. Hernandez, et al. (1989). "Nicotine infused into the nucleus accumbens increases synaptic dopamine as measured by in vivo microdialysis." Brain Research **478**: 365 - 367.

Mountcastle, V. B., J. C. Lynch, et al. (1975). "Posterior parietal association cortex of monkey: Command functions for operations within extrapersonal space." Journal of Neurophysiology **38**: 871 - 908.

Muir, J. L., B. J. Everitt, et al. (1995). "Reversal of visual attentional dysfunction following lesions of the cholinergic basal forebrain by physostigmine and nicotine but not by the 5-HT3 receptor antagonist, ondansetron." Psychopharmacology **118**: 82 - 92.

Muller, H. J. and P. M. A. Rabbitt (1989). "Reflexive and voluntary orienting of visual attention: Time course of activation and resistance to interruption." Journal of Experimental Psychology: Human Perception & Performance **15**: 315 - 330.

Mumenthaler, M. S., J. L. Taylor, et al. (1998). "Influence of nicotine on simulator flight performance in non-smokers." Psychopharmacology **140**: 38 - 41.

Murphy, F. C. and R. M. Klein (1998). "The effects of nicotine on spatial and non-spatial expectancies in a covert orienting task." Neuropsychologia **36**(11): 1103 - 1114.

Nebes, R. D. and C. B. Brady (1989). "Focused and divided attention in Alzheimer's disease." Cortex **25**: 305 - 315.

Nisell, M., G. G. Nomikos, et al. (1994). Synapse **16**: 36 - 44.

Nobre, A. C., G. N. Sebestyen, et al. (1997). "Functional localization of the system for visuospatial attention using positron emission tomography." Brain **120**: 515 - 533.

O'Boyle, D. J., J. S. Freeman, et al. (1996). "The accuracy and precision of timing of self-paced, repetitive movements in subjects with Parkinson's disease." Brain **119**: 51 - 70.

O'Hanlon, J. F. (1981). "Boredom: Practical consequences and a theory." Acta Psychologica **49**: 53 - 82.

Oken, B. S. (1994). "Attention deficit in Alzheimer's disease is not simulated by an anticholinergic/ antihistaminergic drug and is distinct from deficits in healthy aging." Neurology **44**: 657 - 662.

Oken, B. S., S. S. Kishiyama, et al. (1995). "Pharmacologically induced changes in arousal: effects on behavioral and electrophysiologic measures of alertness and attention." Electroencephalography and Clinical Neurophysiology **95**: 359 - 371.

Oken, B. S. and M. C. Salinsky (1992). "Alertness and attention: basic science and electrophysiologic correlates." Journal of Clinical Neurophysiology **9**: 480-494.

Parasuraman, R. (1998). The Attentive Brain. Cambridge, Massachusetts, The MIT Press.

Parasuraman, R., P. M. Greenwood, et al. (1992). "Visuospatial attention in dementia of the Alzheimer type." Brain **115**: 711 - 733.

Pauly, J. R., M. J. Marks, et al. (1996). "An autoradiographic analysis of cholinergic receptors in mouse brain after chronic nicotine treatment." Journal of Pharmacology and Experimental Therapeutics **258**(3): 1127 - 1136.

Peeke, S. C. and H. V. S. Peeke (1984). "Attention, memory and cigarette smoking." Psychopharmacology **84**: 205 - 216.

Petersen, S. E., D. L. Robinson, et al. (1987). "Contributions of the pulvinar to visual spatial attention." Neuropsychologia **25**: 97 - 105.

Phillips, J. M., K. McAlonan, et al. (2000). "Cholinergic neurotransmission influences covert orientation of visuospatial attention in the rat." Psychopharmacology **150**: 112 - 116.

Pineda, J. A., C. Herrera, et al. (1998). "Effects of cigarette smoking and 12-hour abstention on working and memory during a serial-probe recognition task." Psychopharmacology **139**: 311 - 321.

Polich, J., M. Aung, et al. (1988). "Long latency auditory evoked potentials: Intensity, interstimulus interval, and habituation." Pavlovian Journal of Biological Sciences **23**(1): 35-40.

Polly, L. M., S. J. Vodanovich, et al. (1993). "The effects of attributional processes on boredom proneness." Journal of Social Behavior and Personality **8**: 123 - 132.

Posner, M. I. (1980). "Orienting of Attention." Quarterly Journal of Experimental Psychology **32**: 3 - 25.

Posner, M. I. (1998). Attention in Cognitive Neuroscience: An Overview. The Cognitive Neurosciences. M. S. Gazzaniga. Cambridge, Massachusetts, The MIT Press.

Posner, M. I. and Y. Cohen (1984). Components of visual orienting. Attention and Performance X. D. Bouma and D. Bonwhuis. Hillsdale, NJ, Erlbaum: 531 - 556.

Posner, M. I., Y. Cohen, et al. (1982). "Neural systems control of spatial orienting." Philosophical Transactions of the Royal Society of London, Series B: Biological Sciences **298**: 187 - 198.

Posner, M. I. and S. E. Petersen (1990). "The attention system of the human brain." Annual Review of Neuroscience **13**: 25 - 42.

Posner, M. I., R. D. Rafal, et al. (1985). "Inhibition of return: Neural basis and function." Cognitive Neuropsychology **2**: 211 - 228.

Rafal, R. and A. Henik (1994). The neurology of inhibition: Integrating controlled and automatic processes. Inhibitory processes in attention, memory and language. D. Dagenbach and T. H. Carr. San Diego, CA, Academic Press.

Rafal, R. and L. Robertson (1998). The Neurology of Visual Attention. The Cognitive Neurosciences. M. S. Gazzaniga. Cambridge, Massachusetts, MIT Press.

Rafal, R. D., M. Posner, et al. (1988). "Orienting of spatial attention in progressive supernuclear palsy." Brain **111**: 267 - 280.

Rechtstaffen, A. and A. Kales (1968). A manual of standardized terminology: Techniques and scoring system for sleep stages of human subjects. Bethesda, National Institutes of Health.

Robbins, T. W. and B. J. Everitt (1998). Arousal Systems and Attention. The Cognitive Neurosciences. M. S. Gazzaniga. Cambridge, Massachusetts, The MIT Press: 703 - 720.

Robinson, D. L., E. M. Bowman, et al. (1995). "Covert orienting of attention in macaques II: Contributions of parietal cortex." Journal of Neurophysiology **74**(2): 698 - 712.

Ruchkin, D. (1988). Human Event Related Potentials EEG Handbook, Elsevier Science Publishers.

Russell, B. (1930). Conquest of Happiness.

Rusted, J. M. and D. M. Warburton (1992). "Facilitation of memory by post-trial administration of nicotine: evidence for an attentional explanation." Psychopharmacology **108**: 452 - 455.

Samuels, D. J. and M. Samuels (1974). "Low self-concept as a cause of drug abuse." Journal of Drug Education **4**: 421 - 438.

Sargent, P. B. (1993). "The diversity of neuronal nicotinic acetylcholine receptors." Annual Review of Neuroscience **16**: 403-443.

Sarramon, C., H. Verdoux, et al. (1999). "Addiction and personality traits: Sensation seeking, anhedonia, impulsivity." Encephale **25**(6): 569 - 575.

Seib, H. M. and S. J. Vodanovich (1998). "Cognitive correlates of boredom proneness: The role of private self-consciousness and absorption." The Journal of Psychology **132**(6): 642 - 652.

Sherwood, N., J. S. Kerr, et al. (1992). "Psychomotor performance in smokers following single and repeated doses of nicotine gum." Psychopharmacology **108**: 432 - 436.

Smith, R. P. (1981). "Boredom: A Review." Human Factors **23**: 329 - 340.

Steriade, M., S. Datta, et al. (1990). "Neuronal activities of brainstem cholinergic nuclei related to tonic activation processes in thalamocortical systems." Journal of Neuroscience **10**: 2541 - 2559.

Steriade, M., P. Gloor, et al. (1990). "Basic mechanisms of cerebral rhythmic activities." EEG in Clinical Neurophysiology **76**: 481 - 508.

Steriade, M. and R. W. McCarley (1990). Brainstem Control of Wakefulness and Sleep. New York, Plenum Press.

Stolerman, I. P. (1991). "Behavioral pharmacology of nicotine: multiple mechanisms." British Journal of Addiction **86**: 533 - 536.

Stolerman, I. P. and M. J. Jarvis (1995). "The scientific case that nicotine is addictive." Psychopharmacology **117**: 2-10.

Tanaka, Y. and S. Shimojo (1996). "Location versus feature: Reaction time reveals dissociation between two visual functions." Vision Research **36**: 2125 - 2140.

Tassinari, G. and G. Berlucchi (1996). "Covert orienting to non-informative cues: Reaction time studies." Behavioral Brain Research **71**: 101 - 112.

