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Nicotine's Effect upon the Eye Movements Associated with Reading and Reading Comprehension

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30 March 2003
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Abstract:

Nicotine ingestion has been shown to have a significant effect on many cognitive functions and induces nystagmus in some subjects. This experiment was conducted to evaluate how nicotine affects reading comprehension and the eye movements associated with reading in nicotine-deprived smokers. The Visagraph instrument was used to monitor subjects' fixations, regressions, basic visual motor skills, and comprehension levels while reading standardized passages of text. Thirty subjects were measured in a double blind, treatment order-randomized, repeated-measure format, using nicotine gum and a placebo product. Subjects were divided into three groups based upon their smoking histories and experimental nicotine dose. Reading performance indicators with and without nicotine exposure were analyzed with an analysis of variance. There was not a significant effect of nicotine upon reading-associated oculomotor behavior. However, there was a significant negative effect upon reading comprehension as measured by the Visagraph system. Subjects achieved significantly lower reading comprehension scores after nicotine treatments than with placebo treatments. Neither the smoking history of the subject nor dose of nicotine significantly affected experimental outcome.

Nicotine's Effect upon the Eye Movements Associated with Reading and Reading Comprehension

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30 March 2003
By Laura Barnes, O.D.

It is estimated that one out of every four American adults smokes cigarettes (National Health Interview Survey, 1998).   Why do all these people smoke despite the countless public health campaigns discouraging it? Their answers vary considerably. Many smokers claim that they started smoking to "fit in" with their friends or project a certain image. Others claim that smoking helps them relax or that nicotine improves their ability to concentrate. Some people state that smoking fills a social need—and that they enjoy the camaraderie associated with smoking with their friends either at work or after hours. Other common reasons include weight control (Li et al. 2001), depression, habit, and simple enjoyment. For every smoker there is a reason or collection of reasons why he or she smokes. Some of these reasons may be tied to the neurophysiological effects of nicotine on the brain—and the psychological and physical additions associated with the drug.

Many smokers, it turns out, are children. In 1998, The National Health Interview Survey indicated that about 4.1 million American teenagers between the ages of 12 and 17 smoked on a regular basis. More than 6,000 people under age 18 try their first cigarette each day, and each day more than 3,000 of these persons under age 18 become daily smokers. Little is known about the effects of nicotine on cognitive development in young people. Today, smokers have a higher school drop-out rate than their non-smoking classmates and smoking is more common in the poor. Approximately one-third of persons living below the poverty level smoke on a regular basis. This said, smoking is still very common on college campuses (Rigotti et al., 2000). Nicotine rivals caffeine in popularity as students search for something that will give them "an edge" for studying for exams.

Because of the prevalence of nicotine in today's society, extensive research has been conducted on the drug's effects on a multitude of human and animal processes. Much of this research has centered on the effects of ingesting nicotine in quantities similar to that obtained from smoking one or two cigarettes. These experimental results are mixed—especially those associated with the cognitive effects of nicotine. Some research has indicated enhancement of memory, mental processing, and similar tasks with nicotine exposure. These findings are consistent with the impressions of many smokers that nicotine helps them mentally focus and think more clearly. Philips and Fox (1998) found that subjects who chewed nicotine gum showed improved recollection in specific short-term memory tasks. Similar benefits were found by Pineda et al. (1998) who concluded that smoking a cigarette may improve recall ability in habitual smokers by optimizing the cholinergic pathways involved in some memory processes. Wesnes et al. (1983) reported that rapid information processing was improved after subjects smoked nicotine-containing cigarettes compared to placebo cigarettes. Subjects who smoked higher doses of nicotine (1.5 mg) showed greater improvement than subjects smoking lower doses (0.5 mg). Krebs et al. (1994) found that immediate recall of expository passages was greater in subjects who smoked cigarettes containing moderate levels of nicotine (0.7 mg) than in subjects who smoked placebo cigarettes. Mancuso et al. (1999) found that, overall, chronic nicotine treatment via a transdermal patch positively affected attention and mental processing ability in subjects.

Not all studies have found cognitive benefits from nicotine, however. Some recent research has reported equivocal results with nicotine on cognitive demanding tasks while other papers have reported that nicotine may hinder some types of mental

processing. Park et al. (2000) reported that spatial working memory is impaired by nicotine consumption in smokers. Warburton et al. (2001) recently concluded in a study that incidental memory is improved after smoking a nicotine cigarette only after semantic processing (that associated with speaking), but not phonological processing (that associated with listening). In Kreb's study on expository passage recall (1994), the author found that smoking high doses of nicotine (1.5 mg) actually decreased immediate recall ability. Only low doses (0.7 mg) of nicotine were found to improve recall ability. In Taylor et al's research on rats (2002), only old rats benefited from nicotine ingestion in cognitively demanding maze tasks, not younger rats. Houston et al. (1978) found that smoking nicotine cigarettes significantly impaired subjects' abilities to freely recall words from a list and that these effects lasted for two days. In short, research to date on nicotine and mental processing has been mixed. In some tasks nicotine seems to help the human brain process information, and in other tasks nicotine seems to hinder it.

Nicotine's effects upon mental processing have been studied more extensively than its effects upon oculomotor behavior. However, research indicates that eye movements can be affected significantly by nicotine. Many researchers have dedicated significant effort to identifying how nicotine affects eye movements. Tibbling (1969, 1970) and Sibony et al (1990) have written extensively about nicotine-induced nystagmus and contributed to our understanding of its relationship with the vestibulo-ocular coordination system and incidence among smokers. Pereira and colleagues (2000, 2001) have also described nicotine-induced nystagmus and attempted to pinpoint its neuromotor etiology. Pereira et al have shown that nicotine-induced nystagmus is most likely to occur in subjects without significant histories of nicotine exposure and that it typically

continues for 5-10 minutes after ingesting the dose of nicotine found in an average cigarette. Further, Pereira's work indicates that nicotine-induced nystagmus is most likely related to an imbalance in the vestibulo-ocular reflex system and that nicotinic nystagmus directional patterns (both horizontal and upbeat) can be altered by body position and suppressed by ocular fixation.

Nicotine is a tertiary amine with high cell membrane permeability. Its cell permeability allows smokers to "bathe" their brains in nicotine within a minute of inhaling from a cigarette. The uptake profiles of nicotine gum differ from cigarettes in that it takes about six minutes longer for plasma nicotine concentrations to peak when the nicotine is absorbed through the bucal mucosa instead of the aveoli. Nicotine has been shown to be converted to cotinine by the liver at a rate that varies from individual to individual (Lindstrom, 1997).

Nicotine's biochemical target is the nicotinic-type of cholinergic receptor. Nicotinic receptors in the brain are pentameric structures made up of α and β subunits (Gotti, et al. 1997). The various nicotinic receptor subtypes have unique pharmacologies, physiologies, and distribution in the central nervous system (Jones et al. 1999). The α subunits, of which eight distinct types have been discovered, have two adjacent cysteines. The β subunits lack this cysteine pair and are known to have at least three representative types. In the human brain, the cholinergic system is thought to be made up of a group of closely interknit subsystems. These subsystems consist of eight major and largely overlapping groups of cells, with extensive interconnections (Gotti et al., 1997; Karlin, 2002; Paterson and Nordberg, 2000). This pattern of extensive interconnections may lead to coordinated firing of groups of contiguous neurons, and to

the coordinated activation of different cholinergic subsystems (Barkai and Hasselmo, 1997; Gotti et al., 1997). Some of the major cholinergic subsystems in the human central nervous system are located in the striatum, magnocellular basal complex, hypothalamus, peduncolopontine-lateral dorsal tegmental complex, lower brain stem, and in preganglionic neurons (parasympathetic and sympathetic) of the spinal tract (Jones et al., 1999; Paterson and Nordberg, 2000). The receptors in the frontal, temporal, and parietal cortex are thought to be most closely related to nicotine's effects upon information processing (Karlin, 2002; Levin et al., 1998). The hippocampus, in conjunction with the cerebral cortex, is considered to play a key role in learning and memory function and appears to be sensitive to changes in serum nicotine concentration (Dani et al. 2001; Gray, et al., 1996; Jones et al., 1999; Levin et al., 1999; Rexvani and Levin, 2001). The nucleus basalis of Meynert has further been identified as being important in this respect and is significantly influenced by serum nicotine levels. Nicotine's effects upon oculomotor output, on the other hand, may be most related to concentrations of ACh receptors in the brainstem, particularly in the medial and lateral vestibular nuclei that project to the oculomotor nuclei, to the cerebellum and to the spinal cord. Pereira (2000, 2001) showed that nicotine may mimic an increase in peripheral vestibular input and thus induce the brain to activate vestibular oculomotor responses.

Nicotine does not act alone neurologically. When absorbed into the central nervous system, it stimulates the release of many different neurotransmitters (Picciotto, 2002). Among these secondary substances released in the "nicotinic cascade" are acetylcholine, glutamate, norepinephrine, dopamine, GABA, and serotonin (Tortoro et al. 1990). Although all these neurotransmitters have very complex and interconnected

roles in neurological control, many of their main effects can be summarized simply. Acetylcholine and glutamate have been associated with memory retention and cognitive processing. Norepinephrine causes feelings of stimulation and arousal while dopamine's effects are related to the sensation of pleasure (Cooper et al., 1996). GABA is thought to induce relaxation and to relieve nervous tension (Picciotto, 2002) and seratonin is an important neurotransmitter that affects mood (Palleb et al., 2002; Tortora et al., 1990). The variable pharmacological behavior of the different receptor subtypes (α's and β's) is thought by many researchers to account for different levels of secondary neurotransmitter release and ultimately for variable behavioral effects of nicotine under different routes of administration (Picciotto, 2002).

The mental, hormonal, and baseline neurotransmitter status of the smoker before smoking a cigarette can allow one or more of the chemicals that are released secondary to nicotine stimulation to have greater than normal effect. Expectation on the part of the smoker may play a key role in this tendency. For example, in a nervous person, the anxiolytic properties of the GABA released may be more sought after than the pleasurable effects of dopamine. In a painful situation, the opposite may be true. Smoking in times of fatigue may be stimulating. Smoking before bedtime may provide relaxation. The environment of administration and predisposing factors of the subject can influence nicotine's dominant effects (Gotti, 1997).

One purpose of this research project was to identify whether nicotine has a significant effect upon reading comprehension in nicotine- deprived smokers, and if so, if it helps or hinders the process. Also, does nicotine, with its known effects upon certain oculomotor activities, also have an effect upon the finely coordinated eye

movements associated with reading in this population? The reading comprehension question becomes practical when one considers the number of students who reportedly smoke cigarettes on a daily basis and previous research papers offering variable conclusions about nicotine's effects on learning. How nicotine affects reading eye movements is important because it is generally known that some readers already have fragile oculomotor control systems—especially poor readers. For a poor reader, the oculomotor control required to rhythmically move his/her eyes across a line of text is often challenging enough without having to compensate for nystagmus. Understanding how nicotine affects the oculomotor control system is valuable for both educators and clinicians alike.

Although many papers have been published on nicotine's effects upon various types of mental processing, I have been unable to find any previous research addressing how nicotine ingestion affects reading comprehension. Reading comprehension is the ability to not only recall information, but also to grasp meaning from written material that may not be spelled out in an obvious manner. For example, consider this passage:

The kitten is in the picnic basket. The picnic basket is sitting on the breakfast table.

The reader does not specifically read that the kitten is in the kitchen but can draw that conclusion by knitting together the meanings of both sentences and using prior experience to recall that breakfast tables are usually in kitchens. This skill is different than simply recalling information. Many people can recall a sentence or two from a paragraph even if they cannot understand the language in which it was written. Reading

comprehension is related to language interpretation skill, short-term memory, spatial visualization, sequential logic, and the ability to integrate old and new information together.

The first goal of this research was to determine whether nicotine affects reading comprehension—positively or negatively and if so, to what extent. Developing a prediction for this research question was challenging because of the mixed results published in prior papers by other authors. However, I felt that reading comprehension was most similar to cognitive skills in other experiments that had generally improved after nicotine exposure, such as the work on free recall ability by Phillips and Fox. Therefore, I predicted that the subjects would answer more reading comprehension questions correctly after chewing nicotine gum than after chewing a placebo gum. This hypothesis was reinforced by reports from smokers who described significant improvements in concentration after smoking. I expected the casual smokers to have a more pronounced effect from nicotine than their heavy smoking counterparts due to decreased drug tolerance. Further, in the heavy smoking group, I expected some tolerance to have developed toward nicotine. Because of this, I expected more subtle nicotine effects in the heavy smokers overall, and little or no effect when they were given the lowest dose of nicotine.

