The Effects of Acute Nicotine Abstinence on Vigilance and Verbal Memory in Non-Diagnosed Smokers

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THE EFFECTS OF ACUTE NICOTINE ABSTINENCE ON VIGILANCE AND VERBAL MEMORY IN NON-DIAGNOSED SMOKERS

by

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A Dissertation
Submitted to the
Faculty of The Graduate College
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Dr. Lisa E. Baker, Advisor

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Research has shown a differential prevalence of smoking in the schizophrenic population compared to other psychiatric and non-diagnosed populations. The three most commonly investigated reasons for this differential prevalence in schizophrenics are: the self-medication hypothesis, side effects hypothesis, and sociological hypothesis. The self-medication hypothesis which proposes that schizophrenics smoke at a higher rate to ameliorate cognitive deficits is the most substantiated by the research. Of current interest is the possible role of nicotine in improving performance on vigilance and verbal memory, the two areas shown to be most related to impaired social functioning in schizophrenics. It is difficult to make comparisons among the existing research investigating the effects of nicotine on verbal memory and vigilance in non-diagnosed populations due to the use of differing nicotine delivery mechanisms, populations, and assessment tools. The current study implemented standardized and psychometrically sound assessments of verbal memory (immediate and delayed) and vigilance to assess in smokers the impact of nicotine via the participants' normal smoking behaviors. Following acute abstinence (≥ 6 hrs) 15 non-diagnosed smokers completed the Conner's Continuous Performance Test (CPT) and Rey Auditory Learning Test (RVLT) using a counterbalanced design. Results of the repeated measures analysis revealed no statistically significant effect of nicotine. Subsequent covariate analysis revealed a significant effect of nicotine on RVLT total score when controlling for sex and number of
cigarettes per day. Likewise covariate analysis revealed a significant effect of nicotine on the CPT overall index and hit rate block change sub-measures when controlling for age. An examination of trend lines revealed a consistent decrease in performance on all CPT sub-measures and on RVLT measures related to memory storage as a result of nicotine abstinence, while nicotine abstinence improved performance on RVLT measures of memory storage. While it is difficult to draw conclusions from the current study, a less robust finding in a non-diagnosed population than is typically found in diagnosed populations might be suggestive of different reasons for smoking between the populations.
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David W. Ayer
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CHAPTER I

INTRODUCTION

Research has shown a differential prevalence of smoking in the schizophrenic population compared to both other psychiatric and normal populations. A study conducted by Hughes, Hatsukami, Mitchell, and Dahlgren (1986) was the first controlled study to show higher prevalence of smoking in individuals diagnosed with schizophrenia. In this study, the researchers compared the prevalence of smoking in 277 psychiatric outpatients to the prevalence of smoking in samples of 1440 and 17,000 local and national normal populations, respectively. The authors found that 88% of the schizophrenic population smoked compared to 52% of other psychiatric disorders, 30% of the local population, and 33% of the national population.

Since the Hughes et al study (1986), several other studies have also shown differential prevalence of smoking when comparing the schizophrenic population (70-90%) to other psychiatric populations (30-54%) and to the general population (28-35%) (Diwan, Castine, Pomerleau, Meader-Woodruff, & Dalack 1998; Glassman, 1993; Goff, Henderson, & Amico, 1992; Lohr & Flynn, 1992). Attempts to explain this phenomenon followed from these findings.

Hypotheses for Differential Prevalence

Sociological hypothesis

It is commonly held that environmental and sociological factors are involved in substance abuse of any form (Poling & Byrne (Eds.), 2000). Lohr and Flynn (1992) suggested that sociological factors such as institutionalism, low SES, or boredom may contribute to the high rates of smoking in schizophrenia. Several researchers have examined the possible role these factors may play in the etiology and maintenance of...
smoking in schizophrenics. The Hughes et al (1986) study found that even when controlling for age, sex, marital status, socioeconomic status, alcohol use, caffeine use, or institutionalization of the psychiatric patients, higher prevalence of smoking was still shown to exist for schizophrenic patients. A study conducted by de Leon et al. (1995) also suggested that neither institutionalization nor "boredom" contributed to the increase in smoking for schizophrenics. A replication of this study confirmed these findings (de leon, Tracy, McCann, McGrory, & Diaz, 2002). Strassnig, Brar, & Ganguli (2006) found high rates of smoking in schizophrenics to be unrelated to income, body mass intake (BMI), fat or caloric intake. A Finnish study reported the only sociological factor that correlated with smoking in schizophrenic patients was their father's smoking status (Riala, Hakko, Isohanni, Puota, & Rasanen, 2005)

Other sociological factors proposed to explain the high rate of smoking in schizophrenics include the lack of availability of alternative reinforcers (smoking may represent the schizophrenics only opportunity for socialization) and that isolation from mainstream society may shield them from anti-smoking information (Lyon, 1999; Ziedonis, Kosten, Glazer, & Frances, 1994). A study conducted by Spring, Pingitore, and McChargue (2003) indicate these may not be valid explanations. These authors found schizophrenics to be just as aware of the pros and cons of smoking as the sampled non-psychiatric population. Schizophrenic subjects indicated that the pros outweighed the cons while the comparison group viewed the pros and cons as about equal. The authors also reported that when schizophrenics were asked to rate the reinforcing value of smoking compared to a variety of other items and behaviors likely to be considered reinforcing, they chose smoking at a two to one rate over the comparison group. Of interest, the authors found that both schizophrenic and depressed heavy smokers attributed greater reward value to smoking than did the non-psychiatric comparison group. It may be that cigarette smoking is one of the few reinforcers able to
overcome reward circuitry abnormalities. This will be explored in more detail when we turn our discussion to neurotransmitters and schizophrenia later in the paper.

In summary, although sociological factors have been proposed, to date they have not been demonstrated to account for the high rates of smoking among schizophrenics.

Side effects hypothesis

Another frequently given hypothesis for the higher prevalence of smoking in schizophrenics is its role in the possible amelioration of medication side effects. Several studies have shown nicotine to reduce the prevalence and severity of neuroleptic-induced parkinsonism in schizophrenic patients (Decina, et al., 1990; Goff et al., 1992; Sandyk, 1993; Ziedonis et al., 1994). Investigations into nicotine’s effect on other movement disorders such as akathisia (Goff et al., 1992; Barnes et al., 2006) and tardive dyskinesia have produced mixed results (Goff et al., 1992; Ziedonis et al., 1994).

A related issue concerns which of two types of medication a schizophrenic is taking, typical or atypical (sometimes referred to as novel) antipsychotics. The current body of evidence suggests that typical antipsychotics may increase smoking rates while atypicals decrease smoking rates (George, Ziedonis, et al. 2000; Green, A. I., 1999; McEvoy, Freudenreich, Levin, & Rose, 1995; Barnes et al., 2006) in schizophrenics. However, one study showed that high doses of typical antipsychotics did not increase the rate of smoking in schizophrenics, but did increase the rate of smoking in non-schizophrenics (de Leon et al., 1995). Additionally de Leon et al. (1995) reported smoking to be higher in the schizophrenic population independent of type of neuroleptic received, or dose of antipsychotic (de Leon et al., 2002). A review of the literature reveals that psychiatrists prescribe higher doses of neuroleptics in patients who smoke than in those who do not smoke (Ziedonis et al., 1994; de Leon et al., 1995; de Leon et
al., 2002). So as de Leon and colleagues suggest (2002), smoking to reduce medication side effects appears to be a flawed strategy.

A more serious threat to this hypothesis is the fact that a high rate of substance abuse (Green, A. I., 1999), and specifically nicotine dependence which has been shown to exist independent of general substance abuse in this population (de Leon et al., 1995; de Leon et al., 2002), exists in schizophrenic patients prior to the receipt of any pharmacological treatments. McEvoy and Brown (1999) reported that unmedicated, first-episode patients smoked at the same rate as chronic schizophrenic patients. Barnes, Mutsatsa, Hutton, Watt, and Joyce (2006) also found a high rate of smoking in first episodes schizophrenic patients. Some authors have suggested that smoking in adolescence and early adulthood may be predictive of later development of schizophrenia, and may be evidence of a prodromal phase of schizophrenia. A study of male Israeli military recruits revealed that smokers were at greater risk for later development of schizophrenia, and that number of cigarettes smoked was significantly associated with risk for schizophrenia (Weiser et al., 2004). A Finish study reported that initiation of smoking was temporally related to the onset of schizophrenia suggesting that smoking may be an indicator of the prodromal phase of schizophrenia (Riala et al., 2005). Another study using the same cohort found that individuals who would later develop schizophrenia and who smoked showed poorer school performance overall; specifically in physics, mathematics, reading, and music (Riala, Hakko, Isohanni, Jokelainen, et al., 2005). An interesting study conducted by Zammit et al. (2003) suggests that initiation of smoking at an earlier age (18 – 25) may be a sign of the prodromal phase of schizophrenia, while smoking after this age may offer a protective effect against the development of schizophrenia.
In sum, while medication side effects may or may not contribute to the maintenance of smoking in schizophrenics, it is clear that they are not responsible for the etiology of the disproportionately high rates of smoking in schizophrenics.

**Self-medication hypothesis**

Another commonly referenced explanation for the high rate of smoking in the schizophrenic population is that it is an attempt to ameliorate schizophrenic symptomology and/or cognitive deficits. It is widely held that neurotransmitter abnormalities are responsible for the positive and negative (pathological) symptoms of schizophrenia as well as the cognitive deficits that accompany the disorder. It is proposed that nicotine may ameliorate some of these abnormalities and, in effect, normalize certain schizophrenic symptoms (Lyon, 1999). In the “Schizophrenia, neurotransmitters, cognition and nicotine” section of this paper specific neurotransmitters associated with pathological and cognitive deficits in schizophrenia are discussed. In the current section we will focus on studies regarding the effects of nicotine on positive and negative symptoms, and then review the large body of evidence regarding nicotine effects on cognition; specifically those deficits seen in schizophrenia.