Tolor, A. (1989). "Boredom as related to alienation, assertiveness, internal-external expectancy, and sleep patterns." Journal of Clinical Psychology **45**: 260 - 265.

Tuakli, N., M. A. Smith, et al. (1990). "Smoking in adolescence: Methods for health education and smoking cessation." Journal of Family Practice **31**(4): 369 - 374.

Vodanovich, S. J., K. M. Verner, et al. (1991). "Boredom proneness: Its relationship between positive and negative affect." Psychological Reports **69**: 1139 - 1146.

Voytko, M. L., D. S. Olton, et al. (1994). "Basal forebrain lesions in monkeys disrupt attention but not learning and memory." The Journal of Neuroscience **14**(1): 167 - 186.

Wang, W., M. Timsit-Berthier, et al. (1996). "Intensity dependence of auditory evoked potentials is pronounced in migraine: An indication of cortical potentiation and low serotonergic neurotransmision?" Neurology **46**: 1404-1409.

Warburton, D. M. and C. Arnall (1994). "Improvements in performance without nicotine withdrawal." Psychopharmacology **115**: 539 - 542.

Warburton, D. M. and G. Mancuso (1998). "Evaluation of the information processing and mood effects of a transdermal nicotine patch." Psychopharmacology **135**: 305 - 310.

Warburton, D. M., J. M. Rusted, et al. (1992). "A comparison of the attentional and consolidation hypotheses for the facilitation of memory by nicotine." Psychopharmacology **108**: 443 - 447.

Warburton, D. M., K. Wesnes, et al. (1986). "Facilitation of learning and state dependency with nicotine." Psychopharmacology **89**: 55 - 59.

Watt, J. D. (1991). "Effect of boredom proneness on time perception." Psychological Reports **69**: 323 - 327.

Wesnes, K. and D. M. Warburton (1984a). "The effects of cigarettes of varying yield on rapid information processing performance." Psychopharmacology **82**: 338 - 242.

Wesnes, K. and D. M. Warburton (1984b). "Effects of scopolamine and nicotine on human rapid information processing performance." Psychopharmacology **82**: 142 - 150.

West, R. (1993). "Beneficial effect of nicotine: Fact or fiction?" Addiction **88**: 589 - 590.

Williams, D. G. (1980). "Effects of cigarette smoking on immediate memory and performance in different kinds of smokers." British Journal of Psychology **71**: 83 - 90.

Witte, E. A., M. C. Davidson, et al. (1997). "Effects of altering brain cholinergic activity on covert orienting of attention: Comparison of monkey and human performance." Psychopharmacology **132**: 324 - 334.

Wonnacott, S. (1991). "The relevance of receptor binding studies to tobacco research." British Journal of Addiction **86**: 537-541.

Wonnacott, S. (1997). "Presynaptic nicotinic ACh receptors." Trends in Neurosciences **20**(2): 92-98.

Yang, X., H. E. Criswell, et al. (1996). Journal of Pharmacology and Experimental Therapeutics **276**: 482 - 489.

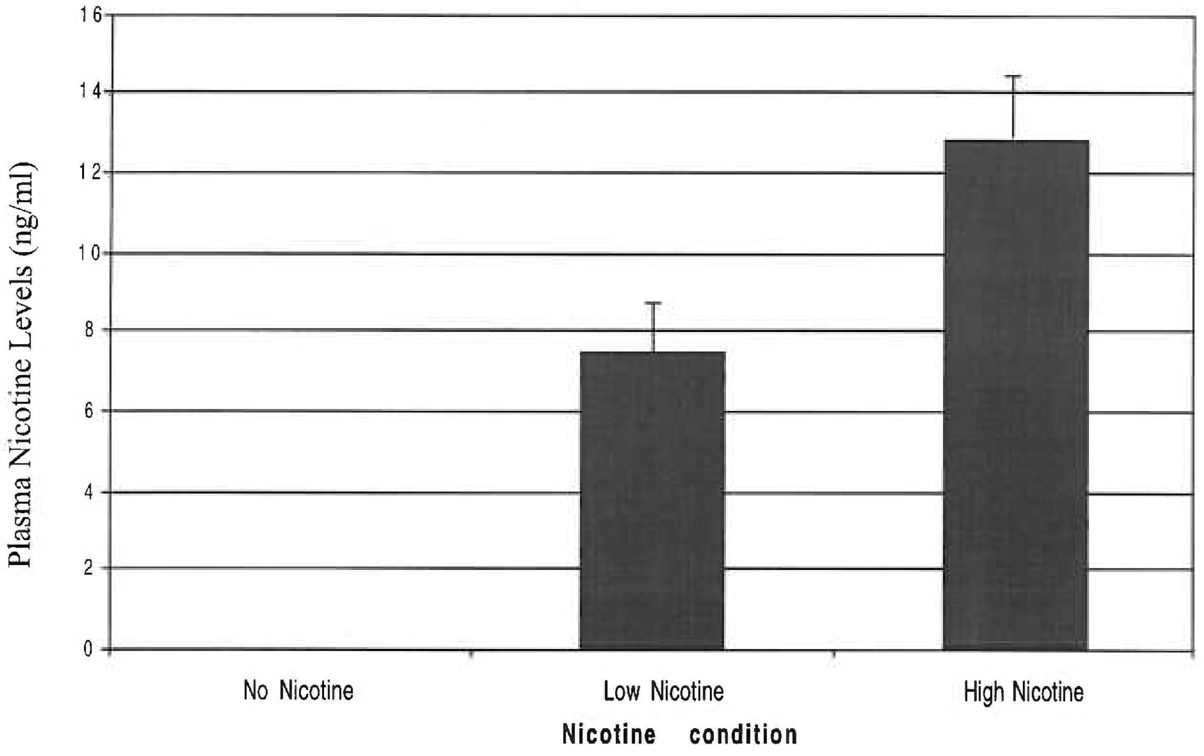
Zuckerman, M. (1969). Theoretical formulations. Sensory Deprivation: Fifteen Years of Research. J. P. Zubek. New York, Appleton-Century-Crofts.

Table 1: Nicotine improved EEG measures of alertness

Drug Condition	**DT/AB Ratio**	**Median Power**	**Peak Alpha**
Placebo	0.766, SD = 0.4	9.09Hz, SD = 1.1	9.63Hz, SD = 1.1
Low Nicotine	0.655, SD = 0.3	9.74Hz, SD = 0.8	10.03Hz, SD = 0.7
High Nicotine	0.617, SD = 0.3	9.88Hz, SD = 0.7	10.08Hz, SD = 0.9
	p = 0.085	p = 0.001	p = 0.049

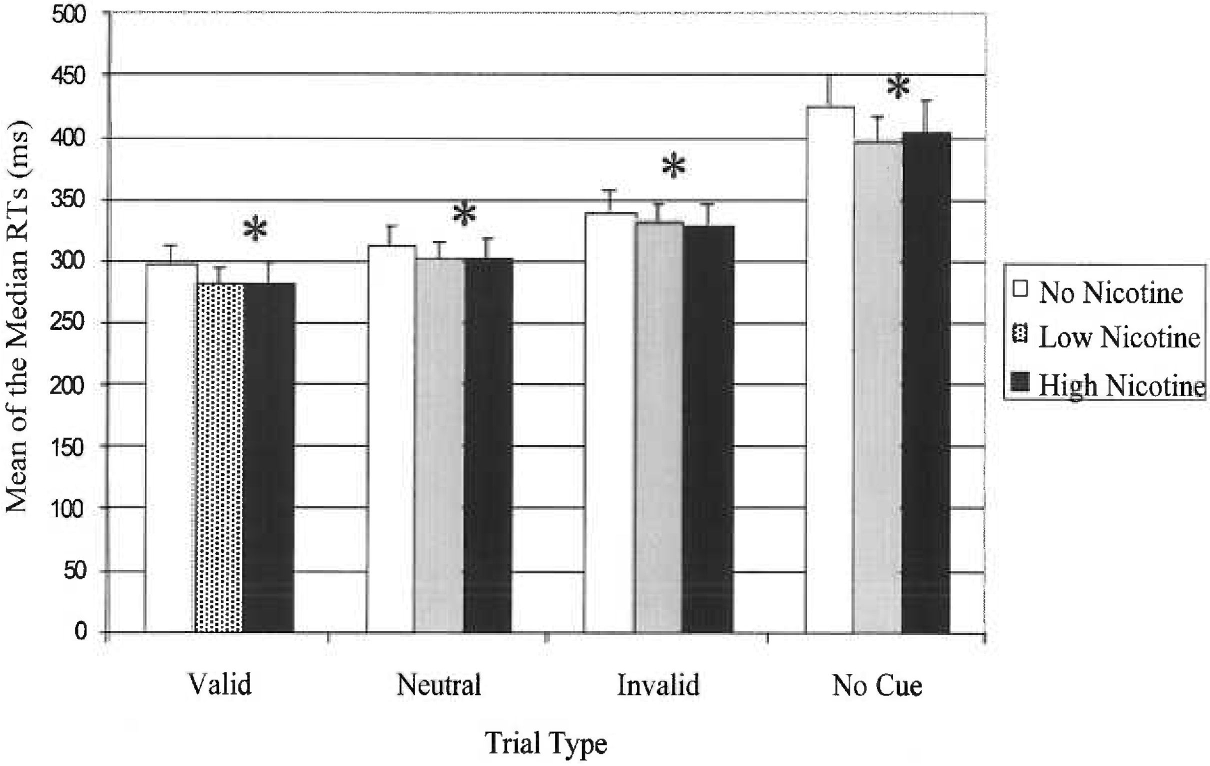
Means and standard deviations for the (delta + theta)/(alpha + beta) ratio (DT/AB ratio), median power, and peak alpha power from subjects in placebo, low nicotine and high nicotine conditions.