The oculomotor demands of reading are significant. As described by Ciufredda and Tannen (1995), readers must make extremely complex eye movements that require fine motor control. Six muscles per eye must be directed to contract and relax in concert as they move the eyes across a line of text and allow the brain to maximally absorb the meaning of the written words. Fixations, small interfixation saccades, and return-sweep

saccades must all occur in harmony for efficient information transfer to occur from written page to mind. Fixations are pauses that the eyes make while recognizing words or syllables (the time the eyes remain paused on a word or segment of written material). Fixation duration varies significantly with text predictability, language ambiguity, and the grammatical purpose of the word being fixated. Between each fixation, a reader makes small interfixation saccades from left to right. These little "hops" allow the eyes to skip from fixation to fixation, absorbing written meaning at each pause. Return sweep saccades are large oblique right-to-left movements that shift the eyes down towards the beginning of the next line. Another type of reading eye movement is called a regression. Regressions are backtracking movements that allow the reader to double check parts of the written material they have already read. Regressions are right to left in direction and normally occur at a rate of approximately 10% of the total number of saccades. Inexperienced readers tend to make more regressions. Regressions are also common in text with grammatical errors (Ciufredda and Tannen, 1995).

As previously mentioned, nicotine has been shown to induce nystagmus in some subjects (Pereira et al., 2000; 2001). The presence of abnormal nystagmus can lead to poor reading performance in affected individuals, making it difficult for affected persons to keep their place while reading. It can reduce visual acuity and has been known to induce compensatory eye movements. These compensatory eye movements have been described clinically in other cases of nystagmus as exaggerated fixations—staring-like behaviors that may be directed in the direction of gaze offering the most significant dampening of nystagmus tremor. I predicted that nicotine consumption would lead to an increase in fixation frequency and duration, particularly in "casually smoking subjects"

because they have been reported to be more prone to nicotinic nystagmus than their heavy smoking counterparts (Pereira et al., 2000; 2001). Again, I expected the casual smokers to generally have a more pronounced oculomotor effect from nicotine than their heavy smoking counterparts due to limited drug tolerance. Further, in the heavy smoking group, I expected significant resistance to have developed to nicotine. Because of this, I expected more subtle oculomotor effects in the heavy smokers overall, and possibly little or no effect in the group given the lowest dose of nicotine. This hypothesis assumed that the visual stabilizing cues found in the testing environment (i.e. central and peripheral objects on which to fixate, like tables and carpet) were not going to be strong enough to completely suppress the nicotinic nystagmus by themselves. In other words, the subjects would also need to alter their oculomotor patterns while reading to compensate for the nicotine-induced-nystagmus.

Methods

Research Format:

The experimental design involved two classes of smokers—one casual smoking group (n=10) that self-reported smoking fewer than a pack of cigarettes a week, and one heavy smoking group that reported smoking more than 24 cigarettes a day (n=20, half of which received a low dose of nicotine and half of which received a lower dose).

Subjects:

Thirty subjects were recruited for this study. Ten of these subjects reported current histories of casual smoking. Twenty subjects reported current histories of heavy smoking. Subject recruitment was primarily focused upon the university student population. The mean age of participants was 22 with a range of 18-33 years and a standard deviation of 3.9 years. After telephone screening to confirm eligibility, each experimental subject was seen a total of three times—initially for a preliminary screening including an eye exam, and then twice for actual experimental visits. One

experimental visit included a nicotine treatment while the other included a placebo treatment. The order of the experimental visits was randomized.

Recruitment Criteria:

Eligible subjects were smokers between the ages of 18 and 35 years and had English as their primary spoken and written language. Subjects were screened for reading skill level with the Woodcock Johnson Reading Test and visual attention with the Test of Visual Perception Skills before being accepted for participation in the study. All subjects received a comprehensive eye examination prior to the experiment to verify normal near acuity (20/30 or better) and binocular status (scoring 40 arc seconds or better on stereo fly and showing no tropia). Subjects were excluded if they had histories of reading disorder(s) or oculomotor pathology. Eligible subjects described themselves as being in good general health. They were not taking any medications known to cause neuromotor side effects. Subjects were asked not to smoke (or consume nicotine in other forms) for at least 5 hours prior to the procedure and to abstain from consuming food or drinks for five hours prior to the procedure because it has been reported that acidic drinks may alter the nicotine uptake profiles of nicotine gum. Subjects were told that consuming nicotine before the experimental visits would make them ineligible for study participation.

After initial contact by telephone, each volunteer who met the inclusion criteria for age, smoking, and health history was invited to have an extended participation

screening in person. Written informed consent was mailed to each participant who passed the telephone interview and was later reviewed at the preliminary examination appointment before being signed by the subject and researcher. Subjects were compensated for their time. All experimental procedures were approved by the institutional review board at the University of Missouri, St. Louis.

Experimental Procedure:

The eye movements associated with reading were recorded on a laptop PC computer running Visagraph software. It is non-invasive, painless, and relatively quick for subject testing. This software also provided questions to test subjects' reading comprehension levels. The software measured the overall time to read each passage, and quantified many aspects of oculomotor behavior while the subjects read silently to themselves. A subtest of the Visagraph, the Visual Skills Test, was used to evaluate basic oculomotor skills while the subjects completed non-text based exercises.

The Visagraph uses a head mounted infrared device to monitor eye movements while the subject reads from paragraphs of standardized difficulty. The program allows the operator to choose the level of reading difficulty. In this study, level 10 was used. Level 10 is designed for people with moderately high levels of reading proficiency. The standardized paragraphs for level 10 are biographical narratives about significant historical figures. The Visagraph's large selection of test paragraphs at each reading level allowed both practice sessions for subjects and repeated experimental measurements to be taken without having to use any paragraph more than once per subject. A photo of the Visagraph device follows.

Figure 1) The Visagraph uses a head mounted infrared device to monitor eye movements while the subject reads from paragraphs of standardized difficulty. The infrared visor is adjusted to comfortably fit the wearer and takes into account his/her papillary distance. The system runs on a personal computer and is capable of measuring a number of fine eye movements associated with reading.

After an initial screening visit lasting approximately 80 minutes, two experimental sessions lasting approximately 20 minutes each were conducted. Subjects were tested in a double blind, two experimental visit format--once with nicotine gum and once with placebo gum. Subjects therefore acted as their own controls. Each type of gum was pre-packaged for each subject and coded by a third party. Nicotine and placebo gums were paired together, and labeled as dose "one" or " two." The subjects were asked to chew their gum in a standardized manner, consistent with the recommended delivery of the manufacturer of Nicorette gum. The chewing method is

described below. Placebo gum had a similar shape, color, and flavor as the Nicorette gum.

The dosage of nicotine varied by smoking history and group. All casual smokers were given the lowest dose of nicotine (2 mg), a dose consistent with the manufacturer's recommended dose for light smokers. Heavy smokers were either given the dose of nicotine recommended on Nicorette package directions for their particular smoking history (4 mg dose) or half that dose (2 mg). Heavy smokers were randomly assigned to their dosage group (4 mg or 2 mg). No casual smoker was given the larger (4 mg) dose of nicotine for safety reasons. An average cigarette delivers 1 mg of nicotine (Thompson et al., 1998). The manufacturer of Nicorette states that only about half the nicotine in each piece of gum is absorbed into the blood stream when it is chewed according to package directions. Therefore, the casual smokers (and the heavy smokers assigned the low dose) absorbed about 1 mg of the nicotine from the gum— which was similar to that obtained from one cigarette with an average inhalation level. The heavy smokers assigned the full strength of nicotine gum (4 mg) were assumed to absorb about 2 mg (per manufacturer data) --which was similar to that obtained from 2 cigarettes smoked consecutively with average inhalation levels. Therefore, all subjects were given doses of nicotine comparable to those obtained in typical "smoking breaks."

At their initial screening visit, subjects became familiar with the Visagraph instrument, the types of passages they would be asked to read, and the types of reading comprehension questions that would be asked. Subjects also had two practice sessions before each experimental session. Each session used a different set of passages and no

passages were repeated during data collection. These practice sessions were used to help relax subjects and decrease learning effects between sessions.

At each experimental session, it was confirmed by verbal questioning that the subject had not eaten, drank, or smoked for at least 5 hours prior to the visit. The subject's blood pressure and pulse were measured and water was used as a mouth rinse. After another two practice sessions on the Visagraph, the subject was given a randomized gum treatment and directed how to chew it properly. The subject was asked to chew each piece of gum for sixty seconds to soften it. After sixty seconds the subject placed the gum against the bucal mucosa for three minutes. After three minutes, the gum was chewed again ten times and then held against the bucal mucosa for another three minutes. After this, it was chewed again ten times and then held against the cheek while the first Visagraph passage was read. Between passages the gum was again chewed ten times and planted against the bucal mucosa for the duration of Visagraph testing. A chin rest was employed to minimize head movement and standardize reading distance and lighting environment. Photometry readings confirmed that lighting conditions were similar from session to session. Each subject read two paragraphs for data collection and completed the visual skills section of the Visagraph program at each experimental visit. After data collection, blood pressure was again measured before the subject was dismissed.

Experimental Measures:

The presence or absence of nystagmus was determined by evaluating the oculomotor tracings produced by the Visagraph instrument during the fixation maintenance portion of the visual skills test. If nystagmus was present, the tracings would show excessive oculomotor activity.

The mean duration of fixation was the length of time, on average, the eyes paused on words and/or parts of words to collect information. It was computed by the Visagraph by dividing the total time required to read a paragraph by the number of fixations. Although this method of calculating the mean duration of fixation also includes the time required to make saccades, the measurement is still a valid approximation of fixation duration. This calculation is appropriate because saccades are very rapid and stable in velocity. The mean fixation frequency was calculated automatically by the Visagraph device by evaluating how many times the subject's eyes paused per 100 words during reading.

The mean regression frequency per 100 words is calculated by the Visagraph, but can easily be counted manually on the Visagraph data tracing. A regression is seen when the eyes make a right to left movement within a line to reread a portion of the text. The Visagraph's automatic calculation of regressions does not have a correction factor for head sway corrections—which can look similar on the tracing. However, in our experiment, this was not an issue because the chin rest prevented head sway.

The mean rate with comprehension was also automatically calculated by the Visagraph program. This measurement refers to the time required by the reader to read through a given selection knowing that he/she must comprehend what he/she reads. The Visagraph measures how long the reader takes to read a passage, and then subtracts out the time the reader took to finish the first and last lines. The first and last lines of text tend to have the greatest variability in rate of all lines in a passage. By subtracting out the time required for the first and last lines, some researchers believe that a better picture of typical reading behavior can be seen (Taylor, 2000).

The Visual Skills portion of the test is a set of three evaluations designed to determine a subject's binocular coordination ability using non-word targets. The visual skills test consists of three parts—fixation maintenance, motility, and tracking. The fixation maintenance portion measures the subject's ability to maintain fixation on a single location for three frames of recording. Any deviation greater than 1% of the mean overall eye movement range is recorded as a fixation (Taylor, 2000). The fewer fixations a subject makes, the better fixation maintenance control he or she is considered to have. This portion of the Visual Skills test was also used to evaluate eye movements for signs of nicotine-induced nystagmus, which would be recorded as oscillating patterns on the eye movement tracings. The motility portion of the Visual Skills test measures the ability of the eyes to move rapidly and accurately between two targets for four frames of trace recordings. The measurement of interest here in our experiment was the average duration of fixation between swing movements. The Tracking portion of the visual skills test measures the ability of the subjects to coordinate exact saccades and fixations across a series of numbers 1-20, arranged in

four lines. Again, the useful information here for our experiment was the mean fixation duration—the average time the eyes spent on each number. The duration of fixation on the tracking portion of the visual skills test is usually calculated automatically by the computer, but can also be calculated manually by dividing the total time required to complete the section by twenty. The resulting mean duration of fixation can then be adjusted for the presence of regressions (if any are present).

Reading comprehension questions were designed to be asked orally immediately following completion of the passage. The questions were crafted by the producers of the Visagraph program to control for vocabulary and sentence structure difficulty. The order of the presentation of the questions was also controlled to prevent information from one question from influencing responses to later ones (Taylor, 2000).

Statistical Analysis:

Using SPSS 11, a repeated-measure analysis of variance was used to identify significant nicotine effects upon a number of oculomotor and comprehension measurements. As planned, the mean duration of fixation during reading, mean fixation frequency during reading, the mean regression frequency during reading, the reading rate, the mean duration of fixation on visual skills portions of the test, and the number of reading comprehension questions answered correctly by subjects were all evaluated for significant nicotine effects within-subjects. Also as planned, we looked for significant between-subjects effects, by comparing experimental outcome between the three groups; light smokers receiving the 2 mg strength gum, heavy smokers receiving the 2 mg strength gum, and heavy smokers receiving the 4 mg strength gum.