Research conducted to investigate nicotine’s role in improving the pathological symptoms of schizophrenia has produced mixed findings (Goff et al., 1992; Smith, Singh, Infante, Khandat, & Kloos, 2002; Ziedonis et al., 1994). The Ziedonis et al. (1994) study demonstrated an increase in positive symptoms for schizophrenic patients who smoked compared to patients who did not smoke and no difference in negative symptoms between the two groups, except for very heavy smokers who showed a decrease in negative symptoms. The Goff et al. (1992) study showed more of both negative and positive symptoms in schizophrenic smokers. As discussed by Zeidonis et al. (1994), these studies were observational in design which allows for discussion about
association but not causation. Dalack and Meador-Woodruff (1996) conducted a review of the existing literature regarding the relationship between smoking and schizophrenic symptomatology and concluded there had been no studies to date that examined this relationship via experimentally controlled manipulation of smoking behavior. These same investigators (Dalack, Becks, Hill, Pomerleau, & Meador-Woodruff, 1999) conducted a study involving 12 patients with the diagnosis of schizophrenia and all active smokers undergoing 3 days of smoking abstinence randomly assigned to either an active or placebo nicotine patch, followed by one day of ad libitum smoking and then a return to the 3 day abstinence condition wherein patients where assigned to the active or placebo patch condition opposite of what they received during the first abstinence session (i.e. crossover design). There were no significant changes in either positive or negative symptoms in relation to patch status (active or placebo). A review of the literature regarding smoking cessation in psychiatric patients conducted by Haustein, Haffner, and Woodcock (2002) led these authors to conclude that smoking abstinence, even if it leads to withdrawal symptoms, has no negative impact on psychiatric symptoms. A study by Smith, Singh, Infante, Khandat, and Kloss (2002) revealed a significant decrease in negative symptoms and no change in positive symptoms. It may be that any positive impact seen on negative symptoms is due to the small correlation between negative symptoms and cognitive deficits, or due to the use of measures of negative symptoms that fail to distinguish these from cognitive deficits.

Irrespective of conclusive evidence for nicotine’s effect on negative or positive symptoms of schizophrenia, as discussed in the previous section, it is commonly found that the initiation of smoking, and other substance abuse, occurs prior to the emergence of obvious positive or negative symptomatology. This raises serious doubt about the legitimacy of the hypothesis for differential prevalence due to self-medicating traditional schizophrenic symptoms.
Research investigating the role of nicotine in ameliorating cognitive and attentional deficits is more promising. Studies have shown rates of cognitive impairment in schizophrenics to be as high as 85% (Palmer, Heaton, Paulsen, Kuck, Braff, et al., 1997). Although the positive symptoms of schizophrenia (e.g. delusions and hallucinations) have historically garnered most of the attention, more recently cognitive deficits have gained prominence as the core psychiatric feature of schizophrenia (Green, 1999; Meltzer, 1999b; Palmer, et al., 1997). Both Green (1999) and Meltzer (1999b) point out that cognitive deficits in patients who later develop schizophrenia are present during their childhood before any positive or negative symptoms are present. In fact, some researchers view certain cognitive deficits as markers for the onset of schizophrenic symptomatology (Green & Nuechterlein, 1999; Park, Puschel, Sauter, Rentsch, & Hell, 1999). Further many cognitive deficits persist long after the positive symptoms of schizophrenia remit (Green, 1999).

Cognitive deficits are also being seen as distinct from schizophrenic symptomatology. Several lines of evidence, in addition to those listed in the preceding paragraph, give support for this view. Traditional pharmacological treatment with typical neuroleptics, while at least moderately effective at treating the symptomology of schizophrenia, fail to not only improve the cognitive deficits, but frequently result in further cognitive impairment (Meltzer, 1999b). Research also shows certain cognitive deficits to be present in the first-degree asymptomatic relatives of schizophrenics (Park, Knopick, McGurk, & Meltzer, 1995; Park, et al., 1999). In a review of the relevant research, Green and Nuechterlien (1999) state that cognitive deficits and positive symptoms show almost no relationship, and while the relationship between negative symptoms and cognitive deficits is a little stronger, the percent of variance explained is still only 10-15%.
The literature investigating the effect of nicotine on cognition is sizeable and thus warrants separate discussion. The evidence put forth in this next section clearly shows that the mitigation of cognitive deficits hypothesis currently garners the most empirical support for the explaining the greater prevalence of smoking among the schizophrenic population.

Nicotine and Cognition

This section will focus on the recent (≤ 20yrs) literature demonstrating a relationship between nicotine and certain cognitive constructs. This begins with a discussion of nicotine's influence on two categories of cognition in the normal population: learning and memory, and attention and vigilance, followed by a discussion of the relationship between nicotine and cognition in the schizophrenic population and any differential effects of nicotine on cognition between the normal and schizophrenic populations. This section closes with a discussion of psychophysiology, neurotransmitters, and nicotine as they relate to important cognitive deficits seen in schizophrenia.

Non-diagnosed

Learning and memory

Mangan (1983) investigated the effects of .7mg and 1.3 mg yield cigarettes in normal smokers on acquisition and retention of verbal material. In the first measure, paired-associate learning, subjects were required to learn a 10-pair set of words, broken into high-interference (HI) and low-interference (LI) pairs, until they could produce two successive error-free reproductions of the 10-pair set. HI pairs consisted of highly associated words such as miss/take or black/white and the individual words were redistributed in pairs that would maximize interference, e.g. miss/white or black/take. LI pairs were words that were not associated in common usage. Acquisition was broken
into three separate sessions where prior to acquisition subjects chatted with the experimenter for 5 minutes in the first session, smoked a 1.3mg yield cigarette in the second, and smoked a .7mg cigarette in the third session. Subsequent to each of these sessions the subjects were asked to sit quietly for 30 minutes and then to recall the 10-pair sets. For the second measure, subjects were required to participate in a serial learning task where they were asked to learn 12 sets of 20 words presented at the rate of one word every three seconds; immediately following the trial they were asked to recall as many words as possible. As with the paired-associate task acquisition occurred in three separate sessions under the same conditions. Results indicated that smoking either yield cigarette improved retention under both HI and LI conditions while the 1.3 mg dose impeded acquisition under the LI condition and improved acquisition under the HI condition (.7mg dose had no effect on acquisition under either condition).

For the serial learning measure both doses improved primacy responses, indicating that the words seen first in the acquisition trials were more frequently recalled.

Similarly, two other studies demonstrated that ingesting nicotine via controlled smoking or nicotine tablet (Peeke & Peeke, 1984; Warburton, Wesnes, Shergold, & James, 1986) prior to acquisition of verbal material facilitated recall of that material. These studies led researchers to question whether nicotine was exerting its influence on recall by an attentional mechanism at the time of acquisition or if it was directly affecting memory storage. Warburton, Rusted, and Fowler (1992) conducted a study designed to answer this question. This study involved normal addicted smokers who had abstained from smoking for at least 10 hrs prior to participating in two experimental conditions. There were two sessions within each experimental condition; low nicotine cigarette (0.6mg) and denicotinised cigarette (<0.1mg) sessions. Subjects were randomly assigned to cigarette type, order of session, and word list. In experiment 1 subjects were given a four-word group for 4s, they then took a puff off a cigarette and rehearsed
the words for 10s. Subjects repeated this procedure for 8 four-word groups. Immediately upon completion of the 8th four-word group, subjects were required to write down as many words as possible from all four-word groups. Experiment 2 involved the same procedures except subjects were asked to recall the four-word groups 10 minutes after the last four-word group. Subjects were required to engage in a task during those 10 minutes to prevent rehearsal. The results showed that nicotine improved immediate recall of the words towards the end of the four-word lists (suggesting an attentional mechanism) and improved delayed recall of words towards the beginning of the four-word lists (suggesting a direct effect on memory storage). Since nicotine was ingested after exposure to the four-word lists the authors suggest that nicotine has a direct effect on memory storage in addition to its attentional effects. More recently, researchers have suggested that nicotine effects on storage may be a result of its attentional effects (Poltavski & Petros, 2005; Newhouse, Potter, & Singh, 2004). Newhouse and colleagues (2004) point out that increased attention on the "front end" would be beneficial for acquisition, storage and retrieval.

Some studies have shown nicotine to exert negative or no influence on memory, and others have shown dose-dependent and task difficulty-dependent effects as were reported in the Mangan (1983) study. Herzig, Callaway, Halliday, Naylor, and Benowitz (1998) administered 3 doses of cotinine, the active metabolite of nicotine, to non-smokers and observed a dose-dependent deleterious effect of nicotine on word list recall, i.e the higher the dose of cotinine administered the fewer the number of words participants could remember. Kleykamp, Jennings, Blank, and Eissenberg (2005) found 2 or 4 mg nicotine gum administered to never smokers had no effect on a working memory task. Poltavski and Petros (2005) investigated the impact of nicotine delivered via a transdermal patch (21 mg for smokers, 7 mg for non-smokers) vs placebo in smokers and non-smokers on prose recall. These investigators found smokers given
the active patch recalled less prose material than smokers given the placebo patch, while non-smokers who were given the active patch performed better on the prose recall task. These authors suggest the 21 mg patch given to predominantly light smokers resulted in too much nicotine for them causing a decrement in performance, while the 7 mg patch given to non-smokers was just enough to optimize performance. The authors point to inconclusive findings in the literature regarding the effect of nicotine on learning and memory as being suggestive of a dose-dependent effect. Later in this section we will see further evidence for a dose dependent, and in fact a Yerkes-Dodson or inverted-U effect of nicotine in normals.