Figure 1: Patches Increased Plasma Nicotine



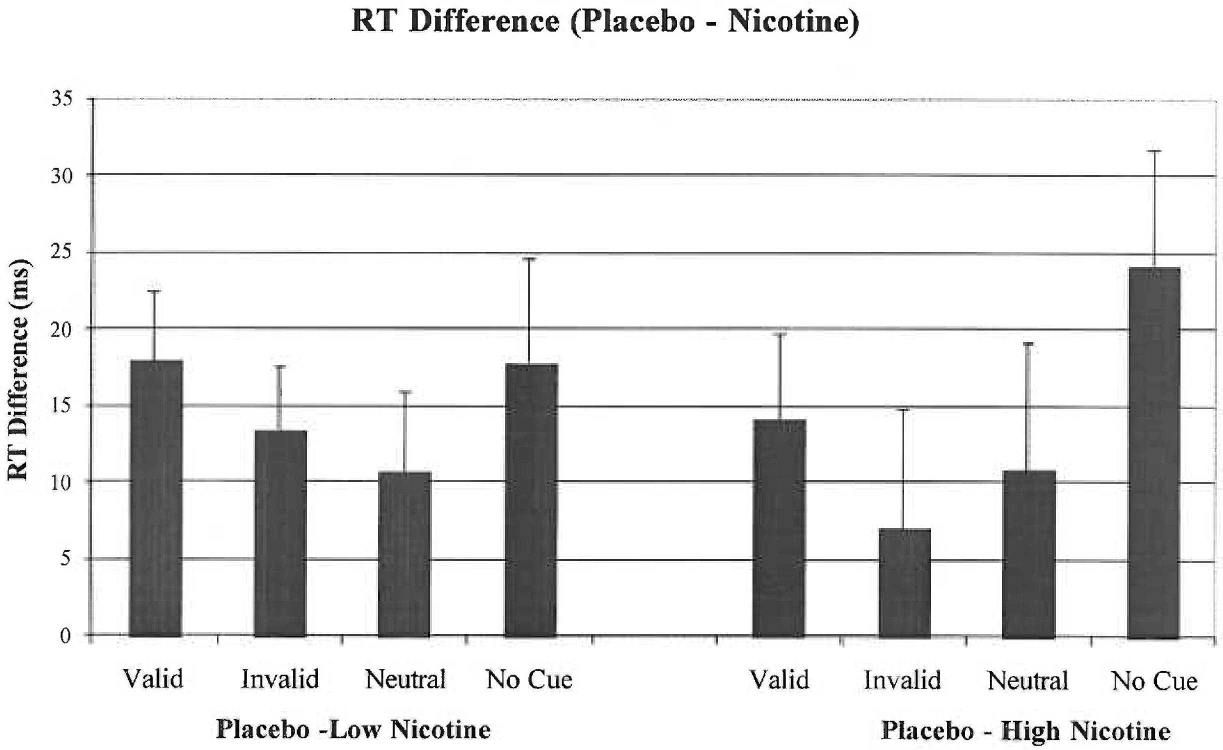
- In Experiment #1, Nicoderm patches increased plasma nicotine levels in a dose-dependent manner. Shown above are nicotine levels, (mean +/- SD, in ng/mal) from blood plasma drawn 150 minutes after attachment of placebo, 7mg patch (low nicotine), and 14mg patch (high nicotine).

Figure 2: Nicotine Reduced RTs



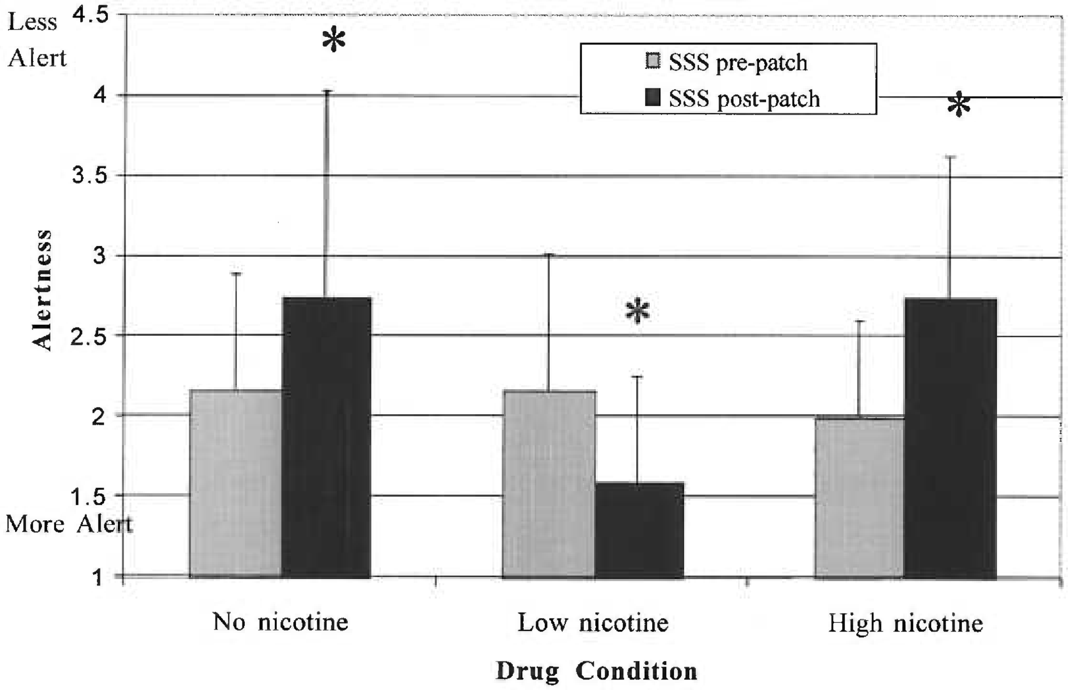
- In Experiment #1, nicotine reduced median RTs on the covert orienting task with endogenous cue stimuli, at both the low and high doses of nicotine. Bars are standard errors.

Figure 3: Nicotine Reduced RTs



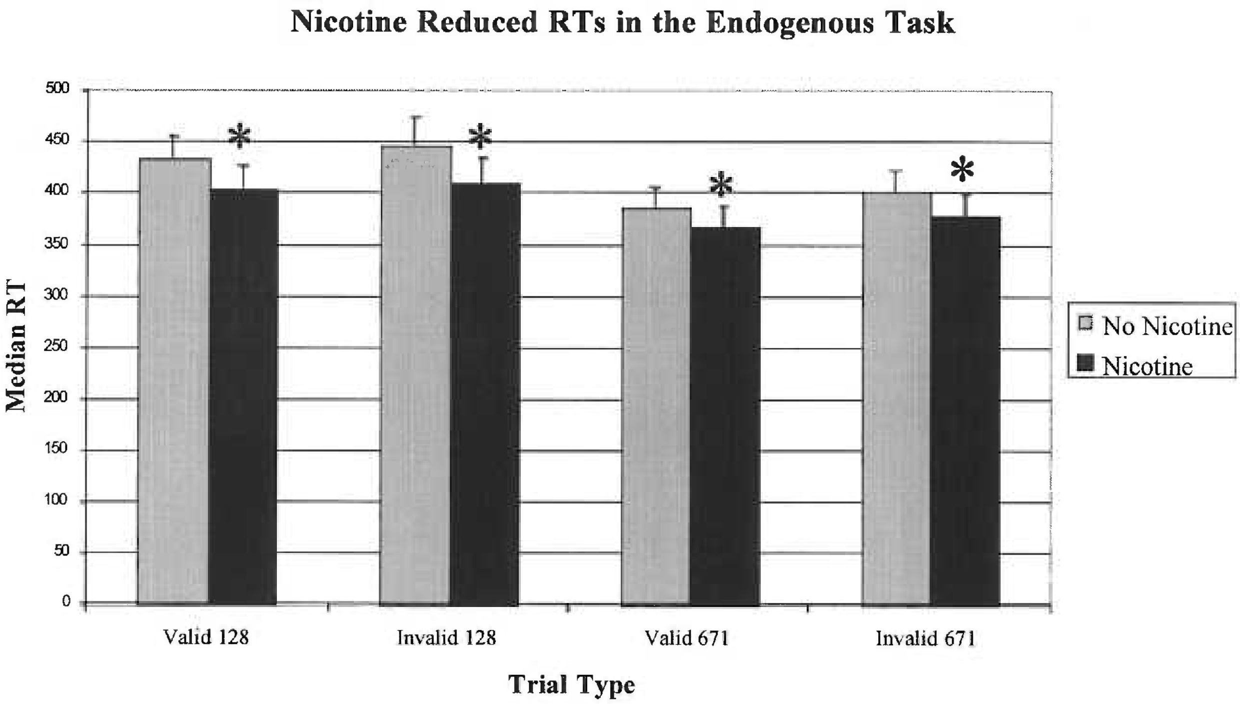
- In Experiment #1, subjects exhibited faster RTs on nicotine than on placebo, at both the low and high drug dose. Subtracting the RT of each subject on nicotine from their RT on placebo produced a consistently positive result. However, the drug had no significant effect on validity; i.e., there was no disproportionate improvement from nicotine on the invalid trials. Bars are SE.