In the course of data analysis, in order to clarify findings, additional statistical operations were performed. Because subjects in the three groups could have varied considerably on reading comprehension abilities and visual memory skills, an analysis of variance between groups was also run for the Woodcock Johnson Reading Comprehension test results and the Test of Visual Perception Skills test results. In addition, because of unanticipated effects of nicotine on reading comprehension, a regression analysis was done on each of these pretests as a function of the difference between subjects' reading comprehension scores with and without nicotine.

Expected Results:

As described previously, I expected nicotine ingestion to improve reading

comprehension scores. Also, I expected nicotine to significantly increase fixation

behavior, both in duration and frequency. The following is a summary of my

hypothesized effects:

	Mean fixation duration compared to placebo (both reading and visual skills tests)	Mean fixation frequency compared to placebo	Mean reading rate compared to placebo	Mean regression frequency compared to placebo	Number of correct answers on reading comprehension questions compared to placebo
Casual Smokers After Nicotine Gum with 2 mg nicotine	Significant increase in duration of fixation with nicotine compared to placebo. Larger effect size anticipated here than that found in 4 mg Heavy smoking group below.	Significant increase in number of fixations per passage with nicotine compared to placebo. Larger effect size anticipated here than that found in 4 mg Heavy smoking group below.	Significant decrease in reading rate with nicotine compared to placebo. Larger effect size anticipated here than that found in 4 mg Heavy smoking group below.	No predicted change	Significant improvement in reading comprehension scores with nicotine compared to placebo. Larger effect size anticipated here than that found in 4 mg Heavy smoking group below.
Heavy Smokers After Nicotine Gum with 4 mg nicotine	Significant increase in duration of fixation with nicotine compared to placebo. Smaller effect size anticipated here compared to casual smoking group above.	Significant increase in number of fixations per passage with nicotine compared to placebo. Smaller effect size anticipated here compared to casual smoking group above.	Significant decrease in reading rate with nicotine compared to placebo. Smaller effect size anticipated here compared to casual smoking group above.	No predicted change	Significant improvement in reading comprehension scores with nicotine compared to placebo. Smaller effect size anticipated here compared to casual smoking group above.
Heavy smokers after Nicotine gum with 2 mg nicotine	No significant difference between placebo and treatment trials	No significant difference between placebo and treatment trials	No significant difference between placebo and treatment trials	No predicted change	No significant difference between placebo and treatment trials

Table I: Expected results prior to data collection.

<u>Results:</u>

The results from this study did not confirm the predictions set forth before data collection began. Nicotine did not induce nystagmus under the conditions in this experiment, nor did it cause an increase in fixation duration and frequency. Also, instead of improving reading comprehension scores, as previously predicted, under the conditions used in this experiment, nicotine exhibited a significant negative effect on reading comprehension.

Oculomotor Results:

The tracings obtained during the fixation maintenance portion of the visual skills test from the Visagraph instrument suggested that nicotine-induced-nystagmus was not present in my subjects. The tracings were consistent with normal fixation behavior and did not show excessive oculomotor deviations while subjects fixated on the test's target.

The average duration of fixation did not significantly change between placebo and nicotine trials (F=0.733, P=0.399). There was no difference among groups (F= 0.130, P=0.879). As shown in Figure 1, fixation duration ranged from 0.200 seconds to 0.385 seconds under placebo and from 0.200 to 0.373 seconds with nicotine. The experimental outcome did not vary significantly among groups, as seen in Figure 2.

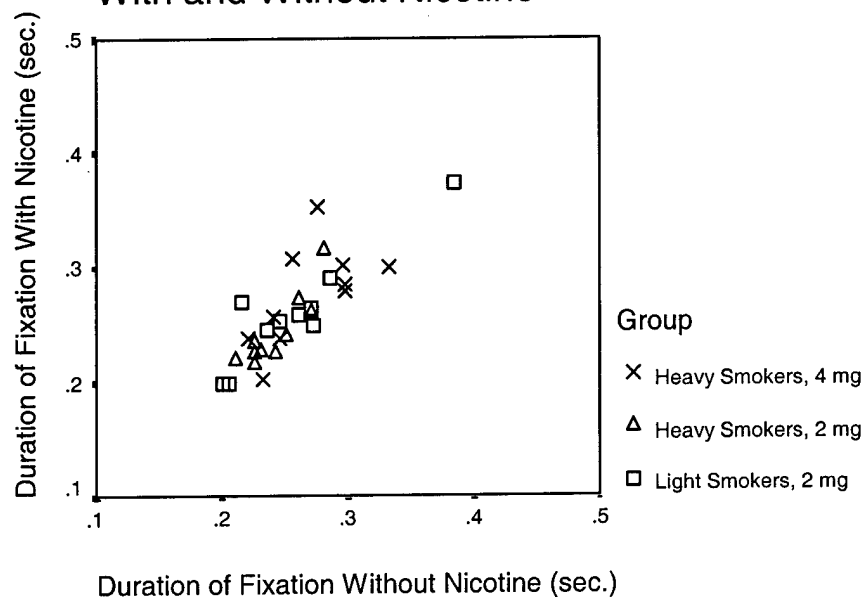## Average Duration of Fixation

With and Without Nicotine

Figure 1: Subject data summary chart for the average duration of fixation for subjects with and without nicotine treatment. Nicotine did not significantly alter the duration of fixation in this experiment. There was no significant difference among groups. There were 13 data points above the equality line, and 17 below the equality line. Here relatively "outlying" data points have been evaluated and found to be reliable.
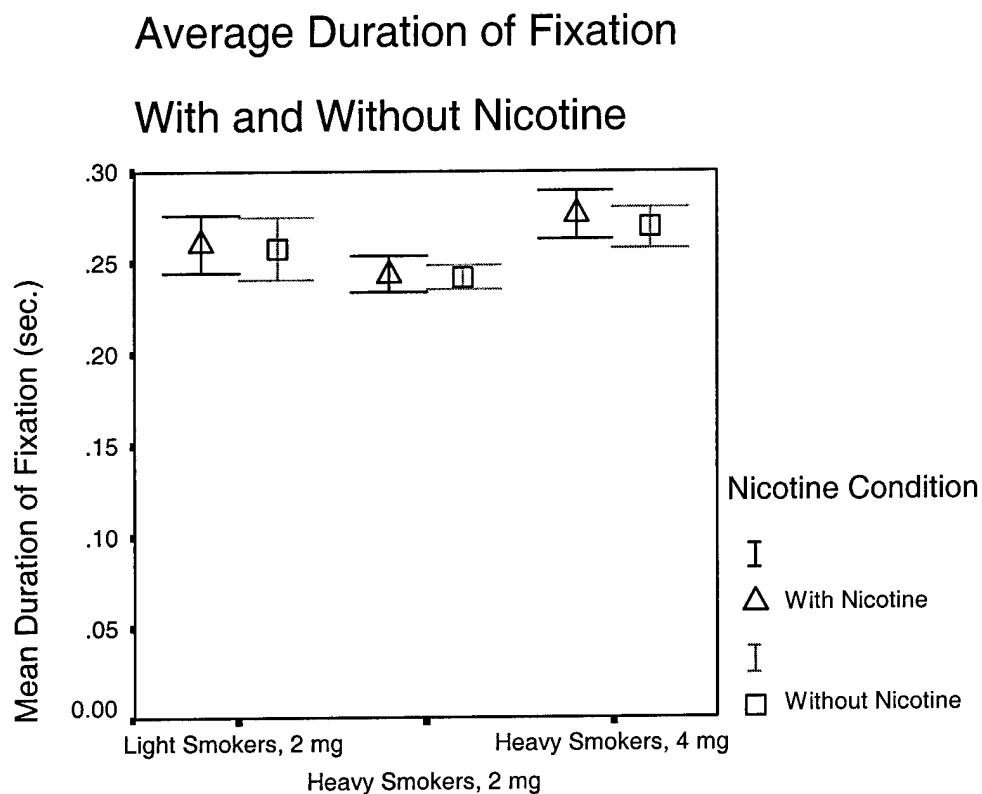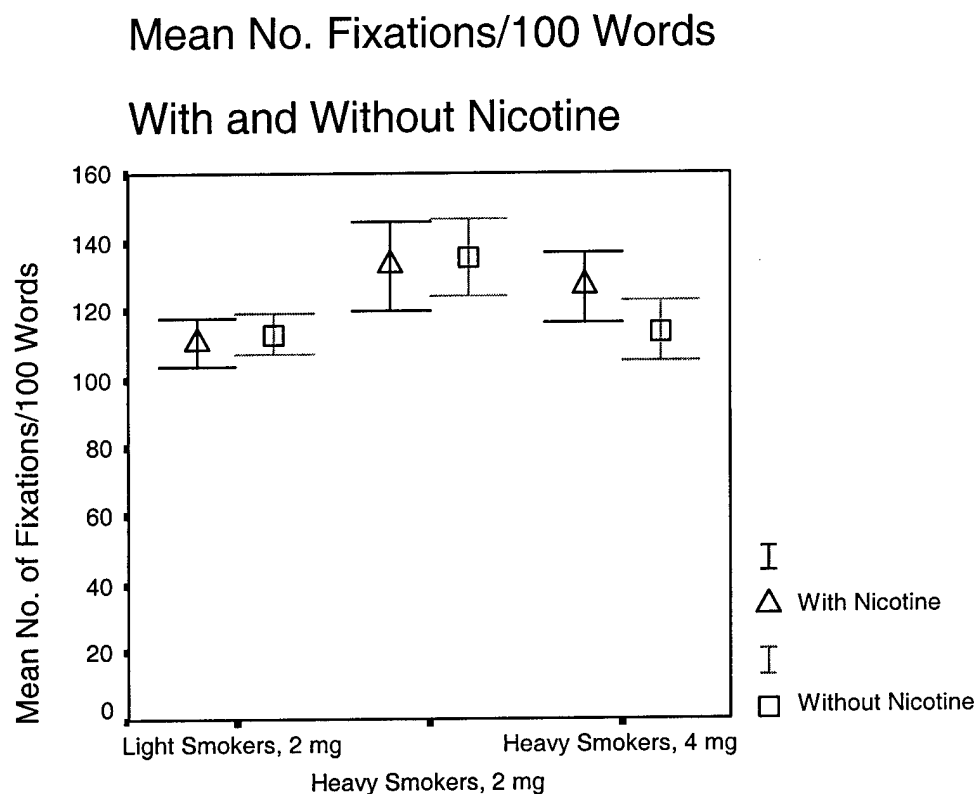
Average Duration of Fixation

With and Without Nicotine

Figure 2: This graph depicts the average durations of fixation while reading with and without nicotine exposure for all three experimental groups. Error bars indicate one standard deviation of data variability. There was no significant difference among groups.

The mean number of fixations per 100 words of text did not change between nicotine and placebo trials (F=0.569, P=0.457). There was no significant difference between groups either (F=1.955, P=0.161). As shown in Figure 3, fixation frequency ranged from 60 to 188 fixations per 100 words under placebo conditions and from 61 to 192 with nicotine. This outcome did not vary significantly among groups, as seen in Figure 4.
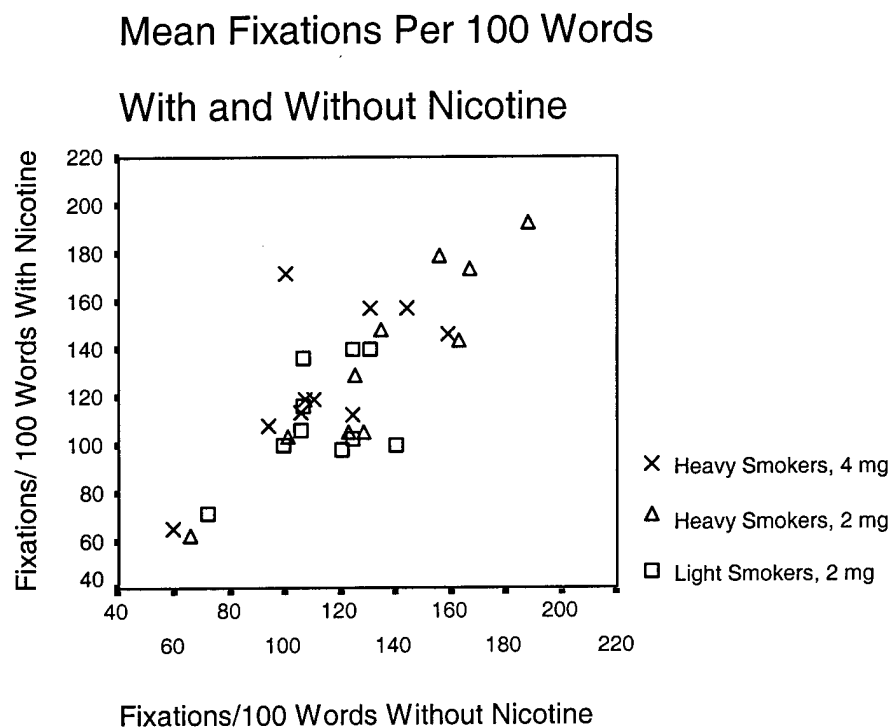
Figure 3: Nicotine did not significantly alter the fixation- frequency between nicotine and placebo trials. Further, no group produced significantly different results from the others in this respect. There were 21 data points on or above line of equality, and nine points below.

