THE EFFECTS OF NICOTINE ON THE COGNITIVE PROCESSES OF ADOLESCENTS AND ADULTS

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ABSTRACT

THE EFFECTS OF NICOTINE ON THE COGNITIVE PROCESSES OF ADOLESCENTS AND ADULTS

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Though much is known about the addictive properties of nicotine, much remains to be learned about its effects on various cognitive processes, especially as they might differ between adolescents and adults. The purpose of this study is to determine what effect, if any, nicotine has on attention and spatial memory, and to determine if age-related differences in the effects of nicotine exist. Based on Posner and Petersen's model of attention, it was hypothesized that nicotine would not have an effect on the alerting network of attention, though nicotine would have a positive effect on the orienting and executive control networks of attention. Further, nicotine was expected to have a greater positive effect on the orienting and executive control networks of adolescents than adults. It was also hypothesized that nicotine would have a positive effect on spatial memory and that nicotine would also have a greater effect on spatial memory of adolescents than adults.

Participants were recruited and randomly assigned to wear nicotine patches or placebo patches for four days. Posttest attention and spatial memory data were analyzed to determine if there were differences between the nicotine and placebo groups, or the

adolescents and adults. While the results appear to suggest that nicotine did not have an effect on attention or spatial memory and there was not an age-related difference in nicotine's effects on cognition, the small sample size led to low power in all the analyses, and the effects of nicotine can not reliably be interpreted.

INTRODUCTION

Millions of Americans are smokers. According to Meyer and Quenzer (2005), 30% of the U.S. population over 12 years old is currently using tobacco. Interestingly, young adults make up the majority of tobacco users (Meyer & Quenzer, 2005). A large number of adults who use tobacco report that they smoked cigarettes as adolescents (Kandel & Chen, 2000). People start smoking cigarettes regularly for various reasons. Some people start for social reasons. If their friends are smoking, they may pick up the habit to fit in. Others start smoking because of the rewarding effects of nicotine. Smoking can help people relax, focus, deal with stress, and aid with weight loss. However, the long-term health consequences that come with smoking cigarettes far outweigh the benefits (Meyer & Quenzer, 2005).

Meyer and Quenzer (2005) report that up to one-half of regular cigarette smokers die prematurely as a result of smoking. On average, over 440,000 Americans die every year due to tobacco-related causes, making it the most frequent preventable cause of death in the United States. People who smoke cigarettes are at an increased risk for various types of cancer, including lung cancer, cardiovascular disease, and other respiratory diseases (Meyer & Quenzer, 2005). Adolescents and adults who began smoking cigarettes as adolescents have a harder time abstaining from smoking than people who started smoking as adults (Spear, 2000). Although an overwhelming majority of American smokers report a desire to quit smoking, most are not able to quit due to the highly addictive properties of nicotine (Meyer & Quenzer, 2005). While progress is being made toward understanding addiction, much remains to be learned about the effects of

addictive substances, such as nicotine, on various cognitive processes, especially as they might differ between adolescents and adults. The purpose of this study is to determine what effect, if any, nicotine has on attention and spatial memory, and to determine if there are age-related differences in nicotine's effect.

REVIEW OF THE LITERATURE

Adolescents and Adults

Developmentally, adolescence is defined as that time period between childhood and adulthood when individuals become more independent from their childhood caregivers (Spear, 2000). It is known to be a unique time period in many important ways: socially, emotionally, physically, and most importantly, neurodevelopmentally. Although significant changes take place throughout the adolescent brain, the prefrontal cortex appears to be the site of some of the most dramatic changes (Spear, 2000; Steinberg, 2005). In general, these neurodevelopmental changes allow for the development of higher cognitive functioning (Steinberg, 2005). In particular, Steinberg reports that brain regions involved in behavioral regulation (the frontal lobes) are developing at a unique pace during adolescence. Adolescents are typically more likely than children to engage in deviant or risk-taking behaviors, which may be attributed the changes in brain development (Spear, 2000). Spear believes that experimenting in such deviant behaviors helps the adolescent achieve independence and transition into adulthood. Unfortunately, this brings with it the tendency to engage in dangerous and maladaptive behaviors such as illegal drug use, including nicotine.

It is believed that adolescents who are first time users have a different experience than adult first time users (Kandel & Chen, 2000). According to Kandel and Chen, adolescents are more sensitive to low dose nicotinic effects, and because of this, are more susceptible to become addicted to nicotine than adults. Spear (2000) reports that adolescents become dependent on drugs quicker and experience more severe withdrawal

symptoms than other age groups. While most adolescent smokers attempt to stop smoking soon after they start, 97% continue to smoke 2 years after starting (Spear, 2000). This is indicative of the difficulties adolescents have with dealing with withdrawal symptoms and abstaining from smoking. It is believed that the differences in reactions to nicotine are a result of the changes taking place in adolescent brains, as they are still developing (Spear, 2000).

Nicotine

Pharmacological Properties. Nicotine is a psychostimulant that can be absorbed into the blood stream. After it crosses the blood-brain barrier, nicotine increases activity at nicotinic acetylcholine receptors and mesolimbic dopamine receptors (Corrigall, 1991; Grenhoff & Svensson, 1989). Corrigall found that self-administration of nicotine decreases when participants are given dopaminergic antagonists. Grenhoff and Svensson also note that nicotine has an effect on dopamine receptors, though nicotine's most significant effects occur in the cholinergic system. Although nicotinic receptors are found throughout the brain, areas such as the cerebral cortex, thalamus, and hippocampus have high-affinity receptors (Meyer & Quenzer, 2005). This means these areas are more sensitive to the effects of nicotine. The effects of nicotine depend on many factors such as dosage and smoking history. The effects range from the positive, such as producing feelings of calmness and alertness, to the adverse, such as nausea and lightheadedness (Meyer & Quenzer, 2005). Higher doses are likely to produce adverse effects especially among non-smokers. Like almost every other drug, nicotine is a toxic substance that can cause nicotine poisoning or death, though this is only likely to occur at very high doses. The most severe cases are due to absorbing nicotine through the skin from nicotine-based

insecticides and death can occur with 60 mg of nicotine or more (Meyer & Quenzer, 2005).

Nicotine is considered one of the most addictive drugs (Meyer & Quenzer, 2005). This is likely due to the quick reinforcing effects that users experience after inhaling nicotine through cigarette smoke. On average, inhaled nicotine has a half-life of 2 hours, and therefore, users must regularly take in nicotine in order to avoid symptoms of withdrawal (Meyer & Quenzer, 2005). Although there are several ways for nicotine to be absorbed into the bloodstream, smoking cigarettes and using other tobacco products are the most common. Other, less common modes of administration are typically used to treat an addiction to tobacco products. Examples of these less common modes of exposure to nicotine are intranasal administration with nasal sprays, oral administration with nicotine pills, transdermal exposure with skin patches, buccal administration with chewing gum, and intravenous administration (Matta et al., 2007). Transdermal nicotine patches are widely used in nicotine studies. Min, Moon, Ko, and Shin (2001) noted that using nicotine patches is the preferred method of nicotine administration because of its pharmacokinetic properties. The patch allows the experimenter to have more control of rate and dosage of absorption and eliminates possible confounds due to differences in motor abilities (i.e., the act of smoking). Also, it is relatively easy to make a convincing placebo for a nicotine patch. Depending on the type of patch chosen, nicotine blood levels peak between 3 to 6 hours after administration of the patch (Min et al., 2001).

Developmental Effects. Several studies (Badanich & Kirstein, 2004; Belluzzi, Lee, Oliff, & Leslie, 2004; Schochet, Kelley, & Landry, 2004) have found that adolescent and adult rats respond differently to equal doses of nicotine. Badanich and Kirstein found that

adult rats have enhanced dopamine levels in the mesolimbic pathway when given nicotine, but adolescent rats do not. However, the adults only showed this response when given small doses. When given chronic doses, dopamine levels returned to baseline levels, indicative of tolerance effects (Badanich & Kirstein, 2004). Interestingly, Badanich and Kirstein found that adolescent rats preferred the nicotine rich environment to a nicotine-free environment, but the adult rats did not. The researchers proposed that the anxiety-relieving effects of nicotine may be more significant to adolescents than to adults.