Figure 4: Low Dose of Nicotine Increased SSS Alertness



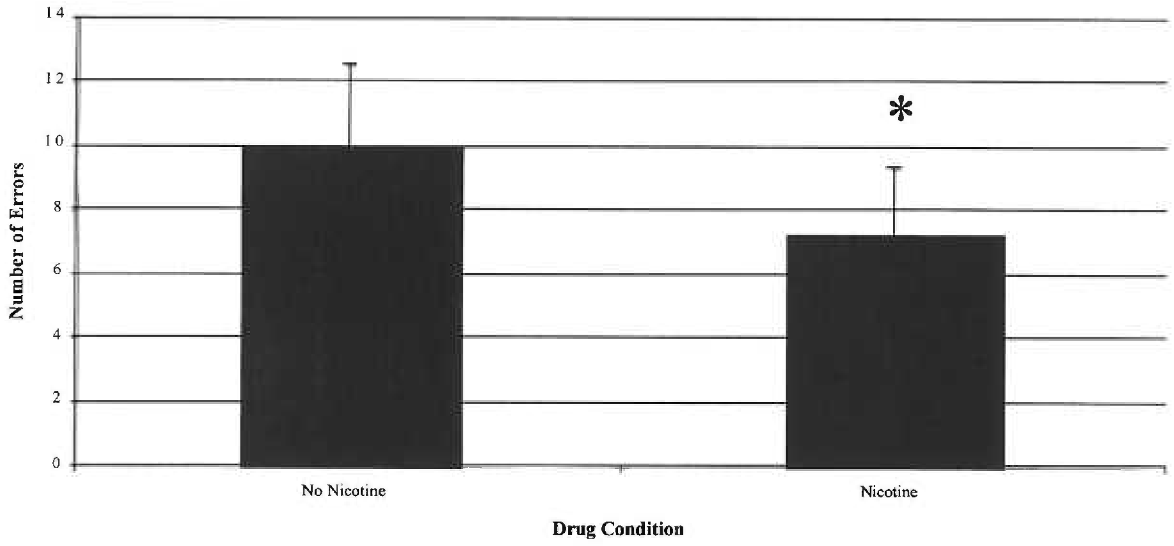
- In Experiment #1, the low (7mg) dose of nicotine increased subject alertness as measured by the Stanford Sleepiness Scale (SSS). Shown above are mean scores and standard error of the SSS administered just prior to application of nicotine patch (pre-patch) and again 130 minutes after patch application (post-patch).

Figure 5: Nicotine Reduced RTs in the Endogenous Task



- In Experiment #2, nicotine reduced median RTs in a subset of six subjects who performed the endogenous task at 75 minutes after application of the nicotine patch (F(1,5) = 21.87, p = 0.005). This was again limited to a within subjects effect, and there was no significant change in the validity effect. Bars are SE.

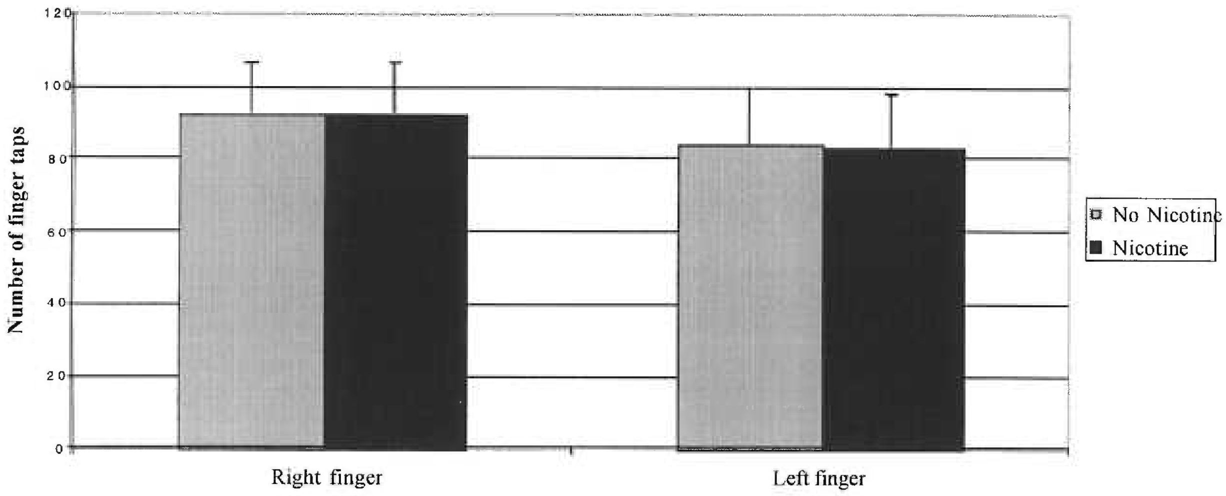
Figure 6: Nicotine Reduced the Error Rate in the Endogenous Task



- In Experiment #2, nicotine significantly reduced errors on the endogenous orienting task (a mean of 10 errors on placebo (SD = 9) versus 7.2 errors with nicotine (SD = 7.5)) (F(1,11) = 6.64, p = 0.026). Bars are SE.

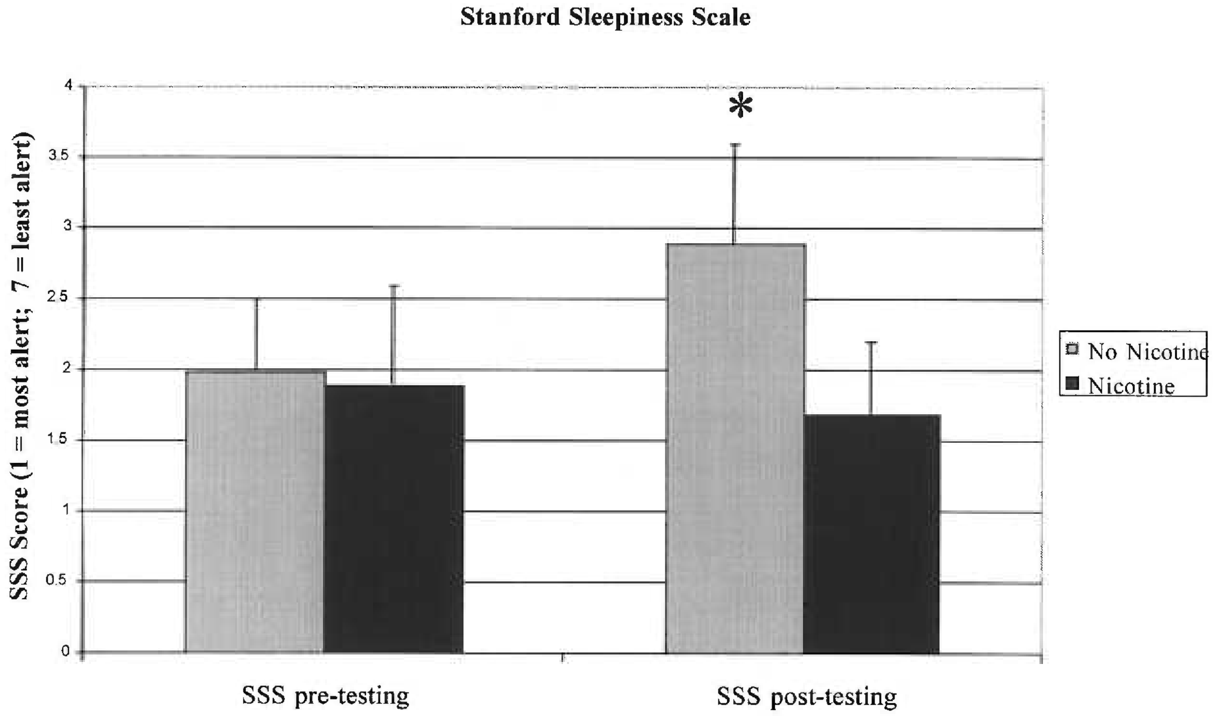
- However, there was no drug effect on errors in the exogenous task, although error rate was lower (5.2 errors on placebo, 6.1 errors with nicotine).