Mean No. Fixations/100 Words

With and Without Nicotine

Figure 4: This graph depicts the mean number of fixations per 100 words while reading with and without nicotine exposure for all three experimental groups. Error bars indicate one standard deviation of data variability. There was no significant difference among groups.

The mean number of regressions per 100 words of text did not significantly change between nicotine and placebo trials (F=0.861, P=0.362). As shown in Figure 5, regression frequency ranged from 3 to 57 regressions per 100 words under placebo conditions and from 3 to 59 with nicotine. The experimental outcome varied only slightly among groups, as seen in Figure 6. This difference was not significant (F=0.394, P=0.678).
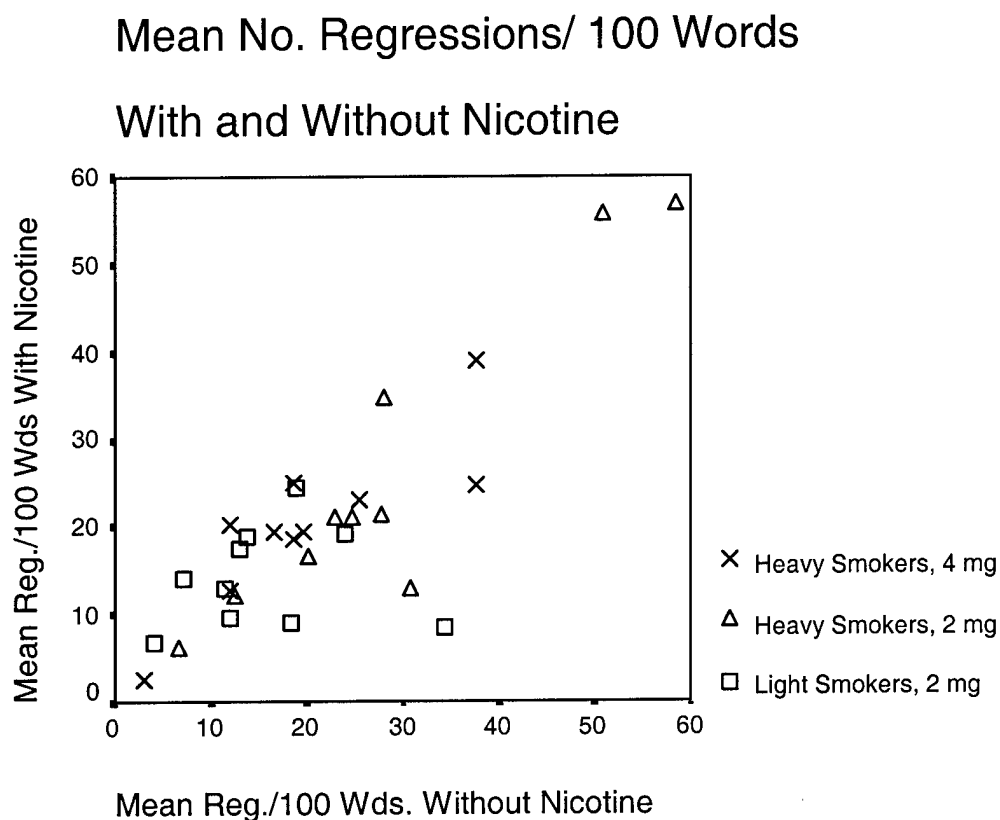
Mean No. Regressions/ 100 Words

With and Without Nicotine

Mean Reg./100 Wds. Without Nicotine

Figure 5: A regression is seen when the eyes make a right to left movement within a line to reread a portion of the text. Nicotine did not significantly influence regression frequency in the subjects. There were 14 data points on or above the line of equality and 16 below it. There was no significant difference among groups.

Mean No. Regressions /100 Words

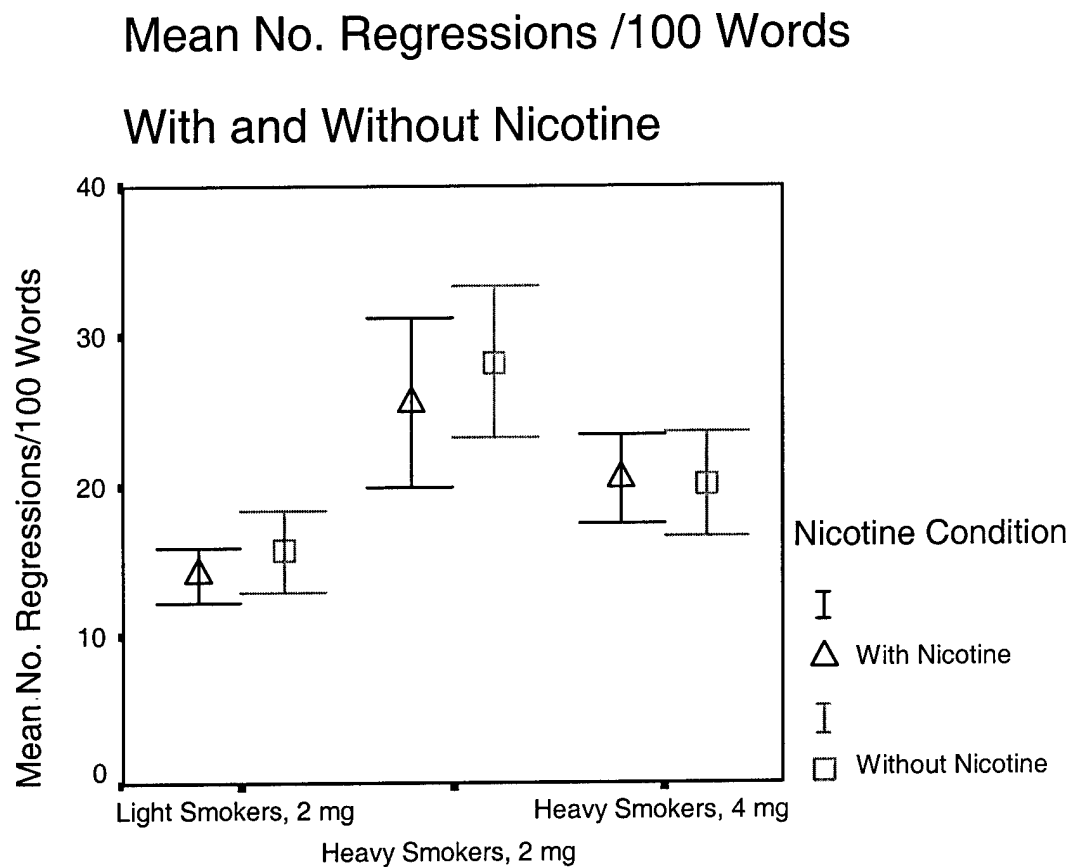## With and Without Nicotine

Figure 6: The mean number of regressions per 100 words read is depicted above with and without nicotine for all three groups. No group had significantly different regression frequencies than the others. Error bars indicate one standard deviation of data variability.

The mean reading rate with comprehension did not change significantly between nicotine and placebo trials. (F=1.154, P=0.292) Further, there was no significant difference between groups. As shown in Figure 7, the mean reading rate ranged from 121 to 452 words per minute under placebo conditions and from 98 to 434 words per minute with nicotine. This outcome did not significantly differ among groups (F=2.398. P=0.110) as seen in Figure 8.
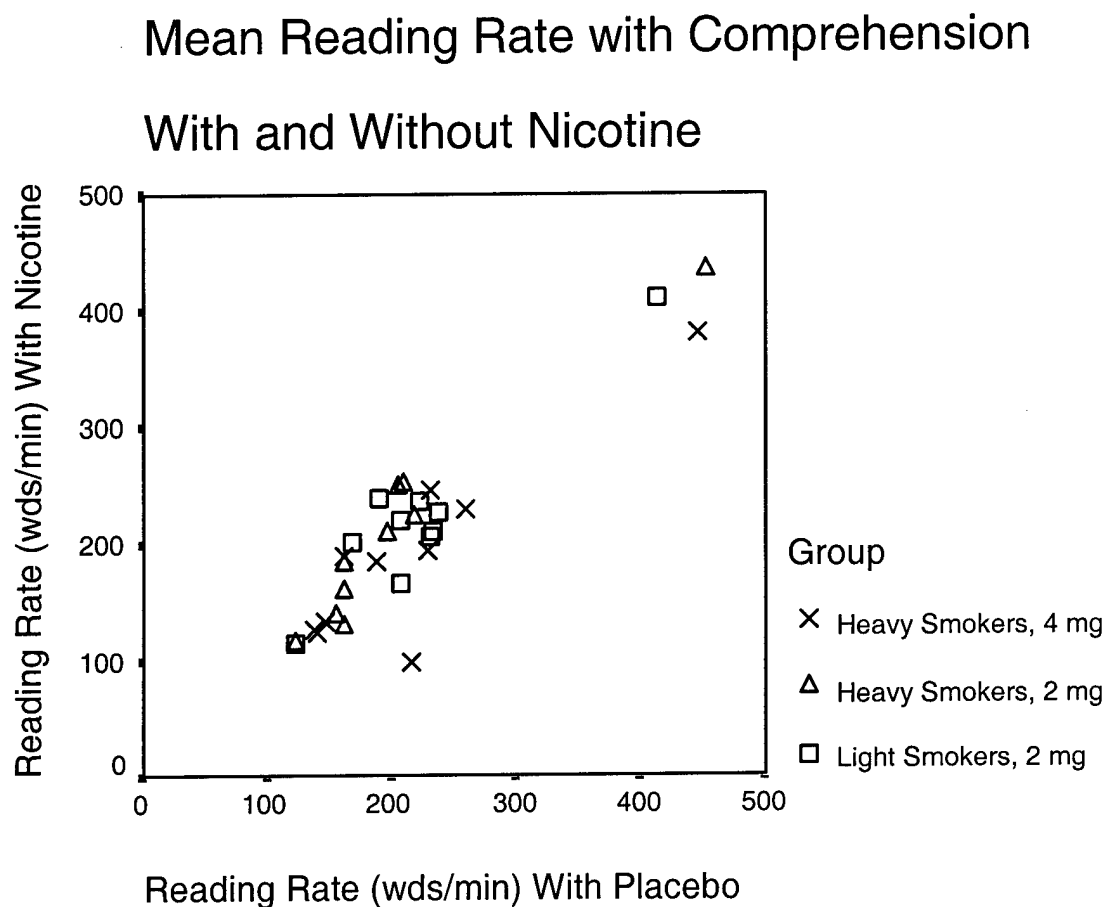
Mean Reading Rate with Comprehension With and Without Nicotine

Figure7: Mean reading rate was not significantly affected by nicotine. There was no significant difference among groups. There were 11 data points above the line of equality and 19 below it. Outlying data points were determined to be reliable.