Belluzzi et al. (2004) report similar nicotine preferences among adolescent rats. They found that early adolescent rats are more sensitive to the reinforcing effects of nicotine and prefer to be in a nicotine rich environment. Although late adolescent and adult rats experienced some positive effects from the nicotine, they still preferred the nicotine-free environment. This supports the findings of Kandel and Chen (2000), who also found that adolescents are more sensitive to nicotinic effects than adults. They found that when adolescents and adults who smoke the same amount are compared, adolescents show higher rates of dependence.

Schochet et al. (2004) found that adult rats were more sensitive to the locomotor effects of nicotine than adolescent rats. Although adolescents were more susceptible to the immediate excitatory effects, overall adults showed more sensitivity to nicotine. Although these results are not completely in concordance with the results from Badanich and Kirstein (2004) and Belluzzi et al. (2004), it is important to keep in mind that Schochet et al. measured motor effects, while Badanich and Kirstein, and Belluzzi et al.

measured physiological effects. All three studies report differences in nicotinic effects on adolescents and adults.

Attention

Attention is a set of cognitive processes that takes place in various anatomical areas of the brain, each performing specific functions. Attention has many definitions and can be measured in various ways. A common predicament within the existing literature is that the term "attention" is given to many different cognitive processes. For example, divided attention, sustained attention, alternating attention, selective attention, and auditory attention are all valid measures of the cognitive process, "attention." However, it would be inappropriate to compare two studies that look at two different concepts of attention. These types of attention are often loosely or variously defined and, therefore, tend not to map very well onto neuroanatomical substrates.

Posner and Petersen Model. For the purposes of this study, attention is broken down into three functions: being able to attend to a stimulus, maintain directed attention, and think about and resolve conflicts concerning a specified stimulus. Posner and Petersen (1990) describe these functions in terms of three attention networks: alerting, orienting, and executive control. Although they are related, these networks have been found to be both functionally and neurobiologically independent (Posner & Petersen, 1990). These three attention networks will be the focus of this study, and other types of attention will be disregarded.

Alerting involves the initial focusing on an object of interest. This network is important for being attentive to the presence of information (Posner & Petersen, 1990). The alerting network consists of a network of neurons in the frontal and parietal lobes in

the right hemisphere of the brain (Fan, McCandliss, Sommer, Raz, & Posner, 2002). Norepinephrine appears to be the primary neurotransmitter involved in the functioning of this network (Fan et al., 2002). The alerting network can be activated in various ways, including visual and auditory cues. This network is especially important, as the orienting network is not able to operate without first being alerted to the stimulus (Posner & Petersen, 1990).

The second network is the orienting network. Orienting involves directing one's attention to the appropriate spatial location of the target. For example, if one is looking at a blank screen with a dot somewhere on the screen, the orienting network would help the person focus his or her attention to the dot instead of looking elsewhere on the screen. The network of neurons that subserve orienting is also found in the frontal and parietal lobes of the brain, but functions on a separate neurotransmitter system from the alerting network (Fan et al., 2002). The ventral occipital lobe is also thought to be of particular importance to the orienting network, as this area is utilized for visual attention (Posner & Petersen, 1990). Researchers have found that orienting reaction times were slower after scopolamine, a cholinergic antagonist, was administered to monkeys, implicating the role of acetylcholine in the functioning of the orienting network (Davidson & Marrocco, 2000).

The final attention network is known as executive control, which occurs in the lateral prefrontal cortex and the anterior cingulate cortex in the midline frontal area of the brain (MacDonald, Cohen, Stenger, & Carter, 2000). Executive control refers to the ability to resolve conflicts in the presented stimuli. An example of executive control involves the classic Stroop effect. If a participant is shown contradictory information,

such as the word 'RED' written in a green colored font, the executive control network aids the participant in saying the correct color of the font and ignoring the actual word. Dopamine has been shown to effect the functioning of this system (Fan et al., 2002).

Attention Network Test. The Attention Network Test (ANT) was developed to test these components of attention (Fan et al., 2002). The ANT is able to distinguish between the three attention networks and shows that the three networks function independently. In other words, the activity of each network can be measured independently and the scores on each measure of the ANT are uncorrelated. The ANT is a short test that is simple enough to be completed in about 30 minutes, yet can accurately measure the attention networks of a variety of populations. The participant is simply asked to indicate whether an arrow is pointing towards the left or right in different conditions. The participant is sometimes shown congruent or incongruent spatial and directional cues before the arrow is shown. The participant's reaction times are measured and means are calculated for each condition to determine how each network is functioning. For example, the alerting network is measured by subtracting the mean cued reaction time from the mean no-cue reaction time. The orienting network is measured by subtracting the mean spatial cue reaction time from the mean center cue reaction time, where the cue alerts the participant but does not give locational cues. Finally, the executive control network is measured by subtracting the mean congruent cue reaction time from the mean incongruent cue reaction time (Fan et al., 2002).

Kleykamp, Jennings, Blank, and Eissenberg (2005) used the ANT to determine nicotinic effects on attention in a sample of 20 undergraduate never-smokers. They used 0, 2, and 4 mg gum and found that nicotine did not have an effect on any of the attention

networks. However, they did find that the 4 mg gum did increase heart rate and subjective ratings of negative effects (such a nausea and dizziness) and negative affect. The negative side effects of the gum is likely to have been a distraction to the participants, and could explain why they did not find an increase in attention.

Effects of Nicotine on Attention. Although several other studies have been conducted to test nicotine's effect on attention, the results have varied across studies. Several studies report that nicotine enhances attention (Ernst, Heishman, Spurgeon, & London, 2001; Gilbert, Dibb, Plath, & Hiyane, 2000; Hahn, Shoaib, & Stolerman, 2002; Levin, Conners, Silva, Canu, & March, 2001; Levin et al., 1998; Mancuso, Warburton, Mélen, Sherwood, & Tirelli, 1999; Mirza & Stolerman, 1998; Warburton & Mancuso, 1998; White & Levin, 1999), while several other studies report that nicotine has no effect on attention (Griesar, Zajdel, & Oken, 2002; Heishman, Snyder, & Henningfield, 1993; Kleykamp et al., 2005).

When there is such a discrepancy in results, it is important to look at possible reasons for differences. When conducting research with smokers, participants sometimes experience withdrawal symptoms during baseline or placebo conditions, which can cause poorer performance. When nicotine is administered to these participants, their results tend to improve because they are no longer experiencing nicotine withdrawal. This is an important possible confound that needs to be considered when exploring previous research. It is also important to look at which populations are being sampled. Some studies (e.g., Mancuso et al., 1999; Warburton & Mancuso, 1998) only look at specific populations, such as adults with ADHD (Levin et al., 2001) or Alzheimer's disease (White & Levin, 1999), and therefore, the results may not generalize to the general

population. This also includes research with animals (e.g., Hahn et al., 2002; Mirza & Stolerman, 1998).

The mode of nicotine administration and dosage amount are additional key factors to consider when looking at outcome differences between studies. When administering nicotine by having participants smoke cigarettes or chew gum, the exact amount of nicotine the participant actually absorbs is more varied than using nicotine patches or injections (Min et al., 2001). It is also possible that lower doses of nicotine create subtle effects that are difficult to detect with our current measures of attention at a behavioral level. However, if side effects of the nicotine are overt, they can be distracting to the participants.

It is also important to consider the type of attention that is being measured. For example, some studies may show that nicotine has a positive effect on divided attention, while other studies found that nicotine does not have an effect on sustained attention. While both findings are accurate, they measure different concepts of attention, and therefore, caution should be used when comparing studies. It is imperative to pay attention to methodological differences between studies and consider explanations for these differences. Based on the previous literature and the neurotransmitters involved with each attention network, is believed that when one carefully controls for possible confounds, nicotine will improve the orienting and executive control networks of attention in non-smokers, but will not have an effect on the alerting network.