Figure 7: Nicotine had no effect on finger tapping rate



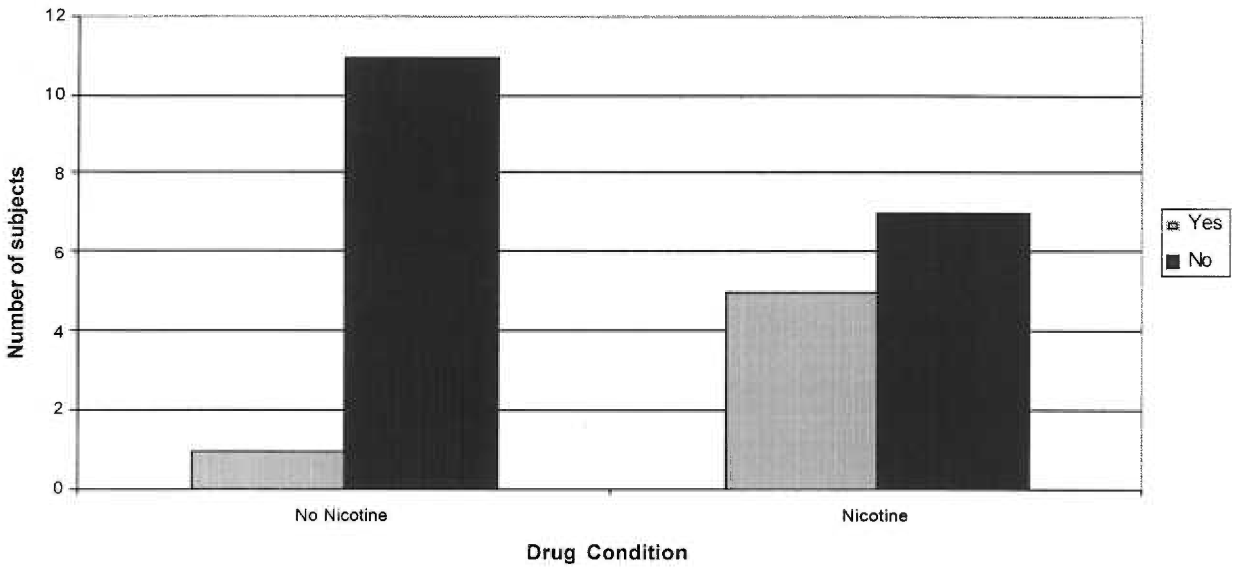
- In Experiment #2, here was no significant effect of nicotine on the total number of finger taps for the right hand (F(1,22) = 0.003, p = 0.957) or the left hand (F(1,22) = 0.002, p = 0.966). Bars are SE.

Figure 8: Nicotine prevents a decline in self-rated alertness on the SSS



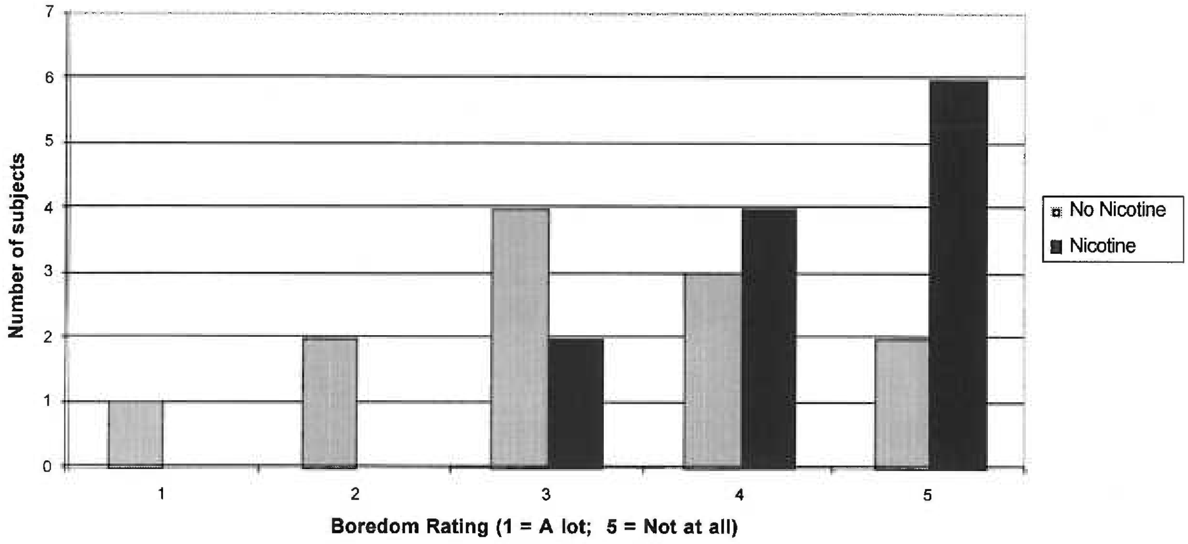
- In Experiment #2, post-drug SSS scores did not change from baseline (indicating maintained alertness) when subjects were given nicotine, while SSS scores increased from baseline (indicating decreasing alertness) when subjects did not receive drug. The SSS was administered both before patch attachment and again 140 minutes after patching. Bars are SE.

Figure 9: Subjects Unaware of Drug Condition in Experiment #2



- In Experiment #2, 6 out of 12 subjects thought they received nicotine during the study (all 12 did). Five of the 6 guessed correctly; one did not.

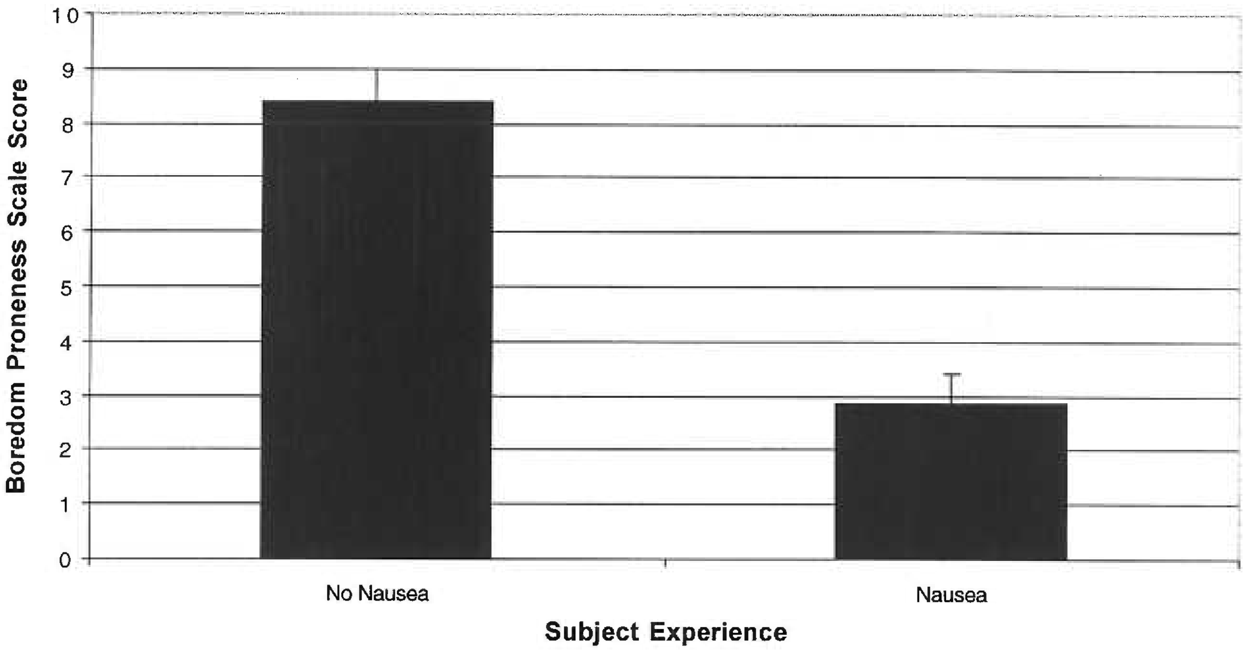
Figure 10: Nicotine reduced boredom



- In Experiment #2, subjects were asked if they experienced boredom, with 1 indicating "a lot" and 5 "not at all." A Mann-Whitney U Test revealed significantly less reported boredom with nicotine (p = 0.022).