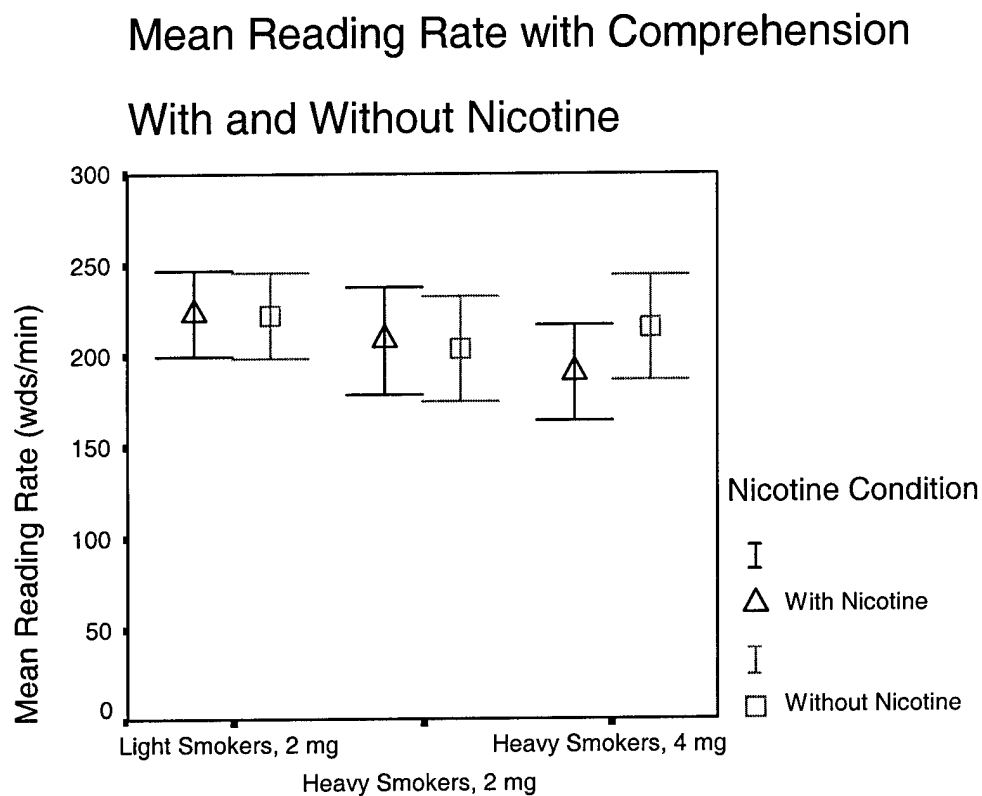**Mean Reading Rate with Comprehension With and Without Nicotine**

Figure 8: Mean rate (with comprehension) score for subjects with and without nicotine for all three experimental groups. No group's scores were significantly different than the other groups' scores. Error bars indicate one standard deviation of data variability.

There were no significant differences between nicotine and placebo trials on the visual skills fixation maintenance portion of the study (F=1.084, P=0.307). Group differences were not significant either (F=0.680, P=0.515). As shown in Figure 9, the number of fixations measured during this exercise ranged from 1 to 22 under placebo and from 1 to 25 with nicotine.

Visual Skills Test--Fixation Maintenance

No. of Fixations With and Without Nicotine

X Heavy Smokers, 4 mg

△ Heavy Smokers, 2 mg

□ Light Smokers, 2 mg

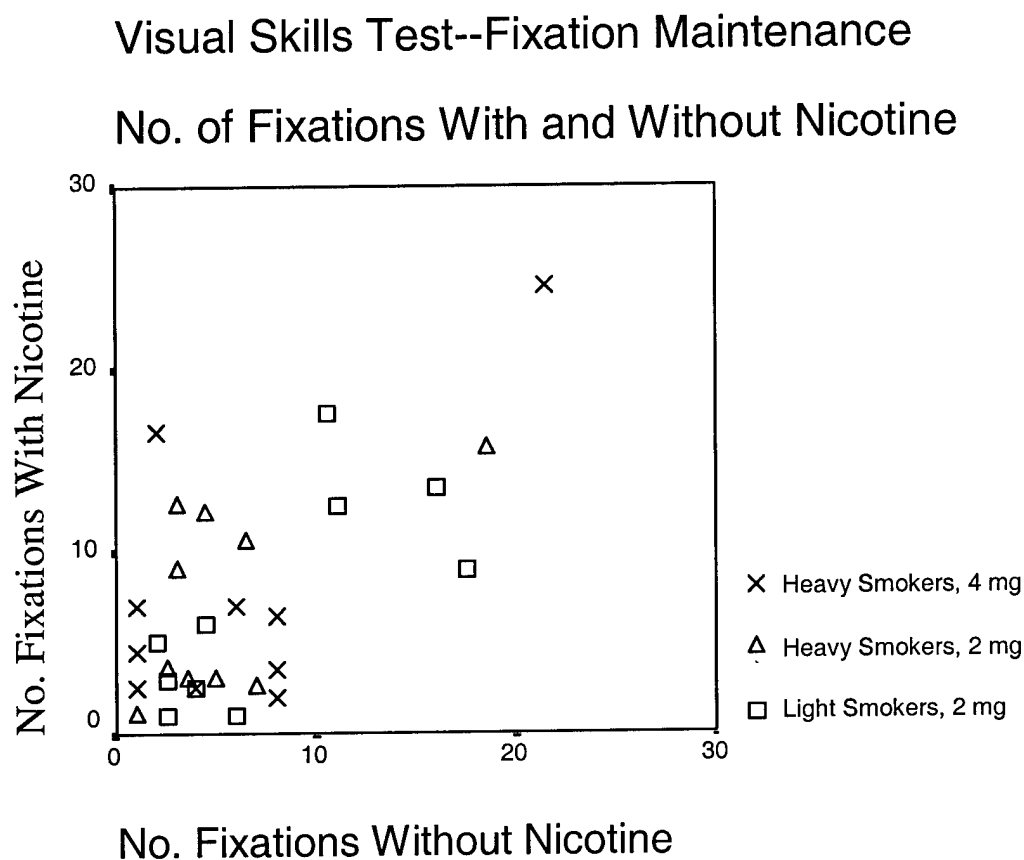No. Fixations Without Nicotine

Figure 9: The fixation maintenance portion measures the subject's ability to maintain fixation on a single location for three frames of recording. The fixation maintenance portion of the visual skills exercise yielded no significant differences between nicotine and placebo trials. There are 17 data points above the line of equality and 13 below it. There was no significant difference among groups. Outlying data points have been evaluated and judged reliable.
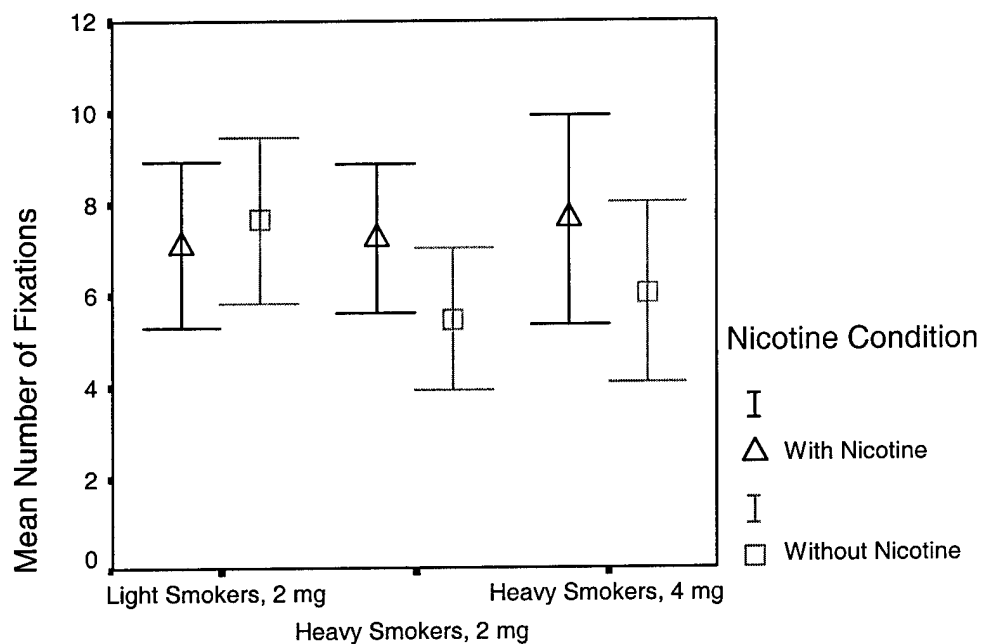
Figure 10: This graph depicts group means for the number of fixations measured with and without nicotine. There was no significant difference among groups on this outcome. Error bars indicate one standard deviation of data variability.

There were no significant differences between nicotine and placebo trials on the visual skills motility portion of the study (F=2.783, P=0.107). As shown in Figure 11, fixation duration ranged from 0.210 to 0.475 seconds under placebo conditions and from 0.215 to 0.665 with nicotine. The experimental outcome did not vary significantly among groups (F=1.843, P=0.178) as seen in Figure 12.
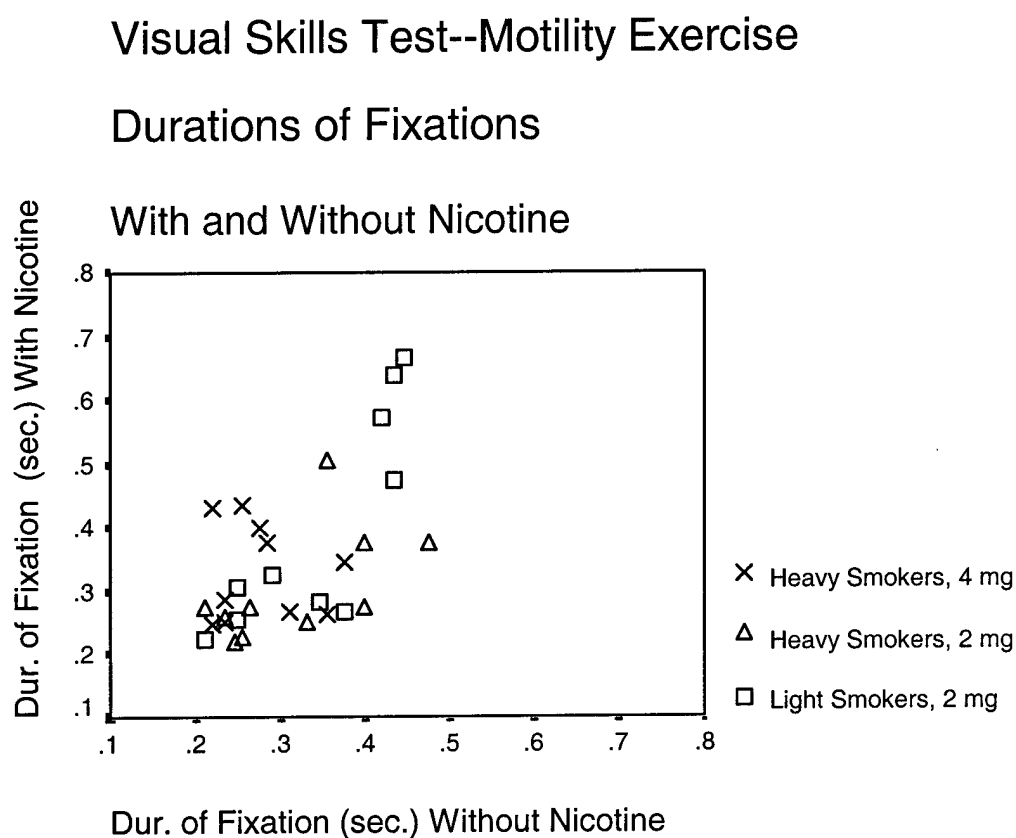

Figure 11: Subject data summary graph for the motility portion of the visual skills exercise. The motility portion of the visual skills exercise required subjects to rapidly "bounce" their eyes back and forth between two targets for a specific period of time. Fixation duration here refers to the mean period of time the subjects' eyes rested on a target before jumping away again. No significant difference in fixation duration was found between nicotine and placebo trials. Further, no significant differences were found among groups.