Memory

Memory, like attention, is not a monolithic process. Rather, it involves various processes such as sensory memory, working memory and long-term memory as well as

several modalities including verbal, spatial, auditory, and olfactory, among others. For the purposes of this study, spatial learning memory is the only type of memory that will be considered because of its specific sensitivity to hippocampal activity (Roche, Mangaoang, Commins, & O'Mara, 2005). Other types of memory involve more complex processes and numerous brain structures. For example, verbal learning memory requires the use of language, which is mediated by culture, level of education, and innate linguistic skill. Spatial learning memory is less affected by these, with the possible exception of innate spatial ability. Measures that test spatial learning memory can be administered to a variety of populations, including children and animals.

Spatial Memory. The ability to remember familiar environments and navigate through space is made possible due to spatial learning memory (Astur, Taylor, Mamelak, Philpott, & Sutherland, 2002). As individuals interact with and navigate through an environment, they pick up spatial cues, which help them remember the configuration of the environment (Kitchin & Blades, 2002). These cues form a cognitive map, which enables people to remember locations that they have already encountered. Cognitive maps are used in various degrees of complexity in every day situations, such as giving directions, finding shortcuts, and simply driving home (Kitchin & Blades, 2002). It is believed that the hippocampus is vital in the acquisition and consolidation of these cognitive maps (Roche et al., 2005).

The hippocampal formation is located in the medial temporal lobe (Roche et al., 2005). This area is important for spatial memory and navigation. Feigenbaum and Morris (2004) studied the performance of 46 participants on the Morris Maze Analogue task. This task requires participants to physically move around while completing the task.

They found that only the participants who had temporal lobectomies in their right hemispheres showed deficits. Therefore, they determined that the right anterior temporal lobe is critical for spatial learning. However, further research seems to conflict with these findings. Brandt et al. (2005) compared 10 patients with bilateral vestibular loss with 10 matched control subjects who had intact hippocampi. Though the participants did not differ on non-spatial memory or attention, deficits were seen in the experimental group with spatial memory when given the virtual Morris water task. In a similar study by Astur et al. (2002), the experimental group consisted of participants with unilateral hippocampus resections, half who were missing the hippocampus in the left hemisphere, the other half who were missing the hippocampus in the right hemisphere. The researchers found that the loss of either hippocampus, right or left, resulted in poorer performance on the virtual Morris water task. Although it can be disputed if the right hemisphere is more important, it seems widely accepted that the hippocampus is important for spatial memory.

A recent study by Saito and Watanabe (2006) has implicated the importance of the parietal cortex with spatial learning. Using near-infrared spectroscopy, the researchers found that the parietal cortices were activated when acquiring new spatial information. Because activity in the parietal cortices peaked soon after starting the first trial, it is believed that this brain area is more important for encoding information, and not so important for retrieval (Saito & Watanabe, 2006). Roche et al. (2005) also note the importance of the parietal cortex with spatial learning, though it is noted that the hippocampus plays a more crucial role.

Acetylcholine and glutamate are both important neurotransmitters that are related to spatial learning memory (Feldman, Meyer, & Quenzer, 1997). Acetylcholine plays a more general role in spatial learning. Scopolamine has been found to impair learning and memory in both animals and humans. Glutamate is necessary for long-term potentiation. Long-term potentiation is a basic physiological process that facilitates a pattern of activity amongst neurons, so in the future, action potentials are more easily activated (Feldman et al., 1997). Basically, long-term potentiation is the memory of neurons. Long-term potentiation takes place throughout the brain, including in the hippocampus. Without glutamate, long-term potentiation could not take place. Without long-term potentiation, spatial memory cannot exist (Feldman et al., 1997). Therefore, glutamate is key in spatial learning memory.

Morris Water Task. The Morris Water Task is a commonly used measure to assess spatial learning and memory in rats (Rowland et al., 2005; Scerri, Stewart, Breen, & Balfour, 2006). In order to replicate the rat studies, a virtual water maze for humans has been developed. The appropriateness of using a virtual water maze to measure human spatial memory is widely accepted (Astur, Ortiz, & Sutherland, 1998; Astur et al., 2002; Brandt et al., 2005; Driscoll, Hamilton, Yeo, Brooks, & Sutherland, 2005; Hamilton, Driscoll, & Sutherland, 2002; Hanlon et al., 2006; Rowland et al., 2005; Skelton, Ross, Nerad, & Livingstone, 2006). The virtual water maze requires a computer screen and a keyboard or joystick for the participant to control. The screen shows a first person view of a round water tank in a room with distal cues on each wall. The participant is given instructions to find a platform that is hidden below the water level. After 60 seconds, the participant will have either found the platform or the platform rises so the participant can

swim to it. Once the participant reaches the platform, he or she is allowed to stand and look around the virtual room for a short time before the next trial begins. When the new trial begins, the participant begins at a new starting point and the process repeats itself. If spatial learning occurs, participants should eventually be able to make a cognitive map of the location of the platform in order to help them learn how to get to the platform based on the cues from the objects around the room. The computer keeps track of the path the participant takes to find the platform. This enables researchers to determine if the participant learned where the platform was, which is indicated by a more direct path in the direction of the platform and by spending more time in the area around the platform. Alternatively, participants may have wandered and randomly found the platform, which is indicated by circling around the perimeter of the tank walls (Kallaia, Makanyb, Karadia, & Jacobs, 2005).

Effects of Nicotine on Spatial Memory. Like attention, the existing literature regarding nicotinic effects on memory contains varied results. There are several studies that report that nicotine improves memory (Bancroft & Levin, 2000; Jacobsen et al., 2005; Min et al., 2001; Rusted, Trawley, Heath, Kettle, & Walker, 2005). Conversely, several other studies report no nicotinic effects on memory (Dawkins, Powell, West, Powell, & Pickering, 2007; Ernst et al., 2001; Heishman et al., 1993; Kleykamp et al., 2005; White & Levin, 1999). One study (Scerri et al., 2006) found that nicotine impairs memory. While it is not clear why there is such a discrepancy between results, the reasons may be similar to those of attention. It is important to consider methodological differences between these studies.

Some of the studies only looked at very specific populations. Bancroft and Levin (2000), and Scerri et al. (2006) studied rats, Min et al. (2001) only studied elderly Koreans, and White and Levin (1999) recruited participants who had been diagnosed with Alzheimer's disease. Some of the studies only studied smokers, some studied only non-smokers, and some studied both smokers and non-smokers. Results from these very specific populations may or may not generalize to the general population. It is also important to look at the dosages and modes of administration. Bancroft and Levin and Scerri et al. both used injections. Jacobsen et al. (2005) and Rusted et al. (2005) both used cigarettes. Min et al. and White and Levin both used the patch. Ernst et al. (2001), Heishman et al. (1993), and Kleykamp et al. (2005) all used nicotinic gum. Finally, Dawkins et al. (2007) used a nicotine lozenge. It is interesting to note that the three studies that used nicotinic gum and the study that used the nicotinic lozenge all found that nicotine did not have an effect on memory.

Finding a plausible reason as to why the Scerri et al. (2006) study found results that were different from all of the others is especially difficult. All of the rats in the this study, including the control rats that did not receive nicotine, showed impairments in memory, though the experimental rats showed greater impairments. If animals are given the same maze to complete day after day, spatial learning should take place unless there is something blocking the learning process. If all other conditions remained the same, the control group should have shown improvements, or at the least maintained the baseline functioning of memory, not regressed in their abilities. Therefore, it is believed that this study is not an accurate reflection of nicotine's effect on spatial memory.

It is also important to take into consideration participants' histories with spatial navigation. For example, if a participant has a job that requires navigation, such as a taxi driver or tour guide, they are more likely to have developed methods to aid in navigation. Hamilton and Sutherland (1999) point out that this detail is often overlooked when recruiting participants, but can cause inconsistencies with the data. Differences in the samples, modes of nicotine administrations, and participant histories can all produce false positive or negative effects and play a role in the outcome of nicotine studies. Based on the existing literature, when one carefully controls for possible confounds, it is believed that nicotine will have a positive effect on spatial memory.