In the previous paragraphs we reviewed the literature on the acute effects of nicotine on learning and memory and found different effects related to nicotine dose, smoking status (smoker vs nonsmoker), construct measured, task difficulty, and the suggestion that nicotine may optimize rather than linearly increase performance on certain constructs. Studies examining the effects of chronic nicotine use reveal a clearly detrimental effect of long-term nicotine use on cognition. For example, Hill, Nilsson, Nyberg, and Blackman (2003) assessed a large cohort (>600) of individuals aged 35–80 and found continuous smokers performed significantly worse than non-smokers on cognitively demanding tasks such as block design and free recall of unrelated word lists. Further, they found a significant negative correlation between the number of years and cigarettes smoked and performance on these tasks. Likewise Deary, Pattie, Taylor, Whiteman, Starr, and Whalley (2003) reported chronic nicotine use decreased overall IQ over time, and Razani, Boone, Lesser, and Weiss (2004) showed heavy smoking history to have a negative impact on executive functioning. Of interest in the current study, Paul et al. (2006) showed older smokers performed worse on delayed recall tasks than either older nonsmokers or younger smokers.
Although it might be thought that cognitive decline in older smokers is due to smoking related illness such as cardiovascular disease, the current research suggests otherwise. In the Hill et al. (2003) study, the investigators screened, by design, to include only healthy adults and further showed no difference in self-reported health between older smokers and nonsmokers making differences due to cardiovascular or other health factors unlikely. Likewise in the Paul et al. (2006) study the investigators screened for any mental or physical condition that may impact cognition (e.g. cardiac disease, hypertension, diabetes, drug and alcohol addiction) and still found older adult smokers to have poorer delayed recall. Razani et al. (2004) included vascular illness status as a covariate in their analysis and found it unrelated to cognitive decline in older smokers. Deary et al. (2003) could not state whether or not the health status of their sample contributed to the observed effect but did comment that previous studies had failed to show the effect on cognitive decline in older smokers was due to cardiovascular disease. Further, Stewart, Deary, Fowkes, and Price (2005) collected ankle brachial pressure (measure of atherosclerosis) on 2,000 men and women over the age of 50 and found degree of atherosclerosis to be independent of and smoking-related cognitive decline in that population. Brody et al. (2004) utilized MRI to study the brains of smokers and non smokers and found smokers had smaller gray matter volumes and lower gray matter densities than nonsmokers in the prefrontal cortex (PFC) bilaterally, along with smaller volumes in the left dorsal anterior cingulated cortex (ACC) and lower gray matter densities in the right cerebellum. This suggests direct effects, rather than secondary health effects, on cognition in chronic older smokers.

**Attention and vigilance**

In a study designed to examine the effects of varying levels of nicotine (via smoking) deprivation on several cognitive tasks (Hatsukami, Fletcher, Morgan, Keenan, & Amble, 1989), these researchers found 24 hr deprivation to result in slower reaction time (RT),
greater variability in RT, and an increase in errors of commission on a vigilance task (Yellin, 1980). On the Trail Making Test (B), Hatsukami et al. (1989) found significant effects on cognitive performance after 4 hrs of deprivation. In a more experimentally rigorous and counterbalanced study, Pritchard et al. (1992) investigated non-deprived smokers' performance on the Conner’s Continuous Performance Task (CPT) in one session after having smoked a 0.6 mg nicotine cigarette immediately prior to the task, and in another session after having not smoked for 20-min. These researchers assessed the effects on RT and errors of commission and found an improvement in RT with no corresponding increase in errors of commission in the smoking sessions. They also found no interaction effect between order of session and smoking condition, indicating no practice effects. Koelega (1993) reviewed 17 studies that examined the effect of nicotine on various vigilance tasks and found a significant overall effect in 11 of these, with two additional studies showing an effect on performance with low dose nicotine only. Koelega noted that those studies that failed to find an effect, failed to use a cross-over or counterbalanced design.

Several other studies have examined the effects of nicotine delivered via patch in both non-smoking and smoking populations. Levin, Conners, Silva, Hinton, Meck, et al. (1998) examined the effect of a 7 mg nicotine patch on CPT performance in non-smokers. In a counterbalanced design the researchers tested subjects on the CPT 3hr and 10-min after either receiving a 7 mg nicotine patch or a placebo patch. Subjects were tested again under the alternate treatment condition (active/placebo, placebo/active) at least four days following the initial testing session and condition. The results showed a decrease in errors of omission, decrease in RT variability and an increase in the overall composite measure of attention (higher scores indicate increased attention) for the nicotine patch group. As with the Pritchard et al. (1992) study, there was no corresponding increase in errors of commission nor were there any order or
practice effects. Another study conducted by Mancuso, Andres, Ansseau, & Tirelli (1999) also revealed 21 mg nicotine patch to increase performance on the Rapid Visual Information Processing (RVIP) test of vigilance in smokers deprived for 10hrs. In a review of studies involving subcutaneous (SC) administration of nicotine, Heishman (1998) found that nicotine administered SC also increased rate and accuracy scores on the RVIP in both abstinent smokers and in nonsmokers.

Although performance enhancing effects of nicotine on vigilance are the most widely and consistently reported, not all studies have found this effect. Poltavski and Petros (2005) randomized smokers and non-smokers to either active (21 mg for smokers, and 7 mg for non-smokers) or placebo transdermal patch and found that nicotine compared to placebo did not enhance performance on the RVIP vigilance task in either the smoking or non-smoking group. Kleykamp et al. (2005) also found no effect of placebo, 2 or 4 mg nicotine gum administered in a randomized fashion to never smokers on attention (alerting) nor on the other cognitive constructs that they measured. These authors noted that studies on nicotine's cognitive enhancing effects in never smokers have produced mixed findings. Trimmel and Wittberger (2004) reported a 5 mg transdermal nicotine patch administered to non-deprived smokers, deprived smokers, and never smokers improved RT on a vigilance task while slowing RT on a visual search task in all groups, showing that nicotine does not have a universal cognitive enhancement effect. These authors also found that nicotine resulted in larger performance increase for females than for males. Bekker, Bocker, Van Hunsel, van de Berg, and Kenemans (2005) administered either 21 mg transdermal nicotine patch or placebo to 16 adult healthy smokers to determine if nicotine has more of an effect on attention or response inhibition using primarily the CPT. The authors reported the 21 mg transdermal nicotine patch resulted in decreased (faster) RT and variability in response which they interpreted as an increase in attention, but they also observed a decrease in the number of correct
rejections indicating poorer response inhibition. As in the Trimmel and Wittberger (2004) study, the nicotine patch in this study had both an enhancing and detrimental effect on cognition depending upon the construct.

An interesting study by Poltavski and Petros (2006) points to differences among non-smokers based on their baseline levels of attention. In this study the investigators divided 62 male non-smokers into two groups, low attentiveness group and high attentiveness groups, based upon their answers on a self-report survey. These groups were then given either 7 mg transdermal nicotine or a placebo patch and administered several cognitive assessments including the CPT, Wisconsin Card Sorting Test (WCST) and the Stroop task 6 hours after application of the patch. The results revealed that the low attention active patch group showed the greatest performance increase while impaired WCST performance was observed in the high attention active patch group. While both the low and high attention nicotine groups committed fewer errors of commission, showed increased d' scores and fewer preservations on the CPT task; between group comparisons revealed the low attention nicotine group showed the greatest improvement on these measures. As was referenced in regards to learning and memory, these authors, and others, suggest that nicotine may optimize rather than linearly improve performance.

Another question raised by researchers, since many studies have been conducted with smokers who had abstained from smoking for some length of time, concerned whether nicotine improved performance or simply relieved withdrawal-induced performance deficits. This latter proposal is frequently referred to as the withdrawal-deficit hypothesis, and it is now widely refuted (Pritchard, Robinson, & Guy, 1992; Koelega, 1993; and Pineda, Herrera, Kang, & Sandler, 1998). Pritchard et al. (1992) point to numerous studies where nicotine was administered via tablet or gum to non-smokers and was found to affect measures of memory and attention. Additionally these
researchers point to several studies where nicotine administered to non-deprived smokers produced an effect on reaction time and memory tasks. Their own study (Pritchard et al., 1992) also showed nicotine delivered via controlled smoking to improve vigilance in non-deprived smokers. More recently, Trimmel and Wittberger (2004) showed transdermal nicotine patch to both increase and decrease RT on different tasks independent of smoking status, i.e. non-deprived smokers, deprived smokers, and never smokers. In a review of stimulant drugs and vigilance conducted by Koelega (1993), the researcher concluded that nicotine's effect on vigilance is not confined only to situations where subjects were deprived of nicotine, nor only to situations involving long-tasks or fatigued subjects. Koelega (1993) stated that nicotine's effects were probably just easier to detect in these situations.

In summary acute nicotine effects on attention and vigilance appear to be more consistent than on learning and memory. Studies that were not consistent with the larger body of evidence used a nicotine patch or nicotine gum as the delivery mechanism. The review showed some differences in acute nicotine effects based on construct measured, and also saw one study which reported sex differences. Harte and Kanarek (2004) report that performance increases on measures of attention are most consistently found in abstinent smokers. Koelega (1993) suggests that smoking status may still be a relevant factor in determining the size of the effects of acute nicotine abstinence on attention and vigilance. Many authors reviewed in this section discuss small effect sizes in non-diagnosed populations. Kleykamp et al. (2005) suggest modest effect sizes my be showing us that cognitive effects are not a significant factor for initiation of smoking in this population. Issues regarding effect size and other variables influencing nicotine effects on cognition and will be discussed in more detail later. For now, acute nicotine effects in diagnosed populations, specifically, schizophrenia and related disorders, will be reviewed.
Schizophrenia and related cognitive disorders

In a review of the relevant literature, Kumari and Postma (2005) identify sensory gating, eye movement abnormalities, and cognitive deficits as the most likely targets of nicotine self medication in schizophrenia. These are of interest because schizophrenia and related disorders display deficits in these areas, nicotine has been shown to impact these areas, and differential effects of nicotine have been found between diagnosed and non-diagnosed populations.

Sensory gating

Studies on sensory gating fall into two categories; pre-pulse inhibition (PPI) and auditory gating (mostly of the P50 wave). PPI refers to the reduction of response to a second strong stimulus if reliably preceded by a weaker stimulus. Similarly, auditory gating is a decreased response to the second of two closely paired auditory stimuli (typically measured by the P50 wave). PPI is considered a measure of sensorimotor gating, while P50 response is considered a measure of sensory gating as it is measured via EEG and does not involve a motor response. Schizophrenic patients have been shown to display deficits in both PPI and the P50 response. A deficit in PPI (and P50 response) means the individual still displays an exaggerated response to the second, strong stimulus despite the presence of the preceding weaker stimulus. Conversely enhanced PPI (or P50 response) means diminishing the intensity of response to the second, strong stimulus following exposure to the weaker stimulus. A diminished response to the second, stronger stimuli would be the normal, or expected response. Auditory gating, as measured by the P50 wave, has been shown to be diminished in more than 85% of (Adler et al., 1993; Leonard, et al., 2002) schizophrenics. Additionally, first degree relatives of schizophrenic patients have shown these same deficits (Adler et al., 1992) while no studies to date have been done on PPI deficits in relatives of schizophrenic patients.
Kumari and Postma (2005) point out from their review of the literature that nicotine has been shown to enhance PPI in animal studies and in studies involving both healthy smokers and schizophrenic smokers, but not in non-smokers. George et al., (2006) verified the finding of an effect of nicotine in schizophrenics but no effect in normals. However, one study conducted by Kumari, Cotter, Checkley and Gray (1997) did show that high dose nicotine, delivered subcutaneously, enhanced PPI in healthy non-smokers. This result has implicated a low-affinity nicotinic receptor (discussed in detail later).