Visual Skills Motility Exercise
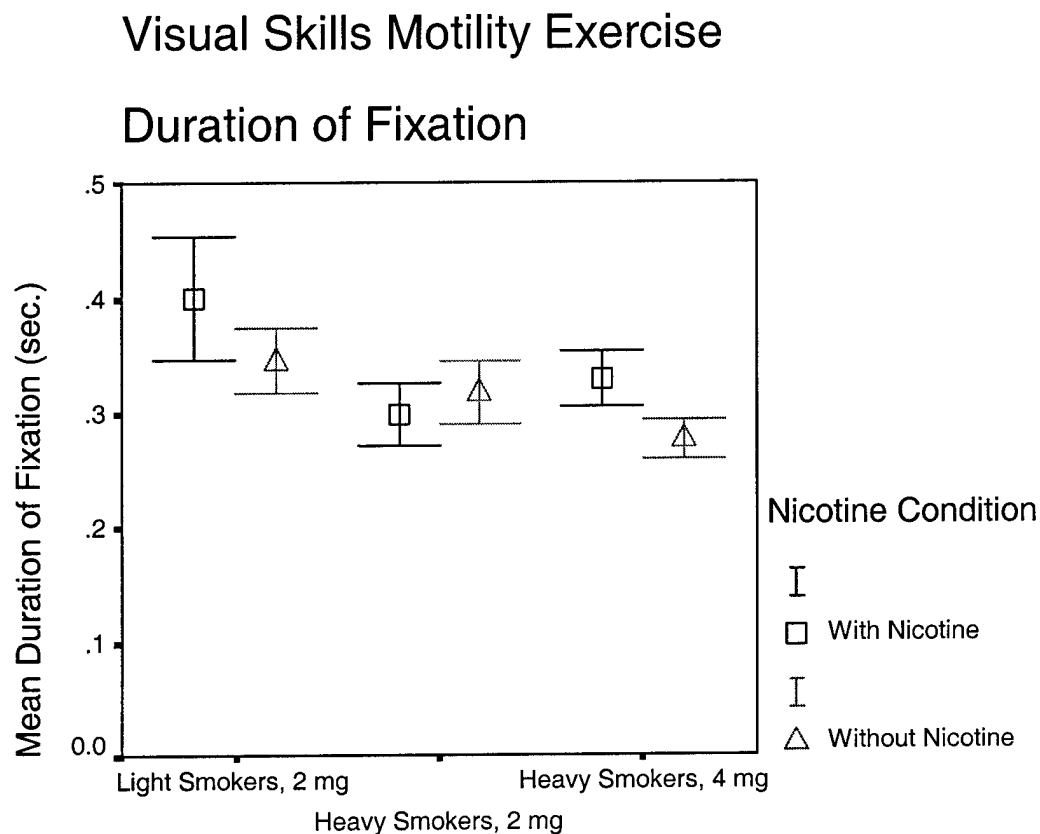
Duration of Fixation

Figure 12 Group results for mean duration of fixations for the motility portion of the visual skills exercise. No significant differences were found among groups. Error bars indicate one standard deviation of data variability.

There were no significant differences in fixation durations between nicotine and placebo trials on the Visual Skills Tracking portion of the study (F=0.922, P=0.346). As seen in Figures 13 and 14, the fixation duration ranged from 0.190 to 0.430 with placebo and 0.140 and 0.390 with nicotine. Group differences were not significant (F=0.899, P=0.419).

Visual Skills Test--Tracking Exercise
Durations of Fixations
With and Without Nicotine

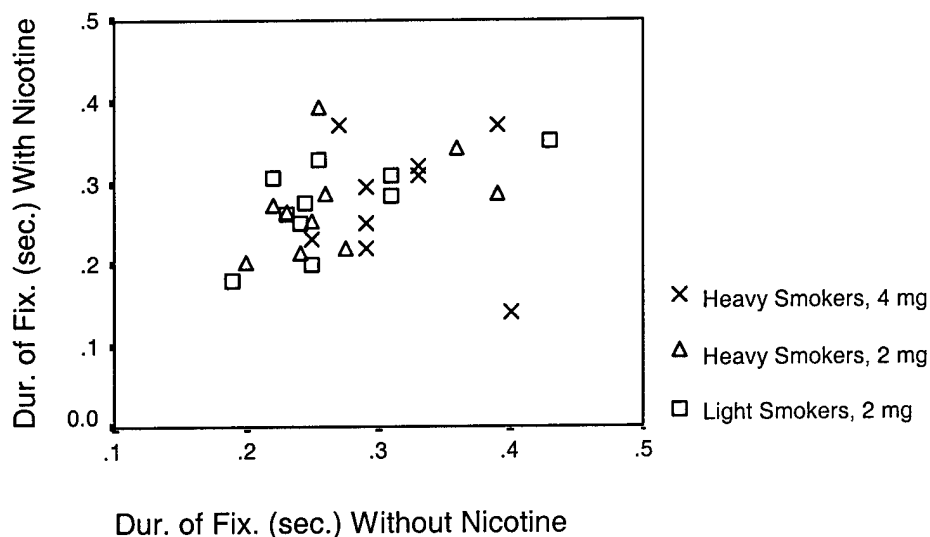X Heavy Smokers, 4 mg

Δ Heavy Smokers, 2 mg

□ Light Smokers, 2 mg

Figure 13: Subject data summary graph for the tracking portion of the visual sills exercise. The tracking portion of the visual skills test measures the subject's ability to efficiently look at the numbers 1-20, in order, presented in four rows with equal spacing between numbers. Subjects are asked to fixate upon each number before moving on to the next. The mean fixation duration was the average time that the eyes rested on each number during the task. No significant difference between nicotine and placebo trials was found in respect to fixation duration. There are 14 data points that fall on or above the line of equality and 16 below it. Further, there was no significant difference among groups.

Visual Skills Tracking Test
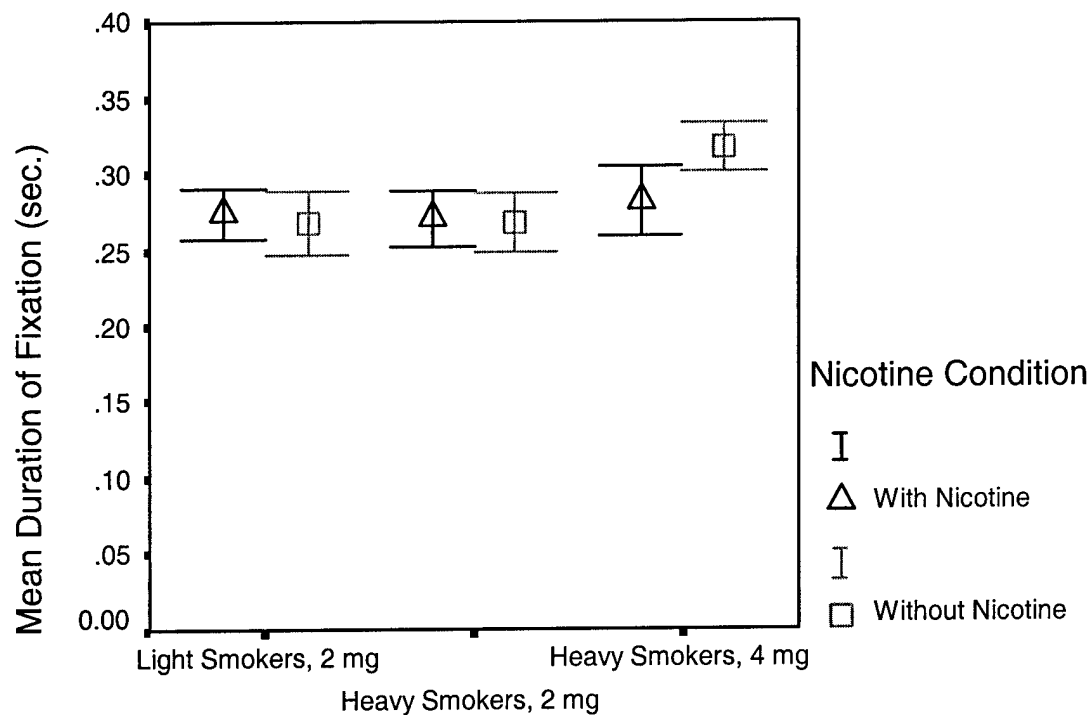
Duration of Fixation

Figure 14: Group summary graph for duration of fixation on the tracking portion of the visual skills exercise. There was no significant difference among groups. Error bars indicate one standard deviation of data variability.

Comprehension Effects:

Mean comprehension scores ranged from 70% to 100% without nicotine and from 60% to 95% with nicotine. As seen in Figure 15, there are 11 data points that fall on or above the line of equality and 19 below it. The repeated-measure analysis of variance showed a significantly negative effect on comprehension scores from nicotine (F=22.624, P≤0.001) but no significant group effect (Figure 16) was seen (F=1.672, P=0.207).

% Comprehension Questions Correct

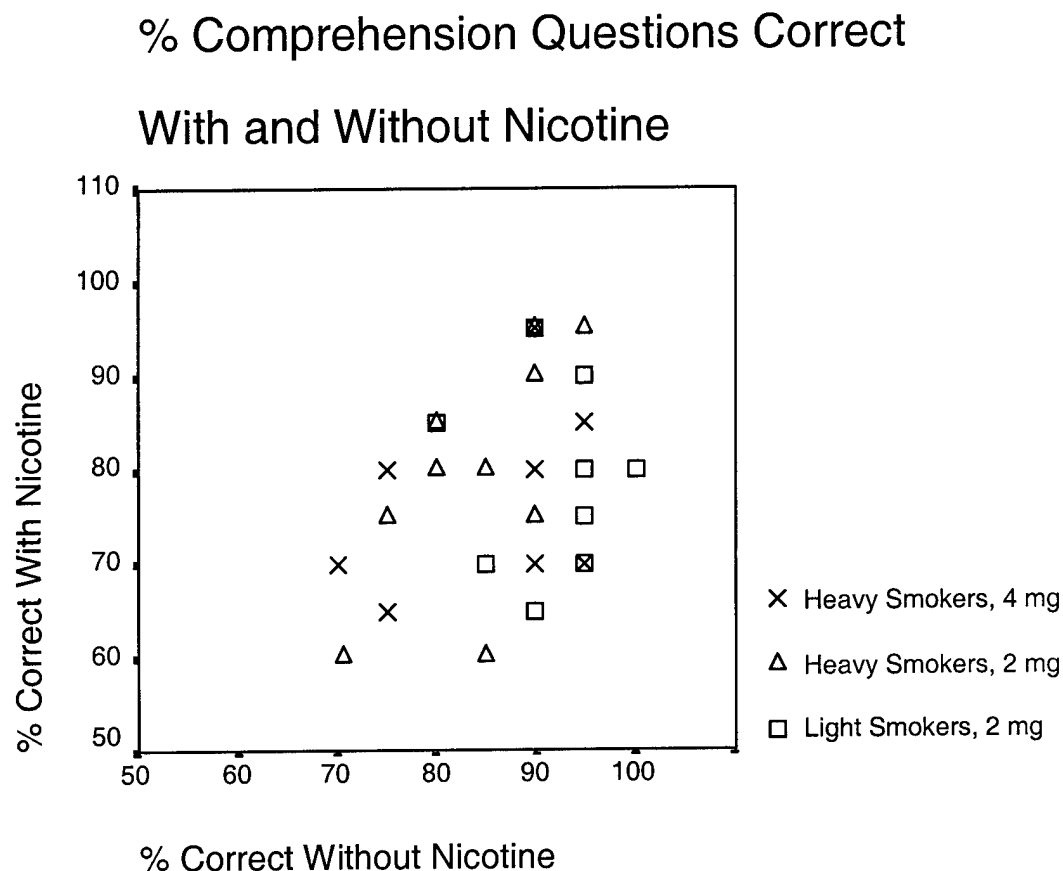## With and Without Nicotine

% Correct Without Nicotine

Figure 15: Data summary graph for subjects' reading comprehension scores. Subjects were asked ten standardized questions after reading each of the Visagraph II paragraphs. The questions were scored by the computer. After completing two Visagraph paragraphs and answering two sets of standardized questions, the two comprehension scores were averaged to obtain the mean comprehension score for that experimental trial. This graph shows the mean comprehension score for each subject with and without nicotine.

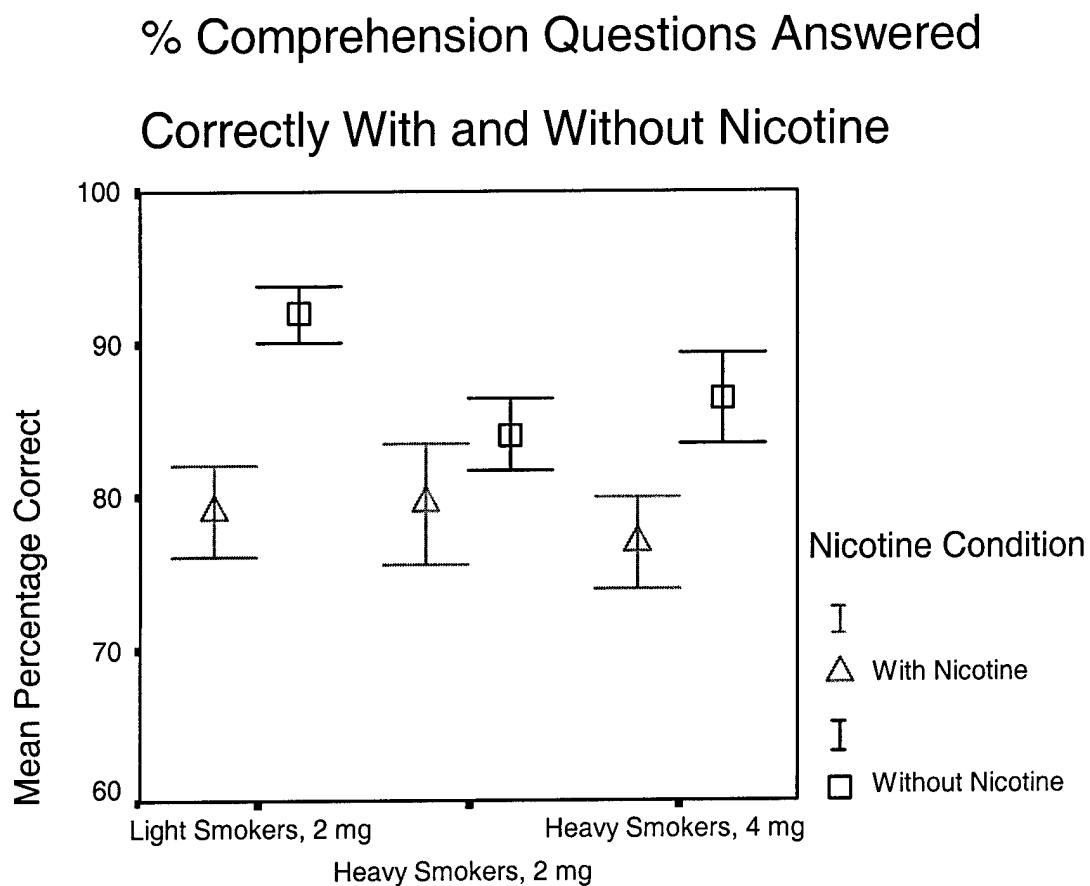# % Comprehension Questions Answered Correctly With and Without Nicotine

Figure 16: Number of comprehension questions answered correctly with and without nicotine for all three experimental groups. Error bars indicate one standard deviation of data variability. There was no significant difference among groups in experimental outcome.