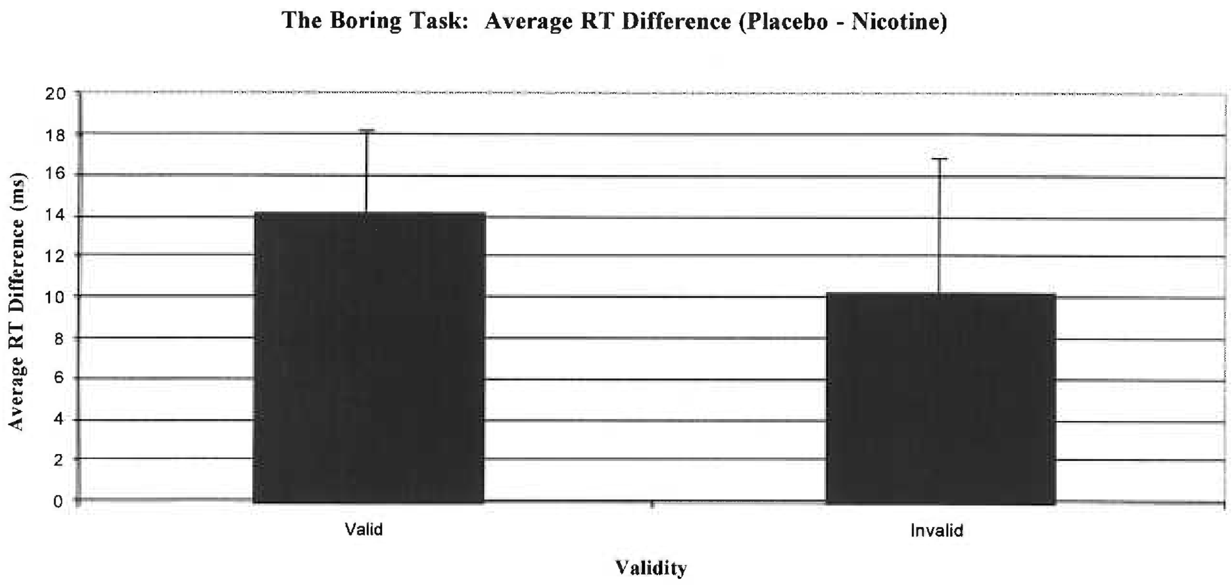
- In contrast, there was no significant effect of nicotine on subjective assessments of euphoria, difficulty with task, increasing/decreasing heart rate, nausea, or dizziness.

Figure 11: Low Boredom Proneness Correlated with Nausea



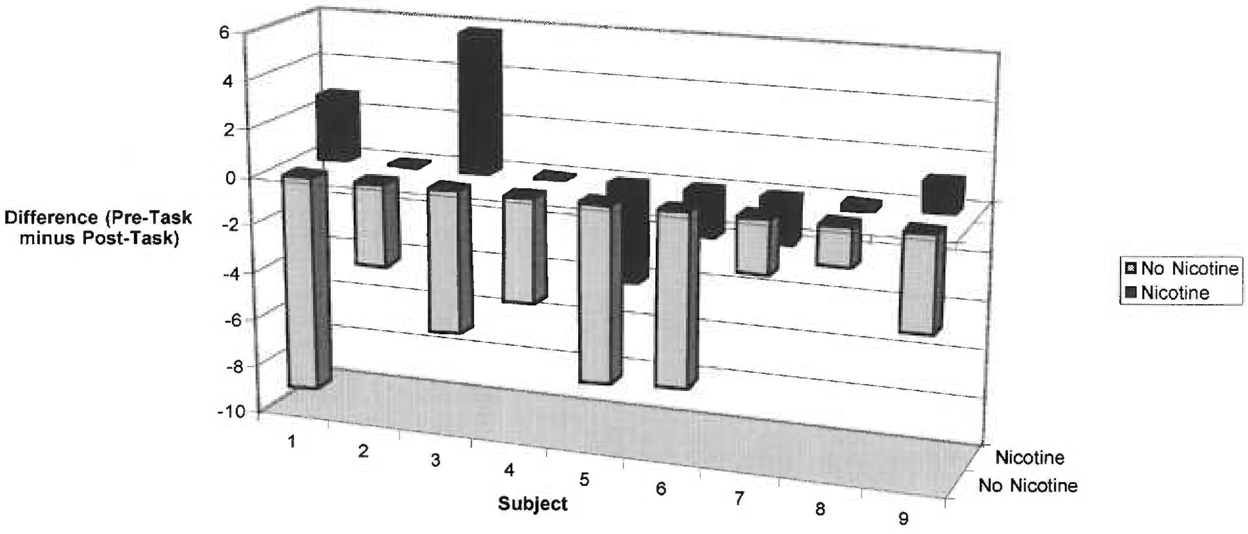
- In Experiment #3, 4 out of 19 subjects experienced nausea significant enough to prevent their completion of the experiment. Three other subjects experienced nausea during the experiment, but still completed all tasks. One additional subject experienced nausea after all tasks were completed. The correlation between low scores on the BPS and the occurrence of nausea was highly significant (r = 0.86). Subjects less prone to boredom were more likely to get sick. Bars are standard deviations.

Figure 12: Nicotine Reduced RTs



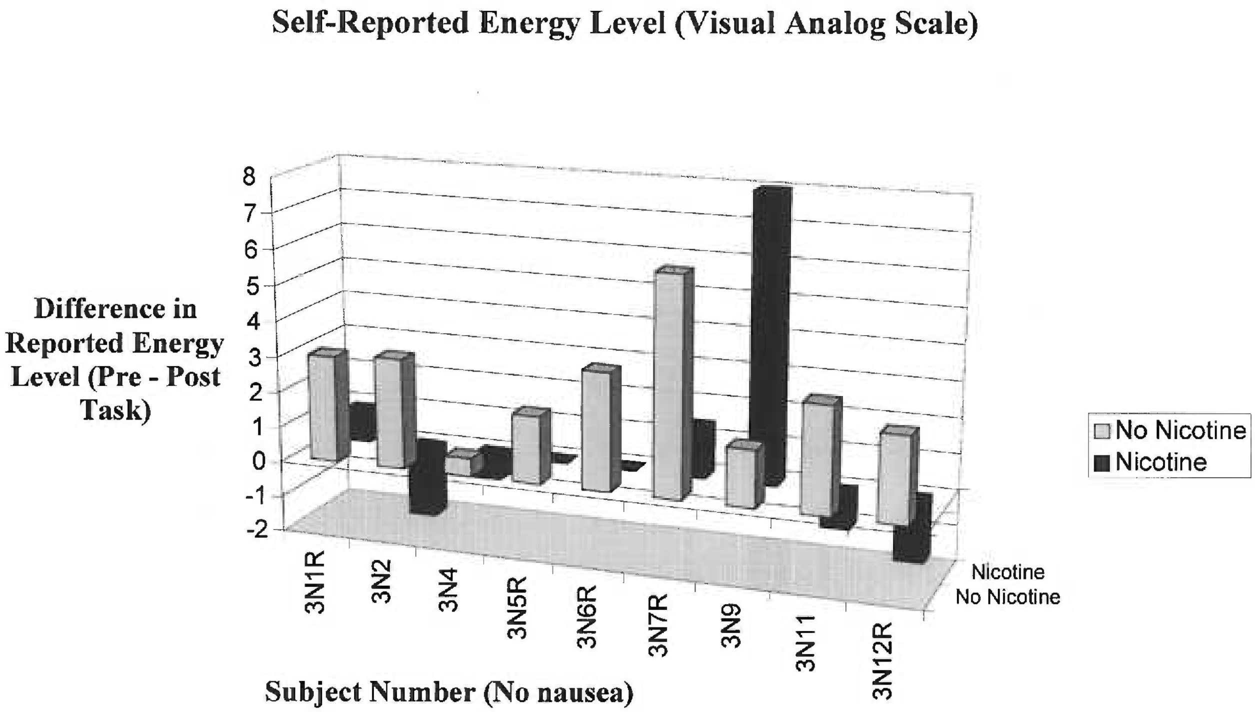
- In Experiment #3, subjects exhibited faster RTs in the Boring Task (a long, covert orienting task using endogenous cues) on nicotine than on placebo. Subtracting the RT of each subject on nicotine from their RT on placebo produced a consistently positive result. Bars are SE.

Figure 13: Nicotine Reduced Boredom



- In Experiment #3, subjects who marked visual analog scales administered before and after performance of the long Boring Task reported consistently less boredom on nicotine than on placebo. The difference scores (Pre-task minus Post-task) are graphed above. Nicotine did not, however, reduce boredom in subjects who became nauseous on the drug.