Two studies related to auditory gating, as measured by the P50 wave, (Adler et al. 1992; 1993) produced interesting results. In the first of the Adler et al. studies (1992), relatives of schizophrenics who were not diagnosed with schizophrenia and who were not being treated with antipsychotic medications but who exhibited auditory gating deficits were given nicotine gum to determine nicotine's effect, if any, on their auditory gating deficits. The results showed transient normalization of their auditory gating deficit (Adler et al., 1992). In the second study by Adler et al. (1993), the effects of nicotine on schizophrenic smokers and smokers in the normal population were examined. The results of this study showed that smoking, at a self-selected rate, produced transient normalization of the auditory gating phenomenon in the schizophrenic group, while the same smoking behavior in the non-diagnosed population resulted in slight impairment of auditory gating (Adler et al., 1993). These studies are significant in that it shows a differential effect of nicotine on auditory gating between non-diagnosed and schizophrenic populations and suggests a shared neurobiological deficit between schizophrenics and their first degree relatives.

Eye movement abnormalities

Two eye movement tasks dominate the relevant literature; 1) smooth pursuit eye movement (SPEM), and 2) antisaccade tasks. SPEM tasks involve presenting a subject
with a small object, typically a dot on a computer screen, and asking the subject to follow the object with their eyes while not moving their head. Pursuit accuracy is the performance measure of interest. Antisaccade tasks, as the name suggests, requires the subject to inhibit the natural inclination to saccade toward a target, and instead to begin a saccadic eye movement in the opposite direction, thereby providing a measure of inclination to saccade toward the target versus the instructed goal of looking in the opposite direction (Kumari & Postma, 2005). While studies have shown both impaired SPEM and increased antisaccade errors in schizophrenia patients versus healthy controls, nicotinic effects on these tasks may be by different mechanisms. Nicotine appears to more consistently improve SPEM performance in schizophrenia patients than in healthy control smokers. When nicotine has been shown to improve SPEM in healthy control smokers as well as schizophrenic smokers, leading or anticipatory saccades (said to represent maximized inhibition and reducing intrusions) were only shown to be improved (by reducing the frequency of leading saccades) in the diagnosed patients, while healthy control smokers showed impaired performance on the same task (Olincy, Johnson, & Ross, 2003).

The literature on antisaccade studies is smaller than on SPEM but appear to point to nicotine improving performance in both schizophrenic smokers and healthy control smokers. Further, PPI, auditory gating, and SPEM performance have been found to correlate with each other but not with antisaccade performance (Kumari & Postma, 2005; Kumari et al. 2005). P50 gating performance has also been shown to correlate with sustained attention and vigilance performance. While none of these measures were shown to correlate with either negative or positive symptoms of schizophrenia, antisaccade error rate has been found to correlate with severity of negative symptoms (Ettinger et al., 2004). Kumari and Postma (2005) suggest anti-saccade performance may be related to frontal cortex dopamine while the other performance measures are
thought to be related to α7 nicotinic receptors (to be discussed in further detail later) and normalization of hippocampus dysfunction in patients diagnosed with schizophrenia (Tregellas, Tanabe, Martin, & Freedman, 2005).

*Cognitive deficits*

Sandyk (1993) provided the first rudimentary evidence that nicotine has a positive influence on cognition in schizophrenics by simply showing that schizophrenic smokers performed better than schizophrenic non-smokers on the Mini Mental Status Exam (MMSE). The MMSE assessed ability related to orientation, immediate memory, and awareness.

As neuroleptic treatments can also cause cognitive deficits (Levin, Wilson, Rose, & McEvoy, 1996), Levin et al. (1996) conducted a study to determine if nicotine only attenuated deficits caused by haloperidol or if nicotine caused performance increases beyond the mere attenuation of neuroleptic-induced deficits. The subjects were schizophrenic smokers who had been abstinent overnight. Each was assigned to four different sessions in which they received a placebo, 7 mg, 14 mg, or 21 mg skin patch on each of the four different occasions. Additionally, the subjects were divided into three groups according to haloperidol dose: low-dose (one-third of the neuroleptic threshold (NT) dose), medium (NT dose) and high (three times NT dose). Subjects were tested using four tests from the Automated Neuropsychological Assessment Metrics (ANAM) battery: simple reaction time, complex reaction time (spatial rotation), delayed-matching-to-sample (DMTS), and a modified Sternberg Memory Test. After the ANAM battery, subjects were administered the CPT. The results showed no effects of nicotine or nicotine x haloperidol on simple reaction time or the modified Sternberg Memory test. On complex reaction time haloperidol significantly slowed RT while nicotine significantly improved RT. On this measure nicotine not only attenuated the haloperidol-induced deficits but had a reversal effect. For the DMTS procedure nicotine was found to
reverse the decrements caused by medium and high dose haloperidol. On the CPT, RT was improved with the 7 mg and 14 mg dose of nicotine but slowed with the 21 mg patch irrespective of haloperidol dose. The results of this study show that while schizophrenics receiving typical neuroleptic treatments may smoke in part to relieve neuroleptic-induced deficits, the performance enhancing effects of nicotine are superfluous to these deficits.

A study by White and Levin (1999) provide additional evidence of nicotine's effect on attention and vigilance in diagnosed populations. These researchers examined the effect of a 5 and 10 mg nicotine patch on performance of the CPT in non-smoking patients with Alzheimer's disease (AD). AD patients are of interest because they share a receptor deficit with schizophrenic patients, a loss of nicotinic acetylcholine receptors (this deficit, and other neurotransmitter theories, are discussed later in this paper). White and Levin (1999) used the same measures and design as the Levin et al. (1996) study. The results showed that nicotine reduced errors of omission, RT variability, and total errors on the CPT while improving the CPT's composite measure of attention (d'). The authors note that nicotine's effect on the CPT has been observed in AD, schizophrenic, and normal populations and thus represents a notably robust and consistent finding.

**Differential effects between diagnosed and non-diagnosed populations**

Evident from some of the studies discussed above, the effects of nicotine appear to be different for diagnosed versus non-diagnosed populations. Additional studies demonstrate such findings more explicitly. For example, George, Vessicchio, et al. (2000) showed differential effects of nicotine between diagnosed and non-diagnosed populations. They examined the effects of acute (<1 week) and prolonged (8-10 weeks) nicotine abstinence on the Stroop Color-Word Test and the Visual Spatial Working Memory (VSWM) test in nicotine-dependent and control schizophrenic and non-diagnosed populations. The results showed no effect of smoking status in either group.
on the Stroop test. Non-diagnosed smokers were shown to have impairments on the VSWM task as compared to non-diagnosed non-smokers while schizophrenic smokers were shown to have slightly improved VSWM function compared to non-smoking schizophrenics. Furthermore, smoking abstinence led to impaired VSWM function in schizophrenic smokers and to an improvement in VSWM function in non-diagnosed smokers. Further evidence for nicotine impairing spatial working memory in non-diagnosed smokers was provided by Park, Knopick, McGurk, and Meltzer (2000). Myers et al. (2004) found that nicotine delivered via nasal spray significantly improved delayed recognition on a visuospatial task for smoking schizophrenics but had no significant impact on non-smoking schizophrenics or smoking or non-smoking controls. Likewise, Smith et al. (2006) demonstrated that nicotine nasal spray resulted in modest enhancement of spatial working memory in schizophrenic smokers. This same study found no effect of nicotine on verbal memory. Of note, while the Myers et al. (2004) found an effect on the visuospatial recognition of design test, they found no effect on a non-verbal working memory task involving delayed matching-to-sample of unfamiliar faces. Harris et al. (2004) found no effect of nicotine administered via gum to smoking and non-smoking schizophrenics on visuospatial, immediate or verbal delayed memory, but again found nicotine to have an overall impact on the attention measure. Of interest, the overall effect on attention appeared to be due to an increase in performance in non-smokers and a decrease in smokers, suggesting an inverted-U or optimization effect of nicotine even in diagnosed populations.

Depatie et al. (2002) investigated the effects of a 14 mg nicotine patch on CPT (Cornblatt, 1988 version), antisaccade, and smooth pursuit performance in schizophrenic and normal smokers. These authors included type of antipsychotic medication, presence of anticholinergic medication, order of drug administration (nicotine/placebo vs. placebo/nicotine) and Positive and Negative Syndrome Scale...
(PANSS) scores as factors in their statistical analysis. Subjects in both groups were abstinent for 9 hours prior to receiving either a 14 mg nicotine or placebo patch. Testing commenced 7 hours following patch administration to assure testing coincided with plateau nicotine levels. Results revealed no significant effect of type of medication, presence of anticholinergic medications, order of drug administration, or PANSS score on the performance measures. Adler et al. (1993) and Green et al. (1997) also found anticholinergics to play no intervening role between nicotine and auditory gating nor nicotine and CPT performance, respectively. CPT results showed nicotine to increase hit rate (correct responses) in schizophrenics but not in normals; additionally, it was found that the increase in hit rate in schizophrenics was not significantly different between the first half and last half of the test indicating that nicotine did not improve hit rate by simply preventing a decline in performance over time. Nicotine also improved performance on the composite measure of attention (d') in both groups. No other significant effect of group or drug was found on this measure. Nicotine was found to improve performance on the antisaccade and smooth pursuit measures in both groups. This study (Depatie, et al., 2002) provides partial evidence for a differential effect of nicotine between schizophrenic and normal populations.