STATEMENT OF THE PROBLEM AND HYPOTHESES

The existing literature on nicotinic effects on cognition is mixed. While it seems to be generally accepted that relatively low levels of nicotine have positive effects on the cognition of nonsmokers, the results of different studies have varied. There are several factors that could account for the vast differences in findings between studies including mode of nicotine administration, dosage, tests used to measure cognition, differences in definitions of the construct (i.e., divided attention versus sustained attention), and differences in populations that are being sampled. It seems that those studies that did not find an effect of nicotine on cognition did not properly address these methodological issues, whereas those that did find an effect, took these issues into consideration. Specific steps will be taken in this study in order to control for these possible confounds. Despite these methodological concerns, the literature appears to suggest that nicotine facilitates cognition.

While Kleykamp et al. (2005) was the only study that was reviewed that used Posner and Petersen's (1990) concept of attention as the basis for their study and used the ANT to measure attention, methodological concerns suggest the findings may not be an accurate measure of nicotinic effects on attention. Other studies have found positive effects of nicotine on attention, though they did not specifically measure the alerting, orienting, and executive control networks of attention (Ernst et al., 2001; Gilbert et al., 2000; Hahn et al., 2002; Levin et al., 2001; Mancuso et al., 1999; Mirza & Stolerman, 1998; Warburton & Mancuso, 1998). However, it is believed that these studies may be a more accurate representation of nicotinic effects on attention.

The studies that measure nicotinic effects on memory have usually relied on measures verbal memory and short-term memory. Bancroft and Levin (2000) and Scerri et al. (2006) both measured spatial learning memory using mazes. The shortcomings of the Scerri et al. study have been previously discussed, and the results are not believed to be an accurate representation of nicotinic effects on spatial memory. The Bancroft and Levin study found that chronic nicotine injections alleviated memory impairments in rats. Although the subjects in this study had impairments, this study is believed to be an accurate measure of nicotinic effects on spatial memory because the researchers controlled for methodological issues such as mode of administration, dosage, and measure of spatial memory.

Acetylcholine and dopamine are both significantly affected by nicotine (Corrigall, 1991; Grenhoff & Svensson, 1989). Acetylcholine plays an important role in the orienting attention network (Davidson & Marrocco, 2000), as well as spatial memory (Feldman et al., 1997). Dopamine has been shown to be key in the executive control network of attention (Fan et al., 2002). Because these neurotransmitters are the most affected by nicotine, it is believed that cognitive processes that involve these neurotransmitter systems would be the most affected by nicotine.

Adolescence represents a unique neurodevelopmental time period, which makes the brain especially vulnerable and sensitive to drug effects (Spear, 2000). Because of this increased sensitivity, adolescents become dependent on drugs quicker and experience more severe withdrawal symptoms than adults (Spear, 2000). Several studies have shown that adolescents and adults react differently, physiologically and cognitively, to equal

doses of nicotine (Badanich & Kirstein, 2004; Belluzzi et al., 2004; & Schochet et al., 2004).

Alerting

It is believed that nicotine will not have an effect on the alerting network of attention and there will be no interaction between nicotine and age. Because the alerting network relies on norepinephrine, and norepinephrine appears to be independent from nicotinic effects, alerting should remain unchanged after the administration of the nicotine patch.

Orienting

Due to the role of acetylcholine on the orienting network of attention, it is believed that nicotine will have a positive effect on the orienting network and there is expected to be an interaction with age. Due to their sensitivity to drug effects, it is expected that adolescents will out perform adults under the influence of nicotine.

Executive Control

The same is believed for the executive control network of attention, due to the role of dopamine on this network. It is expected that nicotine will have a positive effect on executive control, and nicotine is expected to have a greater positive effect on the executive control network of adolescents than adults.

Spatial Memory

It is expected that nicotine patches will have a positive effect on spatial memory. Spatial memory is affected by cholinergic systems, which nicotine has been shown to effect. Nicotine is expected to have a greater positive effect on the spatial memory of adolescents than adults.

METHOD

Participants

Participants were recruited from a 4-year university in the southeastern United States. Participant selection was not limited by sex, ethnicity, or years of education, though participants were required to be non-smokers and meet specific age requirements. For the purposes of this study, volunteers who had not had a cigarette within the last 60 days and had never been addicted to cigarettes were considered non-smokers. Participants were required to be in one of two age groups. The adolescent group members were between the ages of 18 and 20 years old. The adult group members were between the ages of 24 and 26 years old. Because it was expected that many of the participants in the adult group would be graduate students, efforts were made to recruit 18-20 year olds from the Honors College at the university to compensate for a possible discrepancy in achievement between graduate and undergraduate students. E-mail notification was sent to all of the students enrolled in the Honors College and Graduate School. The students were told that participants would be entered into a drawing to win one of two $100 gift cards.

Although 23 people volunteered for the study and scheduled times to participate, the final number of participants was 15. The 8 participants who started the study, but did not complete it all voluntarily left the study. Of the participants who dropped out of the study, 1 participant dropped out because of adverse effects (headache) attributed to the patch, 2 dropped out because of illness unrelated to the patch, and the reason for dropping

out is unknown for the other 5 participants. Of the participants who completed the study, 5 were in the adult age group and 10 were in the adolescent age group.

Design

A double blind mixed design (2 between subjects factors and 1 within subjects factor) was chosen for this study. The nicotine patches were packaged in white wrappers, while the placebo patches were packaged in silver wrappers. The primary researcher was unaware of which patch corresponded to which color until after data collection was complete. The primary researcher randomly assigned equal numbers of males and females from each age group to either a placebo group or a nicotine group. There were 4 groups (adult-placebo, adult-nicotine, adolescent-placebo, and adolescent-nicotine) with 2 participants in the adult-placebo group, 3 participants in the adult-nicotine group, 5 participants in the adolescent-placebo group, and 5 participants in the adolescent-nicotine group.

Because there are multiple dependent variables, data analysis was conducted using multivariate analysis of variance (MANOVA). In order to test the effect of nicotine on attention, a 2 (nicotine vs. placebo) x 2 (adolescent vs. adult) x 2 (pre- vs. post-patch) MANOVA was run using alerting, orienting, executive control as the dependent variables. A similar 2 x 2 x 2 MANOVA was run using path length and latency as the dependent variables in order to test the effect of nicotine on spatial memory. For all analyses, alpha was set at .05.

Materials

Nicotine Administration. A slow blood-nicotine rise 7 mg transdermal nicotine patch was cut in half and used for the experimental group. This patch has slow-onset so

any effects the participant experienced should have been subtle. Participants in the experimental group received approximately 3.5 mg of nicotine with each patch. This dosage amount was expected to be strong enough to have a significant, measurable effect on the participant, but mild enough to rarely cause nausea or other negative side effects. The placebo patch consisted of an inactive patch similar in appearance to an actual nicotine patch. Each participant was given two patches to be cut in half and administered on four consecutive days.

Attention. The ANT was used to assess the three attention networks. The ANT was chosen due to its ease and quickness of administration, and because several other studies have shown its effectiveness at independently measuring the three attentional networks. In order to complete the ANT, the participants sat in front of a computer screen and keyboard. Using the arrow buttons on the keyboard, participants indicated which way the arrow on the screen is pointing. There were various conditions in which the participants had to indicate the direction of the arrow. The conditions were as follows: the participant was shown an arrow in the middle of the screen, the participant was given a cue that the arrow is about to appear, the participant was given directional cues as to where on the screen the arrow will appear, the participant was given incongruent directional cues as to where on the screen the arrow will appear, the participant was given directional cues as to which way the arrow will be pointing, and the participant was given incongruent directional cues as to which way the arrow will be pointing. The alerting network was measured by subtracting the mean cued reaction time from the mean no-cue reaction time. The orienting network was measured by subtracting the mean spatial cue reaction time from the mean center cue reaction time, where the cue alerts the participant

but does not give locational cues. Finally, the executive control network was measured by subtracting the mean congruent cue reaction time from the mean incongruent cue reaction time.