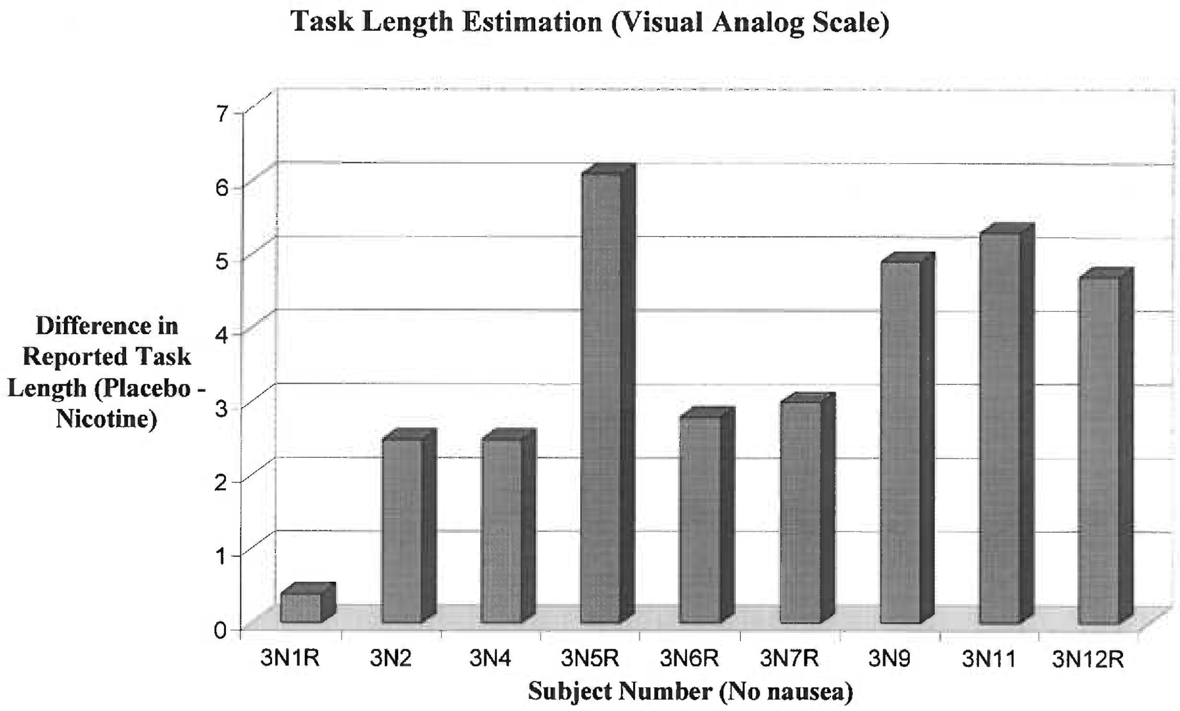
Figure 14: 8 of 9 Non-Nauseous Subjects Reported Increased Energy with Drug



Self-Reported Energy Level (Visual Analog Scale)

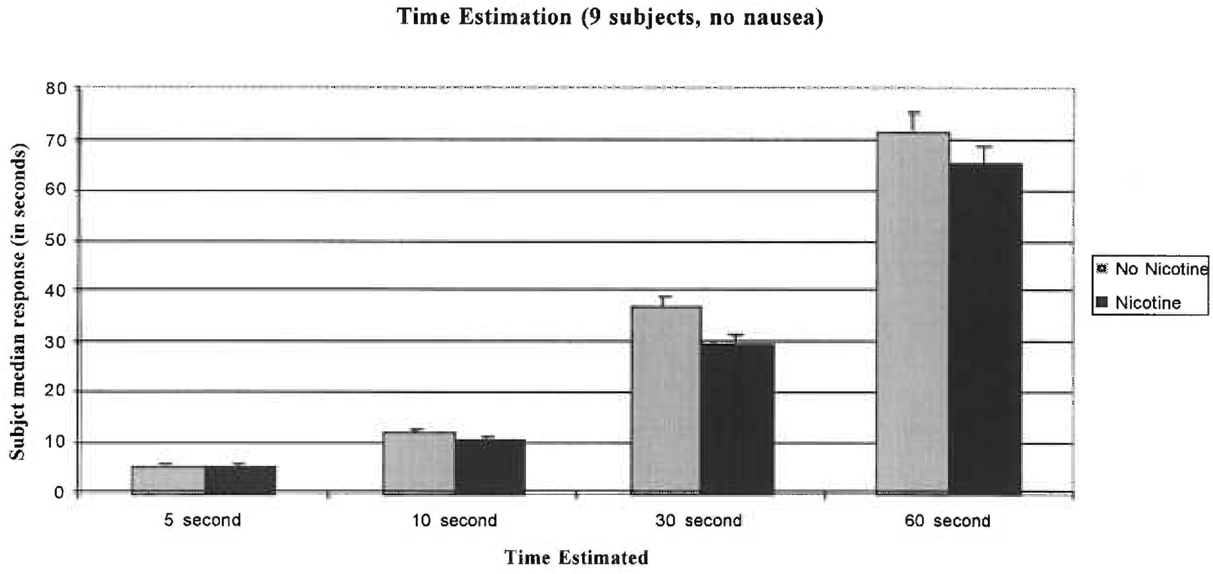
- In Experiment #3, eight of the nine subjects who did not experience nausea with nicotine reported having more energy after completing the Boring Task while on drug than on placebo, as measured by their responses on visual analog scales administered before and after the task. Difference scores are graphed above. In contrast, subjects who became nauseous reported less energy.

Figure 15: Nicotine Reduced Subjective Assessment of Task Length



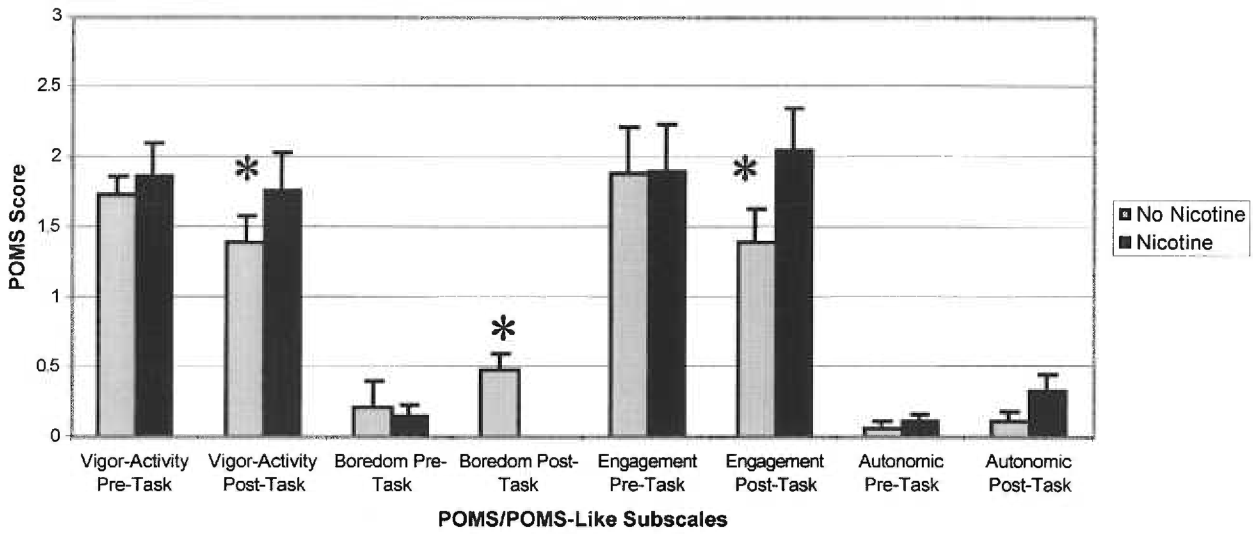
- In Experiment #3, all nine subjects who did not experience nausea during task performance reported (on a VAS) that the Boring Task took less time on nicotine than on placebo. The difference between task length reported on placebo and nicotine days (placebo minus nicotine) is graphed above. In contrast to these results, the three subjects who did experience nausea on nicotine reported that the task took longer with drug.