As previously addressed, it was possible that the three groups could have varied on their baseline reading comprehension abilities and visual memory skills. Therefore, in order investigate this issue, an analysis of variance between groups was also run for Woodcock Johnson Reading Comprehension test results and the TVPS Visual Memory Inventory results (both of which were tested at subjects' prescreening visits). As seen in Figures 17 and 18, there was no significant difference for either test across the groups. (Woodcock Johnson: $F=0.53$, $P=0.948$ and TVPS: $F=2.887$, $P=0.073$).
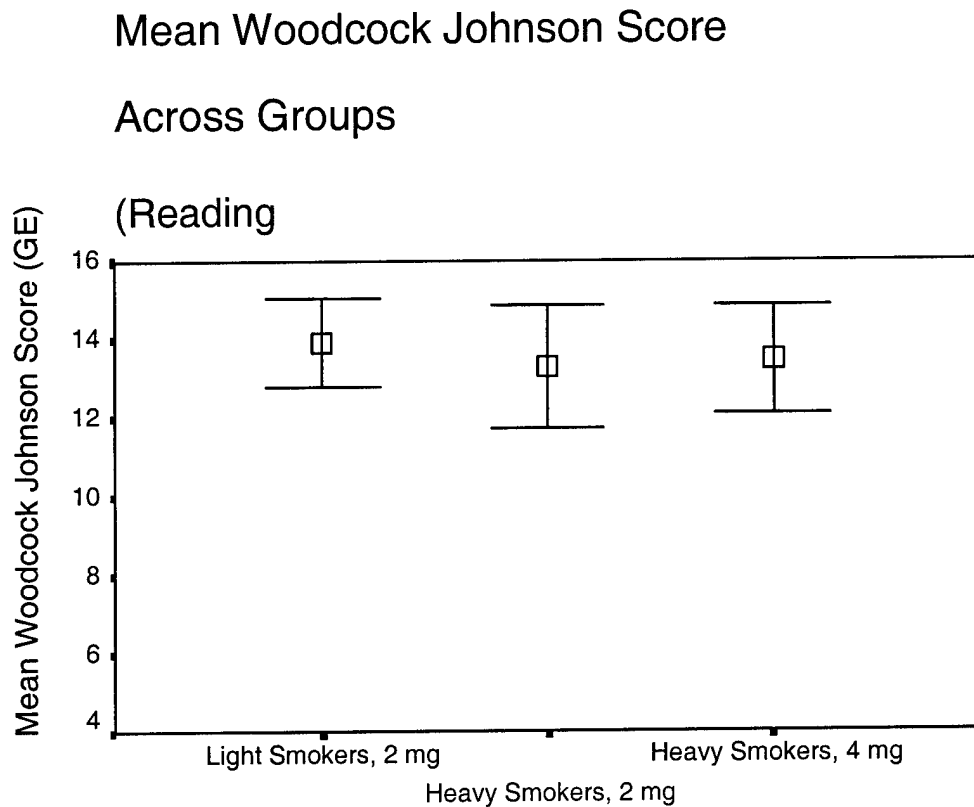
Mean Woodcock Johnson Score

Across Groups

Figure 17: The Woodcock Johnson Reading Mastery Test was used at the screening visit to verify that subjects had adequate reading skills to be able to complete required experimental tasks. The Reading Comprehension Cluster of tests was given to each subject and his/her score was calculated and recorded in grade equivalence units. There was no significant difference in Woodcock Johnson scores between groups. Error bars indicate one standard deviation of data variability.

Mean TVPS Score

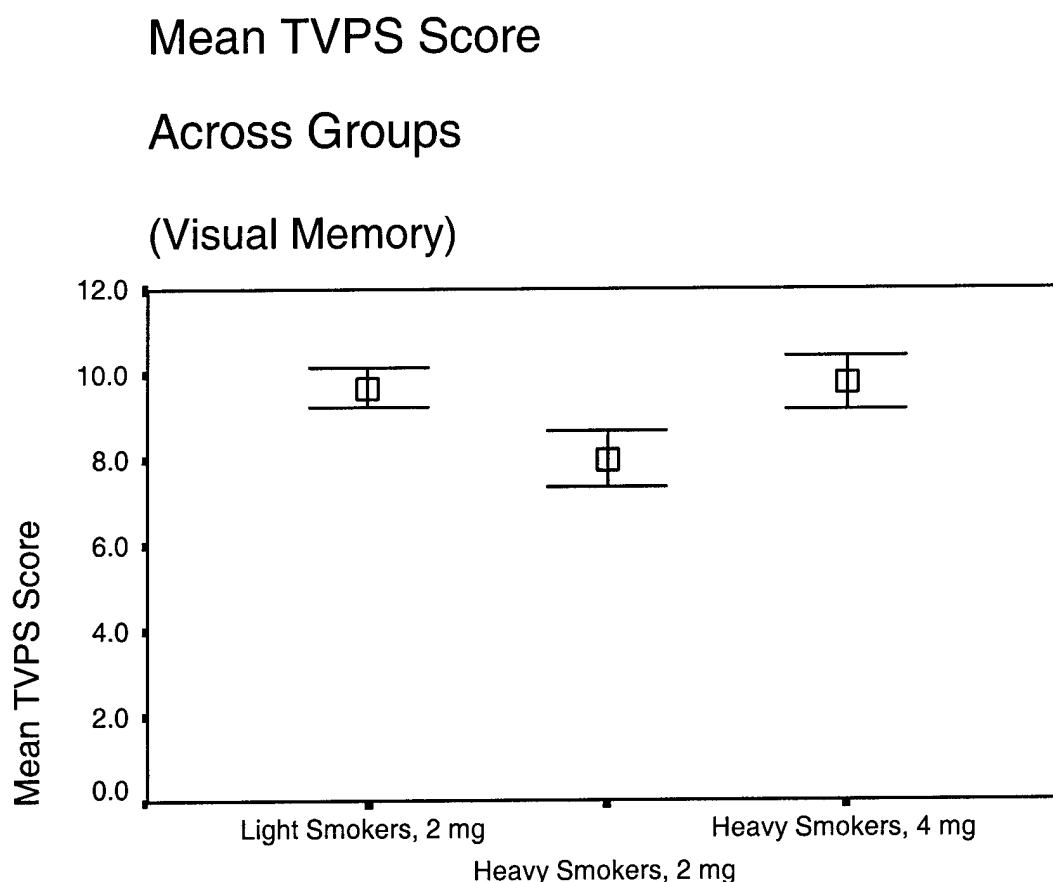## Across Groups

(Visual Memory)

Figure 18: The TVPS is a test of visual memory skill and was administered to each of the subjects at the prescreening visit. There was no significant difference in TVPS scores between groups. Error bars indicate one standard deviation of data variability.

In order to further explore if there was a difference in experimental outcome secondary to subjects' overall reading comprehension levels prior to Visagraph testing, a regression analysis was done to see if the Woodcock Johnson test was a significant predictor of nicotine's effects on reading comprehension in our experiment. Difference scores were calculated that reflected the magnitude and direction of the change in reading scores between nicotine and placebo trials. The regression analysis evaluating the Woodcock Johnson Scores versus reading comprehension difference scores showed no significant correlation. (R=0.178, P=0.348). Moreover, no significant linear trend was

found when a similar test was performed on TVPS data (R=0.031, P= .872). Figures 19 and 20 depict these findings.

Comprehension Difference Score* Versus Woodcock Johnson Grade Equivalence

Difference Score = (W-P)

WOODCOCK JOHNSON reading comp score

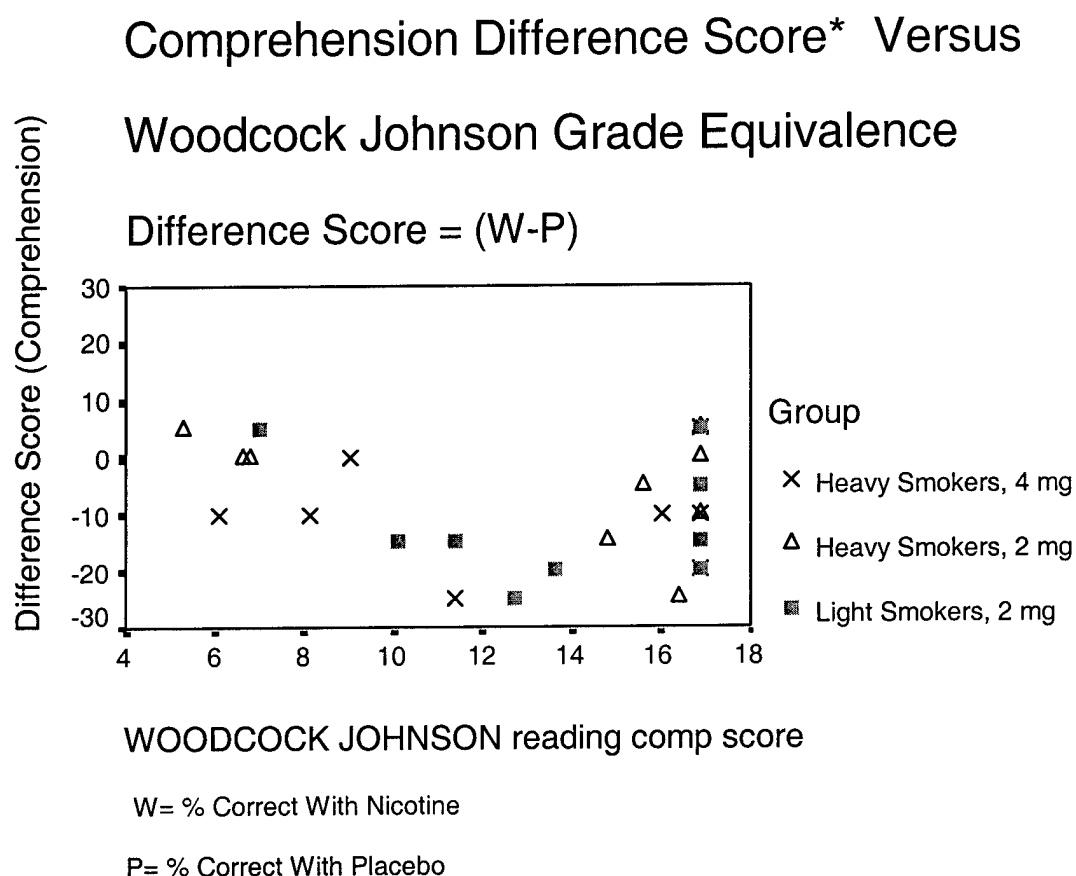W= % Correct With Nicotine

P= % Correct With Placebo

Figure 19: Graphical representation of the subjects' Woodcock Johnson grade equivalence scores versus the differences between the subjects' scores on reading comprehension questions with and without nicotine. Here, a negative difference score means that the subject did better on the reading comprehension test without nicotine. A positive difference score means that the subject did better with nicotine. No significant linear trends were seen linking Woodcock Johnson grade equivalence scores and difference scores on the comprehension questions.