Of particular interest regarding differential effects of nicotine by population are two very well designed studies by Sacco and colleagues (2005; 2006). In the first study (Sacco et al., 2005) the effects of overnight abstinence on CPT and VSWM were observed in 25 smokers with schizophrenia and 25 control smokers. These authors also examined the effects of nicotine reinstatement and the effect pretreatment with the non-selective nicotinic-acetylcholine receptor (nAChR) antagonist (mecamylamine hydrochloride 0, 5, or 10 mg/d) would have on nicotine reinstatement. The results showed nicotine abstinence to impair CPT hit rate performance in both groups while VSWM was only impaired in the smokers with schizophrenia. Smoking reinstatement
reversed these impairments, however mecamylamine was found to block the reinstatement effects (dose-dependently on the CPT) only in the schizophrenia group, suggesting that nAChRs play a role in attentional and VSWM enhancement in schizophrenics. Of interest, the more subjective Positive and Negative Syndrome Scale was unaffected by mecamylamine administration, perhaps suggesting different neurocircuitry involvement for traditional positive and negative symptomology.

Of further interest is the second study conducted by Sacco et al. (2006) in which they evaluated neuropsychological deficits in non-smokers with schizophrenia compared to non-smoking controls. The authors tested the subjects at baseline on VSWM, CPT, WCST, Word Serial Position Test (WPST) and a Stroop (SCWT) task and then again over 3-days on three separate testing weeks after being administered mecamylamine 0, 5, or 10 mg/d. The authors found that the schizophrenia group had baseline neuropsychological deficits on VSWM, CPT (%Hit Rate, Reaction Time, and Variability Index), WCST, and WSPT, while subsequent mecamylamine administration had no significant effect on performance in either group. This study, considered together with the Sacco et al. (2005) and other studies, suggests that smokers, particularly diagnosed smokers, may possess different receptor dysfunction than their non-smoker counterparts. Upregulation of high-affinity nAChRs have been shown to occur dose-dependently in non-diagnosed smokers compared to their non-smoking counterparts. This upregulation was not observed in smokers with schizophrenia (Breese et al., 2000). It is likely that mecamylamine, a non-selective nAChR antagonist, was not exerting enough of an influence on the low-affinity nAChRs (Freedman et al., 1994) implicated in some of the neurocognitive deficits in schizophrenia. Research utilizing more selective nAChR antagonists is needed.

The psychological/neurocognitive evidence reviewed herein shows that nicotine does affect certain cognitive constructs and further that there exists evidence for a differential
effect on diagnosed versus non-diagnosed populations, thus providing some support for
the hypothesis that schizophrenics smoke at a higher rate due to an attempt to mitigate
cognitive deficits. Neurobiological evidence in support of this hypothesis is discussed
below.

Schizophrenia, neurotransmitters, cognition, and nicotine

Although many different neurotransmitters are implicated in playing a role in the
etiology and course of schizophrenia (Lyon, 1999), most research has focused on
dopamine (DA) (Diwan et al., 1998; Green, Zimmet, Strous, & Schildkraft, 1999; Goff et
al., 1992; Lyon, 1999; Sandyk & Kay, 1991; Ziedonis & George, 1997). Meltzer and
Stahl (1976), along with Carlsson (1978), were among the first to put forth the dopamine
hypothesis of schizophrenia. In its most rudimentary form, the dopamine hypothesis
states, “schizophrenia may be related to a relative excess of DA-dependent neuronal
activity” (Meltzer & Stahl, 1976, p. 19). These early theories dealt primarily with the
positive symptoms of schizophrenia and evidence was derived from the DA targeting
pharmacological treatments such as chlorpromazine and haloperidol. A more refined
DA theory implicates hyperactivity of DA synapses in the mesolimbic pathway, which
projects from the ventral tegmental area (VTA) to the nucleus accumbens (NA) and
amygdala, as responsible for the positive symptoms of schizophrenia; while hypoactivity
of DA in the dorsolateral prefrontal cortex is thought to be responsible for the negative
symptoms of the disease.

As noted earlier, cognitive deficits are now considered the core feature of
schizophrenia, and dopamine is again thought to play a role (Meltzer, 1999c). However,
in looking at how nicotine improves cognitive performance, dopamine’s role appears
secondary to nicotine’s effect on the cholinergic system. Nicotine intake acts on the
cholinergic innervations of the ventral tegmental area (VTA) and the substantia nigra
(SN) (both of which are important for working memory function); this results in an increase in ACh input which in turn increases DA activity in these areas, and most importantly in the frontal cortex (Levin, Briggs, Christopher, & Auman, 1994). Dopamine D2-receptor agonists have been shown to improve memory when co-administered with nicotine, but D2 agonists alone had no effect (Levin, McClernon, & Rezvani, 2006).

Nicotine binds to cholinergic nicotinic receptors and results in the release of ACh (Pineda et al., 1998). In aged and demented human subjects, aged rats, and in AD patients a relationship between cholinergic degeneration and various decrements in cognitive functioning has been found, Bartus, Dean, Beer, & Lippa and Collerton (as cited in Giovannini, Casamenti, Bartoloni, & Pepeu, 1997). Of particular interest are the nicotinic-ACh receptors (nAChRs) present in the hippocampus and frontal cortex, as the prefrontal cortex and hippocampus are known to be essential for cognition (Meltzer, 1999c). There are numerous subtypes of nAChRs (see Dani, 2001 for a comprehensive review), but α4β2 and α7 are predominant in the mammalian brain. Mansvelder, van Aerde, Couey, and Brussaard (2006) note that the α7 subunit is even more widely expressed in primates than lower mammals such as rats suggesting that the α7 receptors play a more important role in humans. Both α4β2 and α7 nicotine receptors in the hippocampus are important for cognitive functioning (Levin & Simon, 1998), but the primary function of the α4β2 receptors appears to be the release of DA in the mesolimbic system, thereby contributing to the reinforcing effects of nicotine (Foulds, 2006). The reinforcing effects of nicotine are separate from nicotine’s memory enhancing effects, Grigoryan, Hodges, Mitchell, Sinden, and Gray (as cited in Levin & Rezvani, 2000). Most authors conclude that the α7 receptors are particularly important for cognition (Adler et al., 1998; Dani, 2001; Levin & Rezvani, 2006; Mansvelder et al.,
Post-mortem studies of schizophrenics have shown a deficient number of \( \alpha_7 \) receptors in the frontal cortex (Levin & Rezvani, 2006). In the mouse brain nicotine and ACh have been shown to cause a marked increase in glutamate release in layer V of the frontal cortex (Lambe, Picciotto, & Aghajanian, 2003), which has been shown to be important for cognitive function (Levin et al., 2006). MRI studies have also shown that nicotine's attentional improvements are related to activity in several regions of the cortex including the superior frontal cortex (Levin et al., 2006). Infusion of nicotine in the frontal cortex has been shown to improve choice accuracy (presumed to involve attention) on the 5-choice serial reaction time task (5-CSRTT) in rats (Hahn, Shoaib, & Stolerman, 2003), which again implicates the involvement of nicotinic receptors in the frontal cortex in improving attentional performance (Levin et al., 2006). Studies also show that decreased ACh in the frontal cortex impairs attentional functioning (Mansvelder et al., 2006). The exact location of the \( \alpha_7 \) nicotinic receptors in the frontal cortex that are responsible for attention are unknown (Mansvelder et al, 2006), but there does exist sufficient volume of evidence to say with confidence that nicotinic effects in the frontal cortex have an impact on cognition.

Most neuroimaging studies have found reduced hippocampal volume in schizophrenics (Heckers, 2001; Tanabe, Tregellas, Martin, and Freedman, 2006). In post-mortem studies, schizophrenics have been shown to have a deficient number of \( \alpha_7 \) receptors (Freedman, Hall, Adler, & Leonard, 1995; Leonard et al., 1996; Levin et al., 2006), as well as \( \alpha_4 \beta_2 \) receptors (Durany et al., 2000), in the hippocampus. Administration of an ACh depleting neurotoxin (AF64a) directly into the hippocampus resulted in severe learning and memory impairment (Hiramatsu, Yamatsu, Kameyama,
Induction of Long-term potentiation (LTP: the neural substrate of working memory) via nicotinic stimulation of glutamatergic synapses in the hippocampus has been shown to influence learning and memory (Mansvelder et al., 2006). Levin et al. (2006) cite a wide array of specific evidence that the α7 receptors in the hippocampus are responsible for the effects of nicotine on cognition, including animal and human studies that link performance on a measure of associate learning (eye-blink procedure) to α7 receptors in the hippocampus. Particularly interesting, Levin et al. (2006) report that when either α4β2 or α7 antagonists are injected into the rat hippocampus, memory impairment in the radial-arm maze results. However, chronic nicotine injections reverse the adverse effect of α4β2 blockade on memory but does not reverse the effects of α7 blockade, suggesting that the full activation of hippocampal α4β2 is not necessary for memory and that hippocampal α7 receptors are primary to nicotine's positive effects on memory.

It is difficult to discern a clear picture of distinct effects, due to specific nAChRs, in specific brain regions; and it should be noted that the research in this area is not at a point where direct causal relationships can be drawn. Several of the previously referenced authors discuss reasons why specific conclusions are still yet to be made, those include; the lack of good receptor specific pharmacological compounds, lack of consistent methodologies, technological limitations, and potential developmental compensations in transgenic animals (see Mansvelder et al., 2006 and Gotti et al., 2006 for a more detailed discussion). It was noted earlier that nAChRs are distributed widely throughout the brain, and differently in primates than other lower mammals. It is also a fact that even though one nAChR subtype may predominate a brain region, other nAChRs may coexist (Dani, 2001); and even a relatively small number of nAChRs can have large effects on neural systems. Although α7 nAChRs are of primary interest to the current topic, authors have also shown α4β2 agonists to improve working memory and
attentional accuracy (Levin et al., 2006). In addition to their effects on DA release in the mesolimbic system, α4β2 receptors have been implicated in cognitive deficits related to low DA activity in the PFC. Further, neither nAChRs nor brain regions work in vacuums that prevent them from affecting other regions of the brain. For example, several of the authors reviewed have pointed to nAChR interactions with glutamate, GABA, dopamine and serotonin; and Heckers (2001) points to hippocampal and frontal lobe interactions.