Spatial Memory. The virtual water maze was used to assess spatial learning memory. Previous studies have shown the usefulness of a virtual water maze task to assess spatial memory. The virtual water maze took approximately 10 minutes to complete. As with the ANT, participants sat in front of a computer screen and used the arrow keys to navigate through the water maze. The screen showed a first person view of a round water tank in a room with distal cues on each wall. The participant was given instructions to find a platform that is hidden below the water level. After 60 seconds, the participant had either found the platform or the platform rose so the participant could swim to it. Once the participant reached the platform, he or she was allowed to stand and look around the virtual room for 10 seconds before the next trial began. When the new trial began, the participant was placed at a new starting point and the process repeated itself. If spatial learning occurs, participants should have been able to find the hidden platform quicker with each trial. The computer kept track of the path the participant took to find the platform. This enabled researchers to determine if the participant learned where the platform was, which was indicated by a more direct path in the direction of the platform and by spending more time in the area around the platform. Alternatively, participants may have wandered and randomly found the platform, which is indicated by circling around the perimeter of the tank walls. Participants were given 10 trials to find the platform. The virtual water maze provides data on the amount of time it took each

participant to reach the platform (latency) and how direct the paths to the platforms were (path length).

Demographics. The Achenbach Adult Self-Report for Ages 18-59 was given to each participant to fill out in order to gather information about each participant and screen out participants with depression or ADHD in order to avoid possible confounds. No participants were excluded from the study due to their response on this self-report measure.

Procedures

Email notifications of the study were sent to all students enrolled in the Honor's College and Graduate School of a four-year university in the southeastern United States. Students who responded to the email, confirmed their eligibility, and expressed an interest in participating were scheduled for a specific time to participate at their convenience. Participants were scheduled at one-hour intervals on either a Monday and Thursday, or Tuesday and Friday. When participants arrived, each was given the informed consent to review and sign (See Appendix A). Next, participants were asked to complete the Achenbach self-report form then completed the ANT and virtual water maze.

Once baseline measures of attention and memory were obtained, the participants were given two patches and a set of instructions (See Appendix B). After reading over the instructions, the participants cut one of the patches in half and applied the patch to their body. Participants were instructed to wear a new half-patch each day. On the fourth consecutive day of wearing the patch, the participants returned to the lab and again

completed the ANT and virtual water maze. Afterwards, participants were instructed to remove their patch and their participation was completed.

RESULTS

After the data were collected, several analyses were run in order to test the proposed hypotheses. See Table 1 for descriptive statistics for attention-related dependent variables. Dependent variables are not typically examined individually with a non-significant multivariate result. However, because hypotheses were offered regarding them, the following results describe individual dependent variables.

Alerting

It appears nicotine did not have a differential effect on alerting scores from pre-test to post-test (Patch x Pre/Post interaction): Wilk's $\Lambda = 0.94$, $F(1, 11) = .70$, $p = .42$, and there was no age dependent effect of nicotine from pre-test to post-test (Age x Patch x Pre/Post interaction): Wilk's $\Lambda = 0.99$, $F(1, 11) = .16$, $p = .70$. There were also no main effects of age, $F(1, 11) = .40$, $p = .54$, or patch, $F(1, 11) = .34$, $p = .57$, and no interaction between them, $F(1, 11) = .11$, $p = .75$ (see Figure 1).

Orienting

It was believed that nicotine would have a positive effect on the orienting network and there was expected to be an interaction with age. However, the data suggest that nicotine did not have a differential effect on the orienting network (pre-test to post-test), Wilk's $\Lambda = .95$, $F(1, 11) = .62$, $p = .45$, nor was there an age dependent interaction between nicotine and pre-test/post-test (Age x Patch x Pre/Post interaction), Wilk's $\Lambda = 0.97$, $F(1, 11) = .34$, $p = .57$. There were also no main effects of age, $F(1, 11) = 2.07$, $p = .18$, or patch, $F(1, 11) = 2.24$, $p = .16$, and no interaction between them, $F(1, 11) = .01$, $p = .93$ (see Figure 2).

Executive Control

Although it was expected that nicotine would have a positive effect on the executive control network of attention, this hypothesis is not supported. Data suggest nicotine did not have a differential effect on executive control scores (pre to post-test), Wilk's $\Lambda = 1.00$, $F(1, 11) = .01$, $p = .94$, nor was there an age dependent interaction between nicotine and pre-test/post-test (Age x Patch x Pre/Post interaction), Wilk's $\Lambda = 0.92$, $F(1, 11) = .90$, $p = .36$. As with the other networks of attention, there was not a main effect for age, $F(1, 11) = .17$, $p = .69$, or patch, $F(1, 11) = .47$, $p = .51$, nor was there an interaction between them, $F(1, 11) = 2.50$, $p = .14$ (see Figure 3).

While these results fail to support the hypotheses regarding the effect of nicotine on attention, the lack of power does not allow for an accurate analysis of the attention-related hypotheses.

Spatial Memory

Posttest data suggest there was not a main effect for patch type, $F(1, 11) = .02$, $p = .90$, nor age group, $F(1, 11) = .48$, $p = .50$. Posttest data regarding time to complete the virtual water maze suggest that neither patch type, Wilk's $\Lambda = 0.89$, $F(3, 9) = .35$, $p = .79$, nor age, Wilk's $\Lambda = 0.59$, $F(3, 9) = 2.07$, $p = .18$, had an effect on spatial memory (see Figure 4). Similar results were found with path length with regards to patch type, Wilk's $\Lambda = 0.83$, $F(3, 9) = .63$, $p = .61$, and age, Wilk's $\Lambda = 0.74$, $F(3, 9) = 1.05$, $p = .41$ (see Figure 5). Similarly, the three way interaction between escape latency, age group, and patch type was not significant, Wilk's $\Lambda = 0.96$, $F(3, 9) = .12$, $p = .94$, nor was the interaction between path length, age group, and patch type, Wilk's $\Lambda = 0.91$, $F(3, 9) =$

.30, $p = .82$. While these results fail to support the spatial memory hypotheses, the lack of power in all posttest analyses does not allow for an adequate analysis of the hypotheses.

DISCUSSION

The purpose of this study was to determine whether nicotine would have an effect on the attention and spatial memory of adolescents and adults. Participants were given either nicotine or placebo patches to wear for four days. Participants' spatial memory and attention network scores (alerting, orienting, and executive control) were compared to their baseline scores. Overall, the results suggest that nicotine did not have an effect on attention or spatial memory. The results appear to support the hypothesis that nicotine would not have an effect on the alerting network of attention. The hypotheses that nicotine would have a positive effect on the orienting and executive control networks of attention and on spatial memory were not supported. However, due to the low power observed in all posttest analyses (all of which were < .25), an accurate description of the interactions is not attainable.

There are several limitations to this study that may have affected the results. Participant recruitment was geographically limited. The low sample size reflects the difficulty the researcher experienced with recruiting participants. This small sample size led to low power and had an effect on the results.

Additionally, the researchers did not have a way of ensuring that participants were non-smokers and relied on participant self-reports. Related to this, the researchers relied on participants' compliance with patch application and behaviors while wearing the patch (i.e., abstaining from alcohol). If participants did not give accurate representations of their nicotine use, or if they were not compliant throughout the study, the desired nicotine levels in the blood may not have been achieved and ended up with skewed results. While

all of the participants reported they were compliant, the researchers could not confirm this.

While participants in the experimental group were given two 7 mg patches, it is assumed that each half patch contained 3.5 mg of nicotine. However, because nicotine blood serum levels were not confirmed, the exact dosage of each half-patch is assumed. It is also assumed that 3.5 mg of nicotine is a large enough dose to produce a measurable change in attention and spatial memory. However, McClernon, Hiott, Westman, Rose, and Levin (2006) found that participants given a 3.5 mg nicotine patch did not significantly differ on various cognitive tasks from participants wearing a placebo patch. It may be the case that 3.5 mg of nicotine is not significantly different from no nicotine and therefore no measurable effect could be observed.

Future research concerning the effects of nicotine on cognition should take these limitations into consideration. Particularly, a larger sample size is paramount to ensure a sizeable power is observed. It would also be helpful to monitor participants' nicotine levels, if possible. Additionally, including participants with specific disorders (i.e., ADHD, Alzheimer's Disease) and comparing their results with the results of non-disordered participants may yield significant results.