Comprehension Difference Score* Versus TVPS Visual Memory Score

Difference Score * = W-P

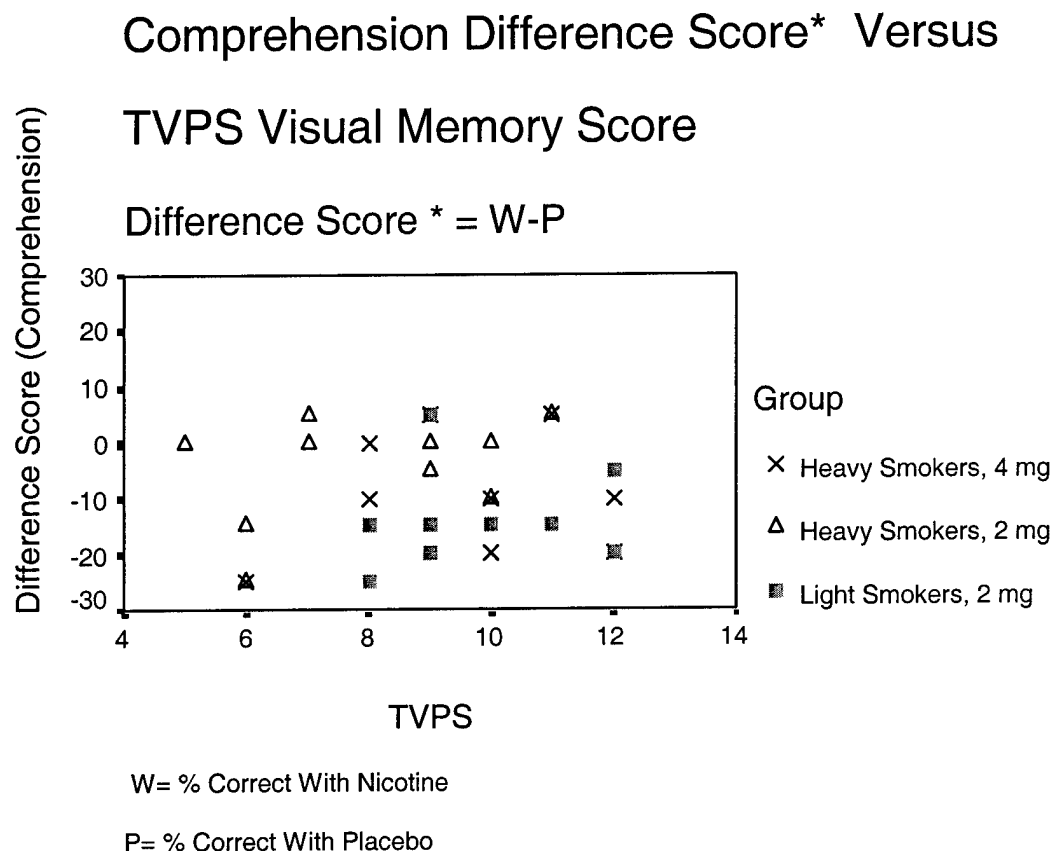W= % Correct With Nicotine

P= % Correct With Placebo

Figure 20: Graphical representation of the subjects' TVPS scores versus the differences between the subjects' scores on reading comprehension questions with and without nicotine. Here, a negative difference score means that the subject did better on the reading comprehension test without nicotine. A positive difference score means that the subject did better with nicotine. No significant trends were seen linking the TVPS scores and difference scores on the comprehension questions.

Discussion:

The prediction that nicotine would cause an increase in fixation duration and frequency was based upon the assumption that nicotine would induce nystagmus in some of the subjects. However, as described in the results section, under the conditions used in this study, nicotine did not cause nystagmus. In addition, nicotine did not significantly affect the eye movements associated with reading or those associated with basic visual skills. The statistical analyses showed no significant effect of nicotine on fixation duration, fixation frequency, reading rate, or regression frequency. Moreover, neither smoking history nor nicotine dose had significant effects on these measures.

The reason why nicotine-induced-nystagmus was not detected in our subjects may have been related to the visual environment of our testing. Pereira et al. (2000, 2001) found that certain visual stimuli prevented nicotine-induced nystagmus from occurring in most subjects. The tendency for nicotine-induced-nystagmus to be suppressed by visual stabilization cues and increase in darkness may be key to understanding the experimental outcome in this study. I believe that the visual environment experienced by my subjects was so rich in visual stabilizing factors (both the Visagraph material and environmental cues around the room) that no extra effort was required from their oculomotor systems (in the form of abnormal fixation behavior) to neutralize the nystagmus associated with nicotine. By just having their eyes open and seeing, their nystagmus was neutralized, and no further compensation behavior was required while reading.

Prior to this study, it was unknown how nicotine would affect reading comprehension under the conditions used in this experiment. Still, the significant

negative effect of nicotine upon reading comprehension was surprising considering the massive volume of literature reporting beneficial effects from nicotine upon cognitive functions. The works of Phillips and Fox (1998), Wesnes et al. (1983) Krebs et al. (1994) come to mind as examples. Each found that nicotine improved a cognitive skill in their subjects—short term memory, rapid information processing, and immediate recall of expository passages respectively. The question arises, why did reading comprehension suffer under the conditions used in this study? There are many possible reasons why this happened. Nicotine may have either directly altered the cholineric balance of the subjects' brains and decreased function in brain areas responsible for reading comprehension, or caused a secondary neurotransmitter to cause a similar reaction. It is also possible that the nicotine deprived state of the subjects played a considerable role in the results. Lastly, it is possible that the Visagraph reading comprehension test did not provide a meaningful measurement of subjects' reading comprehension, due to the limited nature of its true/false quiz format.

If nicotine does alter cholinergic brain chemistry and ultimately decreases reading comprehension, where are such changes likely to occur? Previous work localizing nicotine receptors and cognitive processing areas in the human brain may provide us with a good estimation. The area(s) of the brain that may be responsible for these findings are likely to (1) have significant neural responsibility in information processing and/or memory functions and (2) have a significant population of nicotine receptors. The cholinergic system is thought to consist of a group of closely interknit subsystems. Ten major and largely overlapping groups of specialized cells create a web of extensive interconnections that seem to coordinate various processes in the

brain (Gotti et al., 1997; Utkin et al., 2000). The receptors in the frontal, temporal, and parietal cortex are thought to be most closely related to nicotine's effects upon information processing (Jones et al., 1999; Levin et al., 1993; Rezvani and Levin, 2001). Here, the tissue is both highly active during cognitively demanding activities, especially those requiring integration of old and new information, and rich in nicotine receptors. (Augustine et al., 1997) The hippocampus is another part of the central nervous system that has demonstrated significant activity during several types of memory tasks, especially those related to memory storage and retrieval. The hippocampus has also been shown to be sensitive to changes in serum nicotine concentration (Jones et al., 1999). Recent research has indicated that nicotine may sometimes play a negative role in hippocampal plasticity (Dani et al., 2001), which might explain the role of nicotinic receptors in reading comprehension. The nucleus basalis of Meynert has been identified as being highly important to information processing and to be significantly influenced by serum nicotine levels (Levin et al., 1998). One or more of these areas of the brain may be intimately involved with the negative impact of nicotine on reading comprehension, if the effect is a direct action of nicotine on nicotine receptors.

Another model that may explain our experimental outcome is that one or more of the secondary neurotransmitters in the nicotinic cascade may be responsible for lowering reading comprehension levels in our subjects. As described previously, nicotine stimulates the release of many different neurotransmitters into the blood stream. Serum concentrations of acetylcholine, glutamate, norepinephrine, dopamine, GABA, and seratonin have all been shown to be altered following nicotine ingestion. Of these,

the release of acetylcholine and glutamate have been most often associated with memory retention and cognitive processing (Aigner, 1995) and would be most likely to be linked to lowering reading comprehension scores after taking nicotine, if indeed a secondary neurotransmitter is responsible for the decreased reading comprehension scores.

Another explanation for the significant negative effect of nicotine upon reading comprehension in this study is related to the nicotine-deprived state of the subjects, but not directly. Because the subjects had not smoked for several hours before testing, some baseline level of discomfort and distraction may have been present at the time of testing. This would have been true at both experimental visits, however. Therefore the pre-treatment deprivation level alone cannot explain the significantly different outcomes between nicotine and placebo trials. However, if subjects started "feeling better" after ingesting nicotine at the nicotine treatment trial, this relief sensation could have been distracting. In other words, the satisfaction of ingesting nicotine after being deprived of it for an extended period of time may have been distracting enough for the subjects to reduce their concentration on the reading material and ultimately lower their reading comprehension scores. If this was the primary reason for our experimental findings, however, it is surprising that there is not a greater difference between the experimental groups. I would have expected the heavy smokers to exhibit a more pronounced deprivation effect and euphoric reaction to nicotine treatment than their casually smoking peers. No group had a significantly greater effect from nicotine on performance than another.

Another interpretation of these results involves the limitations of the Visagraph reading comprehension test itself. Each test is made up of ten true/false questions.

Each subject, therefore, answered a total of 20 questions under nicotine conditions and 20 questions under placebo conditions. Under nicotine conditions, subjects answered, on average, approximately 15.5 questions correctly out of 20. Under placebo conditions, subjects achieved an average of approximately 17.5 questions correct. The difference in means between the two experimental conditions, therefore, was only 2 questions out of 20. Since the test was true/false in nature, guessing could have resulted in some score inflation under either experimental condition. Therefore, it is possible that another format of reading comprehension testing may produce different results. An ideal reading comprehension test for future use in this area of research might offer a multiple-choice answer format with twenty or more questions per passage, and multiple versions for repeated testing between conditions.

Conclusion

The outcome of this study may have some interesting implications for educators. If nicotine intake does reduce reading comprehension levels in some people, some of the statistics related to academic underachievement in smokers (National Health Interview Survey, 1998) may deserve further study. As discussed earlier, these studies found that smokers tended to face academic problems more often than their non-smoking peers and were more likely to drop out of school. Previously, the results from these studies have been interpreted very conservatively because of a perceived correlation between underage smokers and lower academic effort (Rigotti et al., 2000). Because under some conditions nicotine reduces reading comprehension, further studies may be indicated to pinpoint why this occurs and whether its effects are short or long term.

Although this study on the effects of nicotine on reading comprehension and the eye movements associated with reading has produced some interesting findings, there is still much more to learn about nicotine's effects on these factors. For example, very little work has been done to identify the minimum visual stimulation that can effectively eliminate nicotine-induced nystagmus. How large of a visual stimulus is necessary to squelch nystagmus? What contrast level does it need to have compared to the background? Where in the visual field does the stimulus need to be? Also, further study on how nicotine-induced nystagmus responds to higher levels of baseline vestibular activity might provide further insight into the neurological etiology of this

type of nystagmus. These studies would produce valuable information, particularly to the military. Fighter pilots, besides being in an environment rich in vestibular stimuli, are also frequently looking into an endless blue sky through a large dome canopy. Knowing if nicotine ingestion increased the risk of developing nystagmus while in the air is important. Related to the reading comprehension effects of nicotine, little is known about the effects of the drug on subjects who have never previously smoked. Would the effects of nicotine be different in this population? Nicotine deprivation issues and drug tolerance issues need to be addressed further, as well. It is possible that if subjects were tested under other levels of nicotine deprivation than what was specified in this experiment that results could have been different.

It has become clear that nicotine acts on the brain in many ways through a number of direct and indirect actions. Some of nicotine's cognitive effects are positive, but some are negative. Nicotine had a significant negative effect upon reading comprehension scores in the nicotine-deprived subjects under the conditions used in this study. Future studies will further define nicotine's role in reading comprehension.

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Nicotine's Effect upon the Eye Movements Associated with Reading and Reading Comprehension

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Abstract:

Nicotine ingestion has been shown to have a significant effect on many cognitive functions and induces nystagmus in some subjects. This experiment was conducted to evaluate how nicotine affects reading comprehension and the eye movements associated with reading in nicotine-deprived smokers. The Visagraph instrument was used to monitor subjects' fixations, regressions, basic visual motor skills, and comprehension levels while reading standardized passages of text. Thirty subjects were measured in a double blind, treatment order-randomized, repeated-measure format, using nicotine gum and a placebo product. Subjects were divided into three groups based upon their smoking histories and experimental nicotine dose. Reading performance indicators with and without nicotine exposure were analyzed with an analysis of variance. There was not a significant effect of nicotine upon reading-associated oculomotor behavior. However, there was a significant negative effect upon reading comprehension as measured by theVisagraph system. Subjects achieved significantly lower reading comprehension scores after nicotine treatments than with placebo treatments. Neither the smoking history of the subject nor dose of nicotine significantly affected experimental outcome.