Despite the challenges and need for refinement of data, a picture with both good research support and good face validity is beginning to emerge. This involves specific regions of the hippocampus and differential effects in regard to receptor desensitization between populations. Chronic administration of nicotine increases the number of nAChRs (upregulation) in the hippocampus, (Marks, Stitzel, & Collins study as cited in White & Levin, 1999; Levin & Rezvani, 2000) and may produce long-term structural changes in the density and/or sensitivity of nAChRs in the frontal cortex (Pineda et al., 1998). Breese et al, 2000 reported a robust finding of upregulation of nAChRs in high-affinity receptors and a less robust finding of upregulation of low-affinity nAChRs in the non-diagnosed group but not in schizophrenics group, providing biological evidence for nAChR differences in schizophrenics. Freedman et al. (1995) reported finding a lower number of α7 receptors in the dentate gyrus, CA3 and CA1 regions of the hippocampus in schizophrenics independent of smoking status, again suggesting normal upregulation does not occur in this population. Mansvelder et al. (2006) discuss findings that show desensitization differences between α4β2 and α7 nAChRs. Stimulation via direct synaptic or indirect non-synaptic actions results in activation and rapid desensitization of these receptors. Mansvelder et al. (2006) state that the physiological significance of high-affinity (α4β2) and low affinity (α7) subtypes may not be in their activation properties but in their desensitization. Low concentrations of nicotine activate both
receptor systems (except for α7 receptors in the VTA), but the α4β2 are completely desensitized at this level while α7 receptors are not and remain available for activation.

These findings support many authors' theories that hippocampal dysfunction, and possible altered nAChR response in this area (Jacobsen et al., 2004), is involved in both the cognitive impairment and symptomology in schizophrenia (Venables, 1992; Hemsley, 1993; Roberts, 1963, as cited in Heckers 2001). One predominate and research-supported theory is that α7 nAChRs in the hippocampus show decreased desensitization (Levin and Rezvani, 2006) and interfere with the ability to distinguish relevant from irrelevant information, and internal cues from external cues (Heckers, 2001). Nicotine may improve this situation and enhance working memory by reducing distractibility (Levin et al., 2006) via nAChRs that increase the signal-to-noise ratio, and helping the process of evaluating the significance and relevance of received stimuli (Dani, 2001). In fact, Tregellas, Tanabe, Martin and Freedman (2005) showed that nicotine-induced performance improvement on a SPEM task was correlated with decreased activity in the hippocampus and contend that nicotine activated nAChRs that normalized hyperactivity in this region and prevented intrusive saccadic eye movements.

The CA 1 and CA3 regions of the hippocampus are specifically implicated in both the neuropathology and the modulation of cognitive impairment by nicotine. Levin et al. (2006) state that long-term potentiation (LTP) in the CA1 region of the hippocampus is the neural substrate of learning and memory and that ACh lesions here impair LTP while nicotine reverses this effect and additionally promotes LTP. Mansvelder et al. (2006) state that the CA1 pyramidal neurons in the ventral hippocampus project to the PFC, and hypothesize that modulation of the CA1 region by nicotine may be at least in part responsible for the effect of nicotine on attentional performance. Additional evidence for the involvement of these regions of the hippocampus and α7 nAChRs have been
provided via research on sensory gating. This research and an eloquent hypothesis provide by L.E. Adler will complete this section.

The sensory gating deficit (P50) in humans discussed previously has been linked to \(\alpha_7\) deficits in the hippocampus (Adler et al., 1998). Additionally, \(\alpha_7\) agonists have been found to increase gating of the analogous P20-N40 auditory-evoked potential (AEP) in rats. This information has resulted in the hypothesis that a deficient population of \(\alpha_7\) receptors in the hippocampus results in inadequate stimulation of inhibitory neurons and results in sensory gating deficits (Simosky, Stevens, Adler, & Freedman, 2002). Nicotine acts on these neurons and maintains them in an activated state producing an inhibitory effect and normalizes this deficit (Mancuso, Warburton, Melen, Sherwood, & Tirelli, 1999). Adler et al. (1998) present the most eloquent theory on how this may occur.

Adler et al. (1998) explain sensory gating as a way for the brain to filter input by habituating to identical stimuli and only attending to the most important information. The authors focus on the CA3 region of the hippocampus because, among other reasons, this is the major point of convergence for cortical and brainstem inputs. Information that reaches the CA3 region projects to CA1 pyramidal neurons; the CA1 region is the site for LTP or extended short-term memory. CA1 deficits cause a nearly complete loss of new learning. The CA3 region filters irrelevant and repetitive stimuli and prevents them from getting output to the CA1 region; in effect it prevents flooding. When CA3 gating fails, it results in a decrease in learning efficiency, and in fact, incorrect learning may occur by attending to the wrong stimuli. The authors contend that the resulting attentional and learning decrements may be responsible for the low social functioning prevalent in schizophrenics.

Additional evidence for the centrality of \(\alpha_7\) receptors in explaining why schizophrenics smoke at a higher rate comes from the smoking behavior of this population. High affinity nicotine receptors (\(\alpha_2,-3,-4,-5 \& \beta_2,-3,-4\)) are activated by low
dose nicotine, while low affinity receptors (α7) are activated by high dose nicotine. Schizophrenics have been shown to smoke high nicotine cigarettes, extract more nicotine from the smoke, and smoke more cigarettes (Adler et al., 1998). It is proposed that normal smokers hit the high affinity receptors that result in the decreased anxiety and elevated mood that may be partially responsible for smoking in this population. The higher dose of nicotine, self-selected by schizophrenics, may be an effort to target the low affinity α7 receptors and normalize the corresponding deficits. Evidence for this was provided in Adler et al. (1992) where low dose nicotine failed to normalize P50 gating while high dose nicotine did. Additionally, Freedman et al. (1994) gave first-degree relatives of schizophrenics with P50 gating deficits both high-dose nicotine and mecamylamine and found the P50 gating deficit to be normalized, again implicating the low affinity nicotine receptors since it has been shown that mecamylamine blocks the effects of low dose nicotine. Freedman et al. (1997) also found genetic evidence for the presence of α7 deficits in schizophrenics. In sum, there is a preponderance of evidence taken from schizophrenics, their first degree relatives, and animal studies that sensory gating deficits involve α7 receptors in the hippocampus and that nicotine normalizes these.

Finally, there is evidence that clozapine, which increases extracellular ACh in the medial prefrontal cortex, reduces smoking in schizophrenics (Meltzer, 1999c). Further, a recent study (Simosky, Stevens, Adler, & Freedman, 2003) showed that clozapine normalized inhibitory processing of the P20-40 (AEP) in mice via stimulation of α7 nicotinic receptors. Of interest is research showing 5-HT2a receptor blockade reduces the enhancing effects of nicotine on attention and memory (Levin et al., 2006), so it raises the question that clozapine may reduce smoking because smoking no longer attenuates the attentional and memory impairments associated with schizophrenia. Levin and Rezvani (2006) state it has been suggested that drugs such as clozapine
which do block 5-HT2 receptors may limit the efficacy of nicotine co-treatment for cognitive enhancement.

To be sure, this section does not constitute a full discussion of all the mounting evidence for the involvement of nAChRs in cognition, their connection to the cognitive impairment in schizophrenia, and the reversal of those impairments via smoking. However, the reader should have a good introduction to the topic and related issues. The reader can turn to the afore-referenced articles by Mansvelder et al., 2006; Dani, 2001, Levin and Rezvani, 2006; Levin, McClernon and Rezvani, 2006; and Heckers 2001 for comprehensive reviews including discussions of the challenges of isolating responsible brain regions and receptors. The reader should turn to Robert Freedman and Sherry Leonard, previously referenced, for information regarding genetic evidence for links between α7 deficits, schizophrenia, and cognitive dysfunction.

Summary

Of the competing hypotheses that attempt to explain the differential prevalence of smoking in the schizophrenic population, the self-medication hypothesis, specifically the mitigation of cognitive deficits, garners the most empirical support. Neuropsychological studies have shown that nicotine does in fact enhance performance on certain cognitive constructs over and above the simple mitigation of withdrawal or fatigue states. Clinical studies show the cholinergic system, specifically hippocampal α7 receptors, to be both involved in cognitive performance and stimulated by nicotine. Differential effects between normal and schizophrenic populations may be related to α7 deficits within the schizophrenic population.
Specific aims of the present study

As the above discussion reveals, the amelioration of cognitive and attentional deficits is currently the most promising explanation for the higher prevalence of smoking among schizophrenics compared to the general population. But the term cognition is too general to be of practical use; Green (1996) corroborated this when he reviewed the literature in this area and found it to be too global. The present study focused on those components of cognition that have been shown to be important for social functioning. Green (1996) reported the most consistent finding in the schizophrenia literature is that vigilance is important to both skill acquisition and problem solving, while verbal memory (most frequently secondary, but immediate as well) was the most consistent predictor of functional outcome. Additionally, research conducted by Herbert Y. Meltzer's group at Vanderbilt University Medical Center shows a strong association between immediate and delayed recall (a common measure of verbal memory) and this population's ability to work (unpublished data). The present study was designed to test the effect of nicotine on these specific cognitive and attentional constructs. Specifically, data were collected to test the following hypothesis: determine if healthy smokers' scores on the RAVLT (sub-measures trial 5 (RVLTV), total for trials 1-5 (RVLTTT), delayed recall trial 7 (RVLTVII), correct recognitions (RVLTCORREC), and recognition discriminations (RVLTRECDISCR); and the CPT (raw scores for all 13 sub-measures, and three test factors Impulsivity, Inattentiveness, and Vigilance based on combined T-scores from relevant sub-measures) will be significantly different in the acute-abstinence session from the free-smoke session.