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APPENDICES

Appendix A: *Informed Consent Form*

Informed Consent Form
Nicotine Effects on Cognition

What is the purpose of this research? The negative effects of nicotine have been widely researched and reported to the general public. However, less is known about possible positive effects of nicotine. It has been suggested that the positive effects of nicotine are overshadowed by the negative effects of smoking cigarettes. The purpose of this study is to determine what effects, if any, nicotine has on cognition.

What will be expected of me? You will be asked to fill-out demographics forms and complete computerized cognitive tasks. Then you will wear four skin patches over a period of four days, each which may contain a 3.5 mg dose of nicotine. There is a 50% chance that you will receive this dose of nicotine. On the fourth day, you will be asked to return to the lab to complete computerized cognitive tasks.

How long with the research take? While the research will span over a 4-day period, you will only be asked to be in the lab for 2 hours: one hour on the first day, and one hour on the fourth day.

Will my answers be confidential? Yes. Your name will not be used at all in this research. You will not put your name on the data sheets, and the researchers will not know how you answered the questions. Your data will be coded using a confidential number.

Can I withdraw from the study if I decide to? You can withdraw from the research at any time, without penalty, and ask that your data not be used.

Is there any harm that I might experience from taking part in the study? While it is unlikely that you will experience side effects from the patch, it is a possibility that you may experience lightheadedness, nausea, dizziness, or other mild effects from the skin patch. If at any point you experience discomfort, you may take off the patch and be excused from the study. Any uncomfortable symptoms you may feel will be short-term.

If I am given a nicotine patch, can I become addicted to the patch or to nicotine? No, the patch is designed to release nicotine very slowly and you are unlikely to even notice if you have a nicotine patch. There are no known cases where someone has become addicted to nicotine patches in the past, and there is no reason to believe anyone will become addicted in this study.

How will I benefit from taking part in the research? You will obtain the satisfaction of knowing that you participated in a study that will shed light on how our society can

use nicotine in positive ways. In addition, if you are interested, we will send you a copy of the results.

Who should I contact if I have questions or concerns about the research? Contact me (Lauren Golden) at llgolden@gmail.com. You can also contact Dr. Shawn Acheson, faculty director of the project, at sacheson@email.wcu.edu or Dr. Meagan Karvonen, who chairs the university's Institutional Review Board, or IRB (the committee reviews all research for compliance with ethical guidelines concerning the treatment of research participants). Dr. Karvonen can be reached at 828-227-3323 (or karvonen@wcu.edu).

Participant Name_____
Date_____

Participant Signature_____

Researcher Signature _____

If you would like to receive a summary of the results, once the study has been completed, please write your email address (as legibly as possible) here:

_____

Appendix B: *Directions for Patch Application*

Directions for Patch Application

- You will have received a Ziplock bag with 2 patches cut in half. Each morning, on four consecutive days you will put on a new (1/2) patch. Remove the (1/2) patch from the previous day before putting on the new patch. Follow the directions below for the administration of the patch.

- Keep patches in the Ziplock bag you received them in until you are ready to use it.

- Only open the sealed package when you are ready to put on a patch.

- Peel the protective cover off the patch and throw the cover away. Try not to touch the sticky side of the patch (the side with the protective cover).

- Put one patch on a clean, dry area of skin on your upper body (between the neck and the waist) that isn't covered with hair, such as your stomach, upper arm or side. Do not put the patch on burned, cut, or sore skin.

- To apply the patch, place the sticky side on your skin and press it firmly with the palm of your hand for 10 seconds. Make sure the patch is flat and smooth against your skin.

- Wash your hands after putting on the patch.

- Do not wear the patch for more than 24 hours.

- When you take off the old patch, fold it in half with the sticky sides together. Put the old patch in the package from the new patch or in aluminum foil. Put the package or foil in the trash where children and pets cannot find it.

- Put the next patch on a different area of skin. Use a different area each day.

- It is normal to feel mild tingling, itching or burning when you put the patch on. This feeling usually lasts 15 minutes to 1 hour. When you take off an old patch, your skin may be red where the patch was. Your skin should not stay red for more than 1 day. If the skin stays very red for 2 days, or if it gets swollen or sore, do not put on a new patch. Immediately notify the researchers.

- You can wear your patch when you bathe, shower, swim or soak in a hot tub. Water will not harm the patch as long as it is firmly in place.

- If your patch comes off, put a new one on a different area of skin. Immediately notify the researchers. Change it again at the usual time the next day.

If at any point you feel discomfort, nauseous, dizzy, or otherwise uncomfortable, or if you decide you no longer want to participate, contact the researchers and the health center (if needed) immediately.

Lauren Golden: 678-524-3575; 828-293-9510; llgolden@gmail.com
Shawn Acheson: 919-286-0411, x-6093; 919-768-2243; shawn.acheson@duke.edu
WCU Health Center: 828-227-7640; Bird Building on WCU campus
Emergency: 911

Table 1

Descriptive Statistics of Attention Data by Session, Age and Treatment Group

	Adolescents		Adults		Total	
Measure	Nicotine[1]	Placebo[2]	Nicotine[3]	Placebo[4]	Nicotine[5]	Placebo[6]
Alerting						
pre-test (M)	39.00	28.40	56.33	43.00	45.50	32.57
(SD)	37.66	3.85	5.51	18.39	30.00	10.81
post-test (M)	31.40	36.20	36.33	28.50	33.25	34.00
(SD)	16.10	27.70	1.53	45.96	12.46	29.63
Orienting						
pre-test (M)	30.60	48.60	42.00	54.00	34.88	50.14
(SD)	5.68	15.92	13.89	16.97	10.41	14.96
post-test (M)	28.00	35.00	40.67	51.00	32.75	39.57
(SD)	24.05	14.02	11.02	21.21	20.20	16.34
Exec. Control						
pre-test (M)	142.80	110.20	94.00	154.00	124.50	122.71
(SD)	79.049	31.85	31.58	59.40	67.033	41.48
post-test (M)	97.60	91.60	96.33	133.50	97.13	103.57
(SD)	10.07	41.36	33.25	28.99	19.342	41.21

Notes: [1 & 2] n=5; [3]n=3; [4]n=2; [5]n=8; [6]n=7.