Figure 16: Nicotine effects on short time estimations



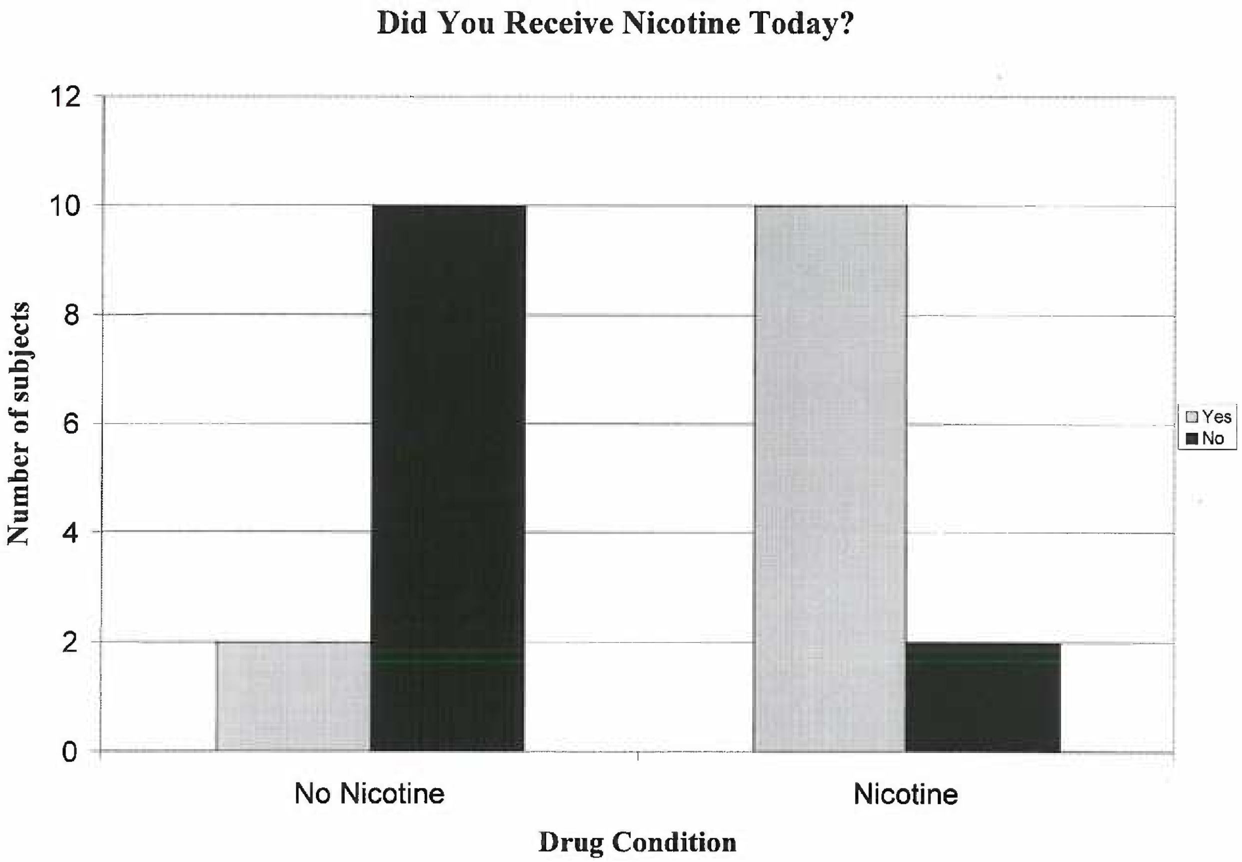
- In Experiment #3, the nine subjects who did not experience nausea in response to nicotine were asked to estimate 5, 10, 30 and 60 second intervals after performance of the long, Boring Task. These subjects were more accurate at longer estimations (of 30 and 60 seconds) when on nicotine than on placebo. There was also a trend towards shorter 30 second estimates in these subjects with drug. Bars are SE.

Figure 17: Nicotine increased POMS vigor; reduced boredom



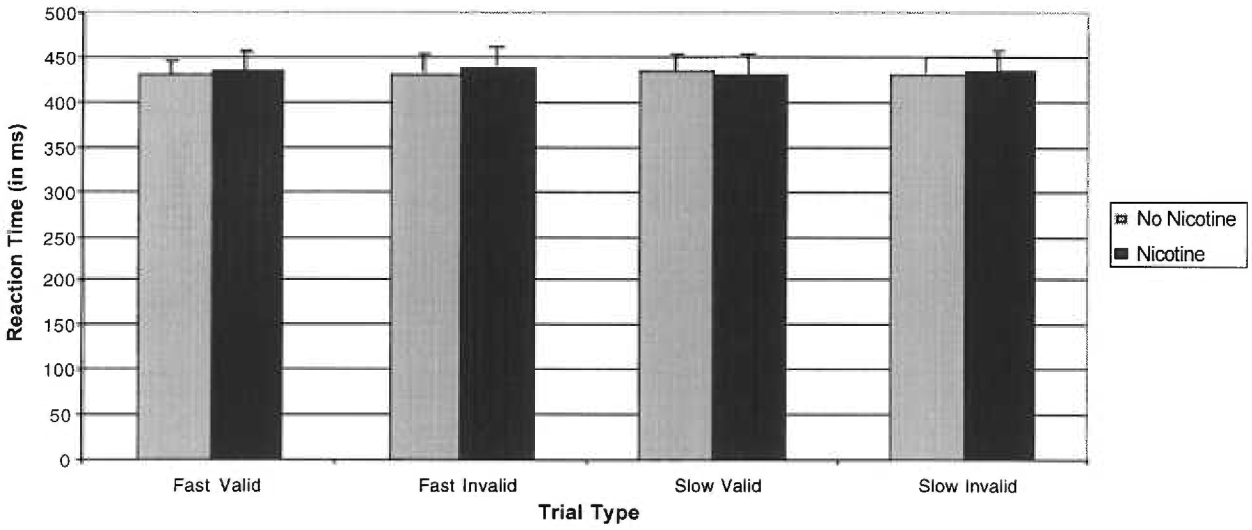
- In Experiment #3, subjects were administered POMS subscales (vigor-activity, anger-hostility) and POMS-like subscales (boredom, engagement, autonomic reactivity) both before and after each experimental session. Subjects did not differ on pre-task scores, but post-task, subjects who did not experience nausea reported more vigor and engagement, and less boredom after receiving drug than after receiving a placebo patch. There was no significant effect of nicotine on subject reports of autonomic reactivity, and no subject ever reported any anger-hostility in this experiment. Bars are SE.

Figure 18: Subjects aware of drug condition in Experiment #3



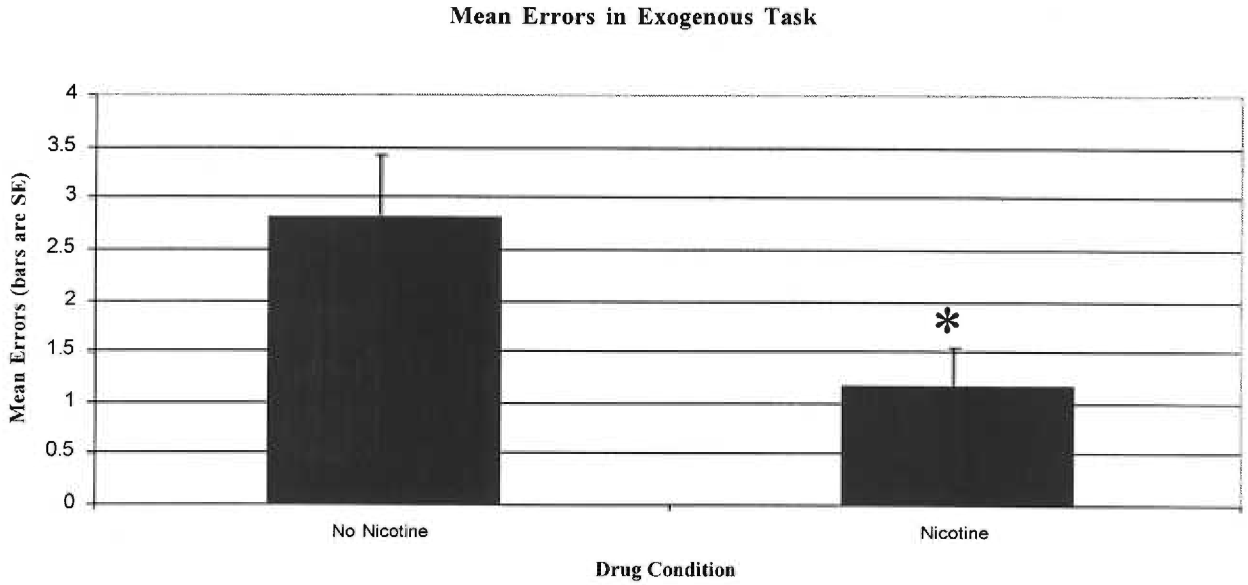
- Unlike results from Experiment #2 (see Figure #9), subjects in Experiment #3 were well aware of when they did and did not receive nicotine. Ten out of the 12 subjects on nicotine knew that they were on nicotine (8 of the 9 non-nauseous), while 10 of the 12 subjects on placebo knew they were on placebo (7 of the 9 non-nauseous).

Figure 19: No Validity Effect in Exogenous Task



- In Experiment #4, subjects performing the main covert orienting task with exogenous cue stimuli at 80 minutes post-patch showed no validity effect (no difference in RTs to valid versus invalid cues), and no drug effects, at either the short or long SOA. Bars are SE.

Figure 20: Nicotine reduced errors in Exogenous Task



- In Experiment #4, there was a non-significant trend towards reduced errors in the short, practice version of the exogenous task performed at 45 minutes post-patch ((F(1,11) = 4.63, p = 0.054)).

- However, subjects performing the main exogenous task at 80 minutes post-patch made significantly fewer errors with nicotine ((F(1,11) = 25, p = 0.000)). Bars above are SE.