Although the high rate of smoking in schizophrenics was the impetus for this line of inquiry, and much of the literature review concerned nicotine effects in schizophrenia, the review of nicotine effects in non-diagnosed controls provides the rationale for the current study.
Regarding effects on verbal memory, while the studies reviewed were creative in testing various aspects of verbal memory, most failed to use standardized assessments for immediate and delayed recall. Also, most of the studies used delivery mechanisms other than smoking to assess the effects of nicotine (the importance of delivery mechanism is discussed in the Methods section below). Finally, some of the studies assessed nicotine effects in non-smokers and provide little help to the task of determining reasons for the initiation of smoking. The current study implemented a standardized and psychometrically sound assessment of immediate and delayed verbal memory to assess in smokers the impact of nicotine via the participants' normal smoking behaviors.

Regarding effects on vigilance, some of the same problems exist here that are seen in the memory research. The majority of the studies reviewed investigated the effect of nicotine patch on different measures of attention. Koelega (1993) stated that 11 of 17 studies he reviewed showed some effect of nicotine on attention. This paper reviewed an additional 10 studies yielding 19 out of 27 studies showing some effect on a measure of attention. However five of the 11 studies that Koelega (1993) referenced also showed no effect of nicotine on other attention variables measured, and two of the studies reviewed in the current document showed impaired performance on some measure of attention. So looking at it another way, 15 out of 27 studies revealed either no or a detrimental effect of nicotine on cognition in healthy controls. Further, as eluded to, attention has been defined in various ways (some unrelated to vigilance) and the measures used to assess these constructs have also varied greatly making comparisons and consensus agreement difficult. As with memory, the current study used a standardized and psychometrically sound assessment of vigilance, as meaningfully defined, to assess in smokers the impact of nicotine via the participants' normal smoking behavior.
CHAPTER II

METHODS

Participants

Subjects were recruited utilizing Vanderbilt University's psychology department research subject pool, Vanderbilt University Medical Center's (VUMC) mass email system, word of mouth, and fliers placed around the VUMC campus, Centerstone Davidson County clinics, and in the internal mailboxes of Centerstone employees.

For inclusion in the study, participants must have been between the ages of 18 and 60, carry no current psychiatric diagnosis, and currently smoke at least 10 cigarettes a day. The age range was selected to include diverse participants, but the high end of the range was selected to control for possible cognitive decline as a result of age. For nicotine levels to be of sufficient strength to possibly affect vigilance and/or verbal memory tasks, only moderate to heavy smokers (≥ 10 cigarettes/day) were included.

Exclusion criteria for participants was any current psychiatric diagnosis including substance dependence or significant abuse, currently taking psychotropic or smoking cessation medications, presence of any organic brain injury or neurological disorder, or history of significant traumatic brain injury.

Out of the over 300 respondents, 14 participants both met the inclusion criteria and gave consent to participate in the study. Of those, 13 completed the majority of the study procedures. All subjects were compensated for their time at the rate of $15 per testing session. Written informed consent was obtained from all participants and all study procedures were approved by both the Western Michigan University and Centerstone Institutional Review Boards (IRBs). Additionally, recruitment activities at Vanderbilt were approved by Vanderbilt following confirmation of study approval by the aforementioned IRBs.
The majority of the respondents were expecting a smoking cessation study and were no longer interested when they learned more about this study. Many others failed to meet the inclusion criteria due to currently taking smoking cessation and/or antidepressant medications. Several other prospective participants were unwilling to abstain from smoking for the required minimum of 6 hours. While the resulting sample size was small, pre-study power analysis indicated that this sample size should be sufficient. Sample size was determined using the Statistical Analysis System (SAS) program using the following values. For power of .80 and type-I error (alpha) of .05 to detect a difference of .8 (taken from previous study) with a population variance (sigma) of 1.06 (also taken from previous study) and with a correlation between measures of 0.5 or 0.7, a sample size of 15 or 9 was needed, respectively. While more participants were desired, previous studies with similar sample sizes, using clinical populations, have found significant effects of nicotine on attention and memory, making comparisons with the current findings of interest in looking at effect size differences between normal and clinical populations.

Materials

As stated in this paper’s introduction, vigilance and verbal memory are the two areas of cognition most consistently related to individual and social functioning in schizophrenics (Green, 1996; Meltzer, unpublished data). Vigilance is often equated with attention and all too frequently vaguely defined, if defined at all. Vigilance can be differentiated from attention in general. Mateer and Mapou (1996) provide subcategories of attention that they refer to as deployment and encoding. Vigilance is subsumed under the deployment subcategory. Lezak (1983) defines vigilance as the ability to sustain attention. This is the more precise definition of vigilance and will be used as the definition for the construct under investigation in this study.
Memory is a complex construct, which while it has been compartmentalized, it is not always easy to maintain these subdivisions in a meaningful manner. For the purposes of this study (verbal) working memory will be subsumed under Mateer and Mapou's (1996) subcategory of attention, referred to as encoding. Additionally, Spreen and Strauss (1998) refer to the type of memory we are interested in (immediate and delayed verbal recall) as explicit memory, which is frequently tested through the recall of word lists. Explicit memory is said to involve the hippocampal system, which has already been demonstrated to be important in the way nicotine facilitates memory, and deficits in this region have been observed in schizophrenia and other diagnosed populations. Dysfunctions of this system often result in the disruption of “the formation/retrieval of new explicit memories” (Spreen & Strauss, 1998, p. 260).

Levin et al. (1996) correctly assert that the nature of the task used to assess the construct critically influences the results. In literature reviews conducted by Koelega (1993) and Heishman (1998) both authors conclude that measures used to assess vigilance vary greatly and have low intercorrelations. Further, both authors state that many of the studies use tests that are not standardized, lack or fail to report validity and reliability data as well as administration procedures. The current study addresses these concerns.

The Conners' Continuous Performance Test-II (2002) was used in this study to assess the primary construct vigilance, and related constructs inattention and impulsivity. Many tests are used to assess vigilance and attention (for example, the WAIS-R Digit Symbol Substitution Test, the WAIS-R Digit Span, and the Stroop test); however, the Conners' CPT is the only standardized, valid, and reliable measure noted in the literature to specifically test vigilance as defined for this study. The 1995 (dos) version of the Conner's CPT has been used extensively in research and clinical settings and has shown to be sensitive to drug treatment effects (Conners & MHS staff, 2002); of
current interest, it has been shown to be sensitive to nicotine and stimulant induced attentional improvements (White & Levin, 1999; Levin & Rezvani, 2000). Administration of the CPT (or CPT-II) takes 14 minutes and the subject is asked to press the space bar on the computer keyboard as quickly as possible when any letter except the target letter "X" appears. Inter-stimulus intervals are 1, 2, and 4 seconds distributed randomly within each of the 6 blocks of the test. A short practice test precedes each administration.

Conners reports that little to no practice effects occur from using the CPT repeatedly (Conners & MHS staff, 2002). Pritchard, Robinson, & Guy (1992) provide independent confirmation of this. Conners states that any potential practice effects are most likely offset by "increased boredom" that results from a very long repetitive task. Normative data on the Conners' CPT (1995) has been collected on a sample of 670 patients with various attentional disturbances, aged 4 to 61 years and 520 normals, aged 4 to 70 years. Data collected from these samples yield high validity and reliability values (Conners and MHS Staff, 1995).

The CPT-II (2002) provides data for 13 sub-measures all of which have some relevance to the study question. Additionally, the test converts raw scores for these sub-measures to age and sex corrected t-scores. Analysis by the test authors reveals that utilizing the t-scores the 13 sub-measures may be grouped into indicators of inattention, impulsivity, and vigilance. Having age and sex corrected t-scores readily available, and having multiple sources contribute to the constructs of interest are additional factors that make the CPT-II ideal for the present study.

The major differences between the Conner's CPT (1995) and the Conner's CPT-II (2002) are the operating system platform (Windows for the CPT-II), broader norms for the CPT-II, and improved psychometric properties related to administration validity checks. Normative data on the CPT-II were collected on 2686 patients and non-patients. Data provided from these samples show the CPT-II to possess the same
desirable psychometric properties as the original Conner's CPT (1995) version. There
do exist some technical differences in the way some of the sub-measures of the CPT-II
are calculated and reported, however these differences do not impact the results of this
study nor their interpretability in relation to previous CPT studies.

To assess verbal memory, this study utilized the Rey Auditory-Verbal Learning Test
(RVLT) (Rey, 1958; Taylor, 1959; Lezak, 1976, 1983). The RVLT is a commonly used
test of verbal learning and memory. It provides a wide range of norms (7 - 88 year olds),
has standardized administration procedures, and is psychometrically sound.
Administration of the test involves the examiner reading a 15-word list at a rate of one
word per second: immediately after which the subject is asked to recall as many of the
words from the read list as possible. This process is repeated 5 times (Trials 1 -5). This
portion of the test assesses the verbal working (immediate) memory construct of current
interest. Immediately following trial-5 the subject is read a second 15-word list and then
asked to recall the words from the first list. This trial, trial 6, is a distracter task. No
construct of current interest is assessed by this trial. Following trial 6 the subject
engaged in an alternate activity (CPT-II + 6 minutes) for 20 minutes and was then asked
to recall as many words from the first list as is possible (trial 7; RVLTII); thus assessing
delayed verbal (secondary) memory. Following trial 7, the subject is given a list of 50
words which include words from the first list, the distracter list, and additional words not
previously seen as part of the test, and asked to circle the words from the first list. This
trial yields number of correct recognitions (RVLTCORREC) and percentage of
discriminations (RVLTECDISCR) derived from correct recognitions + correct rejections
divided by 50 X 100. Spreen and Strauss (1998) state that the RVLT, RVLTTT, and
RVLTII sub-scales assess the retrieval component of verbal memory while the
RVLTCORREC and RVLTECDISCR sub-scales assess the storage component.
There have been numerous normative studies for the RVLT, but the metanorms provided by Schmidt (1996) are appropriate and were used for the administration procedures chosen for this study. This test has been used extensively in both normal and clinical populations (including psychosis) and has shown to be sensitive to verbal memory deficits in both populations (Spreen and Strauss, 1998). The specific constructs assessed by the RVLT, use with similar populations, presence of standardized administration procedures, and desirable psychometric properties make it suitable for use in the present study. Of note, practice effects of 1-2 word improvements upon repeated administration have been noted. The counterbalance design of this study and the ≥1 week interval between administration points helped removed this as a contributing variable.