Figure 1

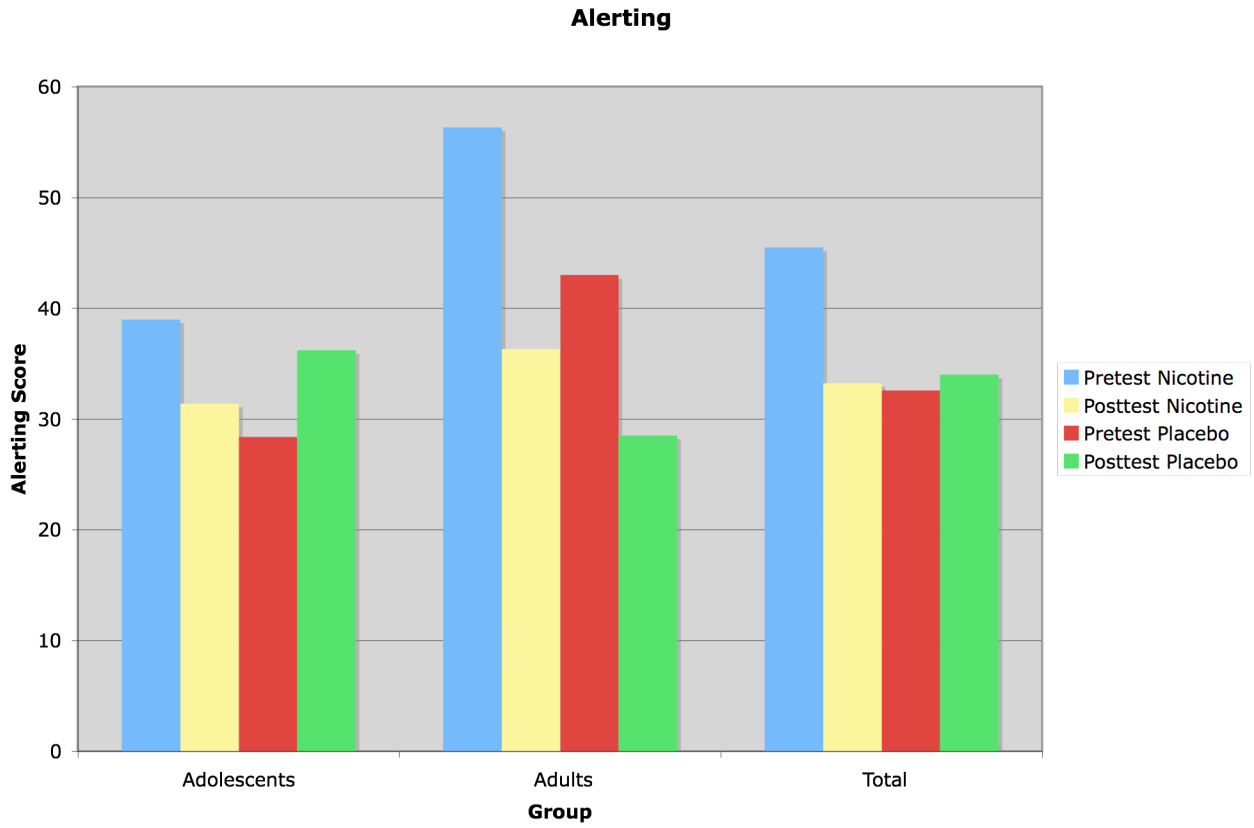

Alerting
Alerting Score
60
50
40
30
20
10
0
Adolescents
Adults
Total
Group
Pretest Nicotine
Posttest Nicotine
Pretest Placebo
Posttest Placebo

Figure 2

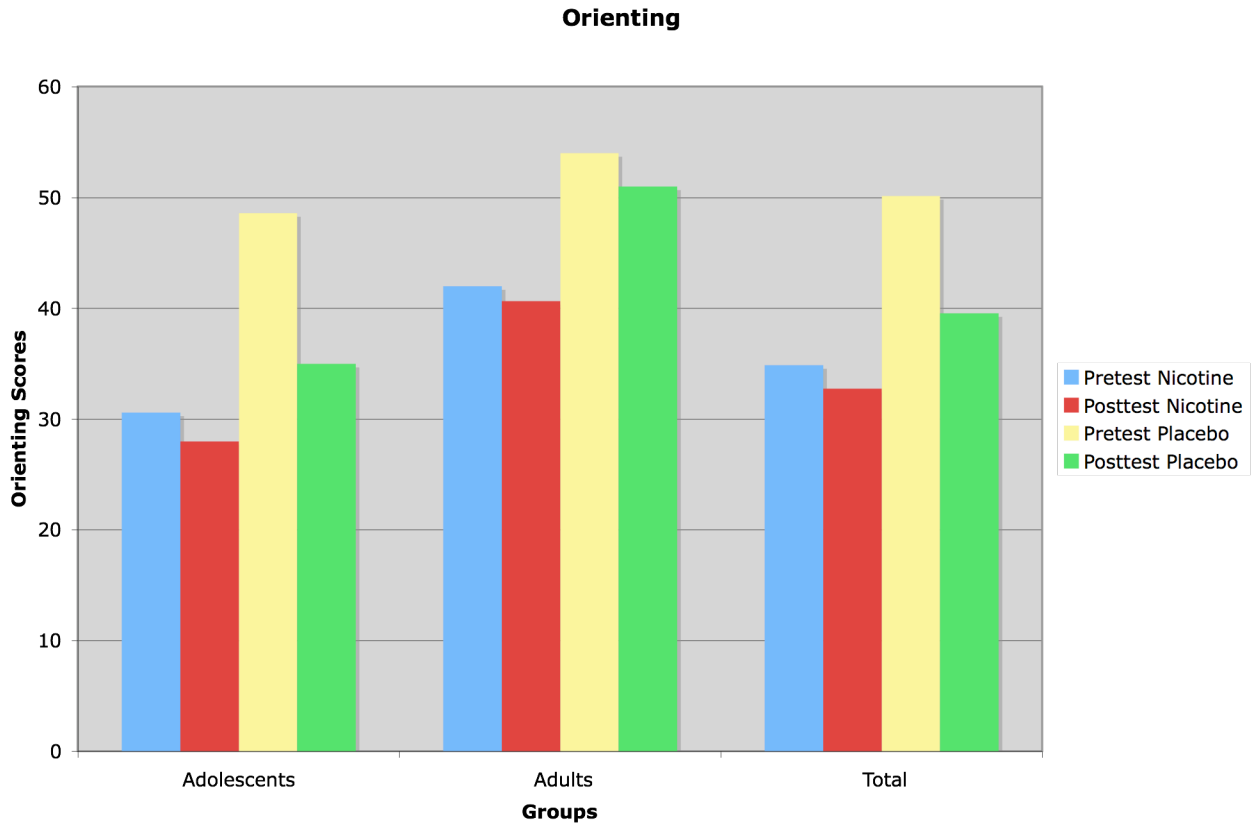

Orienting
Orienting Scores
60
50
40
30
20
10
0
Adolescents
Adults
Total
Groups
Pretest Nicotine
Posttest Nicotine
Pretest Placebo
Posttest Placebo

Figure 3

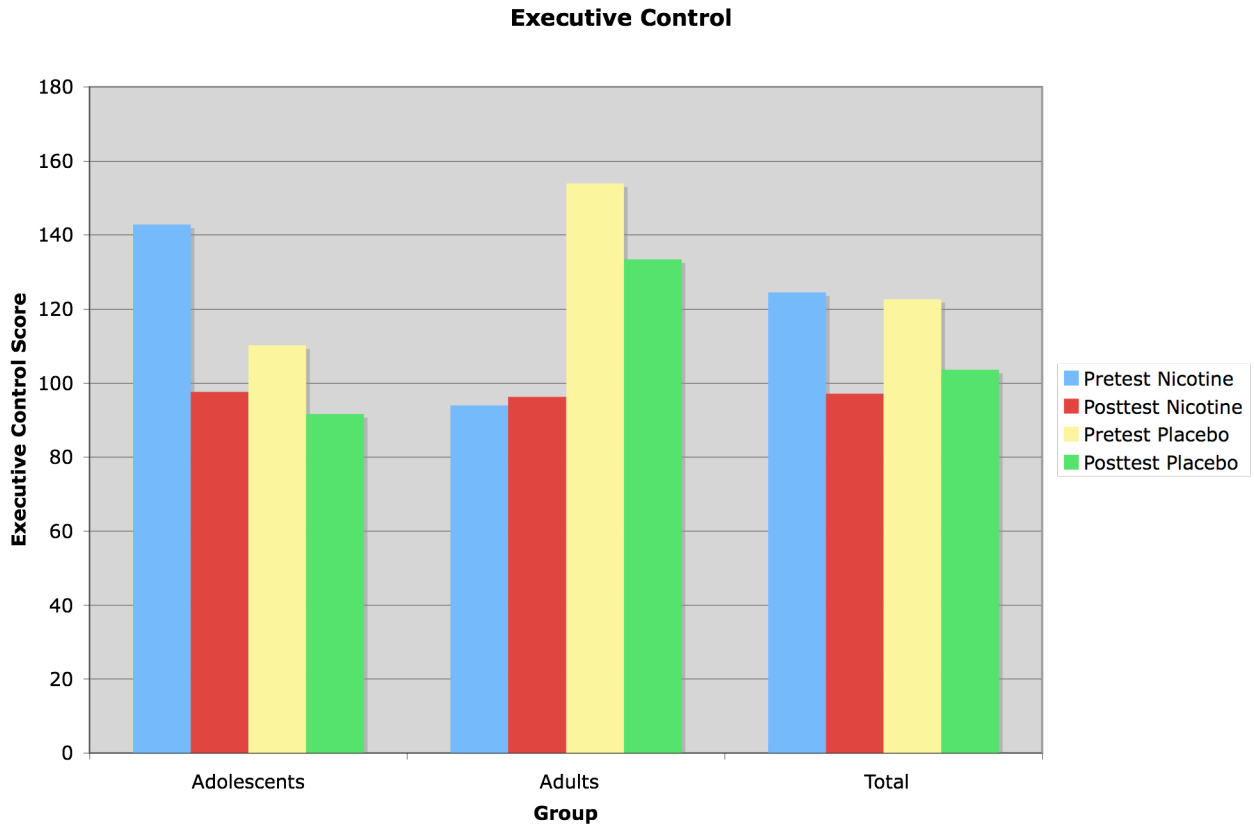

Executive Control
Executive Control Score
180
160
140
120
100
80
60
40
20
0
Adolescents
Adults
Total
Group
Pretest Nicotine
Posttest Nicotine
Pretest Placebo
Posttest Placebo

Figure 4

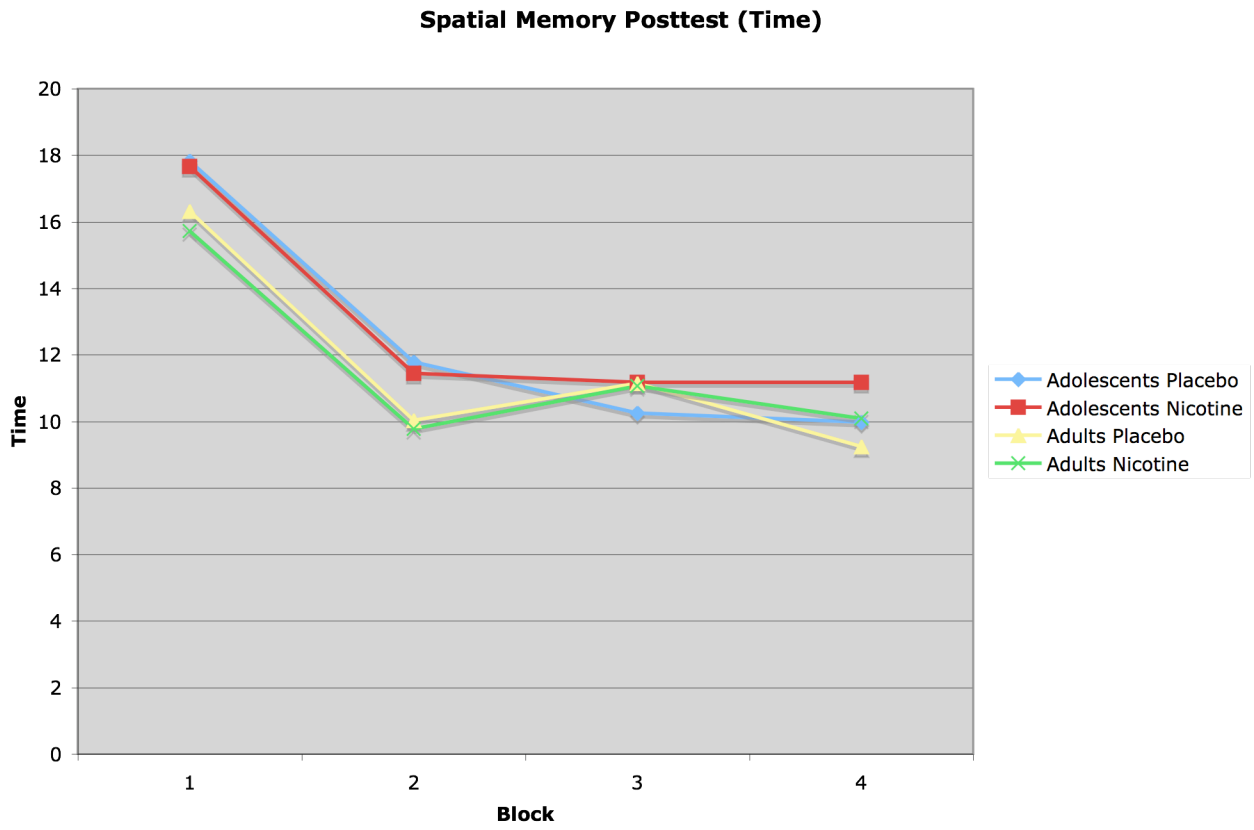
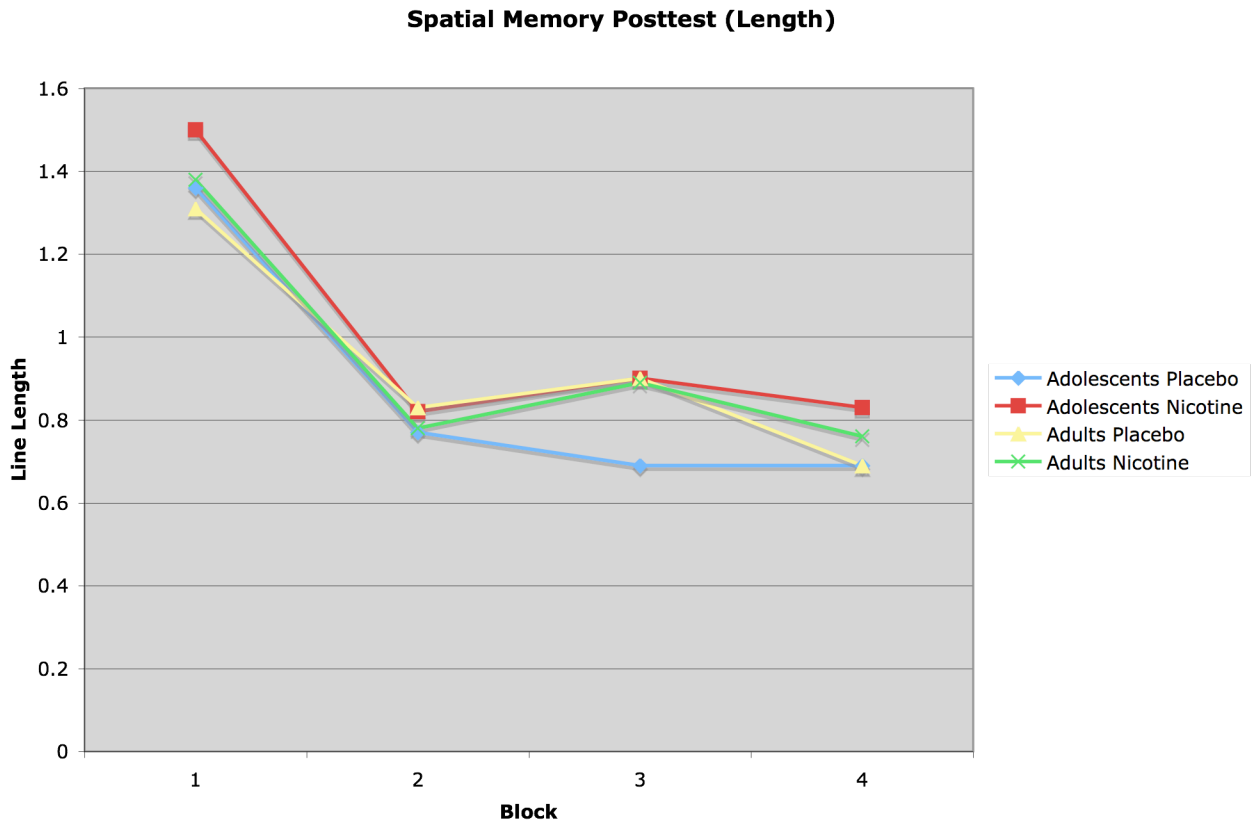

Spatial Memory Posttest (Time)
Time
20
18
16
14
12
10
8
6
4
2
0
1
2
3
4
Block
Adolescents Placebo
Adolescents Nicotine
Adults Placebo
Adults Nicotine

Figure 5


Spatial Memory Posttest (Length)
Line Length
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
1
2
3
4
Block
Adolescents Placebo
Adolescents Nicotine
Adults Placebo
Adults Nicotine