Additional material used in this study was a participant demographics questionnaire that included basic demographic questions along with questions regarding the participant’s current medication regimen and smoking history. The Fagerstrom Test for Nicotine Dependence (FTND; Heatheron, Kozlowski, Frecker, and Fagerstrom, 1991), a six-item self-report questionnaire, was also given to verify smoking status and gauge level of addiction.

Design and procedures

Following initial contact, interested participants were first scheduled for a screening visit where informed consent was obtained and screening and demographic documents were completed along with the FTND. A copy of the signed consent form was given to the subject and the investigator retained the original.

The study employed a counterbalanced (crossover) repeated-measures design. This design controlled for order effects related to nicotine condition (abstinence or free-smoke), possible effects of time, and any practice effects related to the dependent
variables. At the end of the screening visit, participants were randomly assigned to which nicotine testing condition they would participate in first. Each participant engaged in testing in the "free-smoke" and the smoking abstinence condition.

As Levin et al. (1996) assert, regimen (and route) of nicotine administration critically influences the outcome in studies examining the effects of nicotine. Thornton et al. (1996) and Heishman (1998) both state that the use of differing routes of nicotine administration complicates interpretations and makes comparisons difficult. The use of nicotine skin patch or nicotine gum gives the investigator the advantage of being able to determine the exact amount of nicotine the participant will ingest. However, the pharmacokinetics of these routes vary greatly from those of cigarette smoking (Mancuso, Andres, et al., 1999). Most authors now suggest that in order to study the effects of smoking on cognition that you must use nicotine via smoking inhalation as the delivery mechanism (Olincy, Johnson, and Ross, 2003). Since the primary interest of this study is cigarette smoking and there exists evidence that low affinity α7 nicotine receptors are involved (neither nicotine patch nor gum approximate the peak nicotine levels achieved via smoking), cigarette smoking at the participants self-selected rate was used as the route of administration. In an excellent review of nicotine dose and delivery selection in research, Matta et al. (2007) note that use of delivery mechanisms that result in slowly rising nicotine levels may result in desensitizing certain nicotinic receptors without first depolarizing them. The same authors state that cigarette smoking is the most efficient means of rapidly delivering nicotine to the brain. Using the participant’s typical delivery mechanism and their typical rate of ingestion addresses the question if nicotine as typically used improves performance on our chosen measures. A full review of the nuances related to the pharmacokinetics of nicotine delivery is beyond the scope of this paper; however the interested reader should turn to the Matta et al.

Both presence and absence of nicotine was determined immediately prior to assessment using the EC50-Micro III Carbon Monoxide Monitor (Bedfont Scientific, NJ). The assessments for both conditions were conducted at the same time of day to control for possible time-dependent factors such as fatigue and nicotine level fluctuations.

In the “free-smoke” condition (presence of nicotine), the participants were allowed to smoke at their usual rates contingent upon them displaying an 11 ppm or higher carbon monoxide (CO) level prior to assessment. The literature suggests this CO level to be indicative of a nicotine present condition (George, Vessicchio, et al., 2000; Hatsukami et al., 1989). The nicotine abstinent condition began following smoking abstinence by the participants (absence of nicotine condition), operationalized as a CO reading of 10 ppm or less. The literature suggests that this level is sufficient for establishing an absence of nicotine condition (George, Vessicchio, et al., 2000; Hatsukami et al., 1989; Roll, Higgins, Steingard, & McGinley, 1998). Participants were asked to refrain from smoking for 6 hours or more in order to obtain this CO level. Hatuskami et al. (1989) observed nicotine abstinence effects 4 hours after last smoking with the most notable effects seen following 6-hour abstinence. The literature also reports nicotine half-life to be about 2 hours (Thornton et al., 1996; Tidey, Higgins, Bickel, & Steingard, 1999), with CO elimination generally 2-3 times slower than nicotine (Jarvik et al., 2000). These findings taken in unison suggest a 6-hour abstinent requirement is sufficient to establish a nicotine abstinence condition. Length of abstinence to achieve a CO level of 10 ppm or less for participants in this study ranged from 6 to 14 hours.

The principal investigator (PI) conducted all assessments. At time of testing the PI had 3+ years of testing experience, had received extensive cognitive (and pathology) testing training, and was a certified rater on several industry sponsored clinical trials.
Upon arrival for their testing visits, each participant submitted a CO sample. Following verification of smoking presence/abstinence each subject began testing. Testing began with the first 6 trials of the RAVLT followed by administration of the CPT-II. Following completion of the CPT-II, the participant completed trial 7 and the recognition trial on the RVLT. Participants were then retested ≥ 1 week later in the appropriate alternate nicotine condition (presence or absence).

Statistics

Data were analyzed using repeated measures ANOVAs with condition (free-smoke/nicotine abstinence) as the within subjects factor. The cutoff for significance was $p < .05$, two-tailed. Supplementary analyses were conducted to determine if age, sex, education level, change in CO level between testing conditions, number of cigarettes smoked per day, or level of nicotine dependence influenced the results. Continuous and dichotomous variables were entered as covariates, and categorical variables were analyzed using Spearman's rho. Due to low-sample size, each covariate was entered into the model separately. Also due to low sample size, and the need to remove outlier scores on the CPT for one participant, race could not be included as a factor. All analyses were performed using SPSS version 14 for Windows software. Statistical procedures and outcomes were verified by the senior biostatistician for Dr. Herbert Meltzer's group at Vanderbilt, and by the VP for Research at Centerstone who holds a Ph.D. from Vanderbilt in Clinical and Quantitative Psychology.
CHAPTER III

RESULTS

Descriptives

Thirteen subjects, four male and nine female, participated in the study. Mean age for participants was 37.5 years (SD=10.6) and mean education was 15.2 years (SD=1.7). 10 of the participants were Caucasian, two African-American and one Hispanic.

Smoking

Mean nicotine dependence as determined by the FTND was “medium dependent” and mean cigarettes per day was 18.4 (SD=6.4). All participants reported some daily caffeine consumption with mean cup per day of 5.1 (SD=3.8). Correlation analysis revealed a strong correlation between FTND score and cig/day, r (11) = .90, p = .000; FTND and CO level during the nicotine present condition, r (11) = .88, p = .000; and between CO level during nicotine present condition and cig/day, r (13) = .77, p = .002. This indicates that FTND score, CO level, and cig/day are all good measures of daily nicotine intake and is consistent with the literature.

Change in RVLT scores

Means, standard deviations, t scores and p values for relevant RVLT subscales are presented in Table 1. Paired samples t-tests, correlation and repeated measures analysis of variance were conducted on variables RVLTV, RVLTTT, RVLTII, RVLTCORREC, and RVLTIREDISCR. As stated above, additional analyses on potential covariates were conducted on all variables.
Table 1: Mean ± SD and t-scores (p) for RVLT nicotine conditions

<table>
<thead>
<tr>
<th>RVLT sub-measure</th>
<th>Nicotine Condition</th>
<th>t score (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>present</td>
<td>absent</td>
</tr>
<tr>
<td>RVLTIV</td>
<td>13.7 ± 1.2</td>
<td>13.6 ± 1.5</td>
</tr>
<tr>
<td>RVLTIT</td>
<td>62.2 ± 6.9</td>
<td>57.6 ± 7.1</td>
</tr>
<tr>
<td>RVLTVI</td>
<td>12.8 ± 2.1</td>
<td>12.2 ± 1.8</td>
</tr>
<tr>
<td>RVLTICORREC</td>
<td>13.9 ± 1.0</td>
<td>14.2 ± 1.2</td>
</tr>
<tr>
<td>RVLTRECIDISCR</td>
<td>96.6 ± 3.0</td>
<td>97.4 ± 4.0</td>
</tr>
</tbody>
</table>

Note. RVLT = Rey Auditory Verbal Learning Test; RVLTIV = RVLT trial 1 - 5; RVLTIT = RVLT trial 7 (delayed recall); RVLTICORREC = RVLT correct recognitions; RVLTRECIDISCR = RVLT recognition discrimination %.

The repeated-measures ANOVA revealed no statistically significant differences between nicotine conditions on any of the RVLT measures; however, a trend toward significance was found for variable RVLTIV, $F(1,12) = 4.41, p = .057$. Subsequent analyses on potential covariates revealed a significant effect of nicotine condition on RVLTIT when controlling for sex, $F(1,11) = 4.96, p = .05$, and when controlling for cig/day, $F(1,11) = 7.41, p = .020$. Nicotine had a greater effect on females scores than on males. Nicotine also had a greater effect in those who smoked more cig/day with 15+ cig/day smoked showing clearly better scores in the free smoke condition (see Figure 1).
An examination of trend lines from the nicotine presence to the nicotine abstinence condition revealed a worsening of score during the nicotine abstinence condition for variables RVLTV, RVLTTT and RVLTVII, and an improvement in scores for the RVLTCOREC and RVLTRECDISCR. As mentioned above, the former variables are taken to represent memory retrieval while the latter represent memory storage. These differing trend lines are consistent with the literature that shows nicotine to have different effects depending upon the construct.

**Change in CPT raw scores**

Means, standard deviations, $t$ scores and $p$ values for the CPT subscales raw scores are presented in Table 2. Paired samples t-tests, correlation and repeated measures analysis of variance were conducted on variables all 13 subscales. As with the RVLT analysis, additional analyses on potential covariates were conducted on all variables.
Table 2: Mean ± SD and t-scores (p) for CPT nicotine conditions

<table>
<thead>
<tr>
<th>CPT submeasure(^a)</th>
<th>Nicotine Condition</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>present</td>
<td>absent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPTB</td>
<td>0.892 ± 2.220</td>
<td>0.250 ± 0.243</td>
<td>1.08 (0.30)</td>
<td></td>
</tr>
<tr>
<td>CPTOmiss</td>
<td>0.750 ± 1.060</td>
<td>0.750 ± 1.765</td>
<td>0 (1)</td>
<td></td>
</tr>
<tr>
<td>CPTCommiss</td>
<td>9.920 ± 3.630</td>
<td>11.580 ± 5.230</td>
<td>2.13 (0.06)</td>
<td></td>
</tr>
<tr>
<td>CPTHITRT</td>
<td>366.250 ± 43.653</td>
<td>366.717 ± 31.873</td>
<td>0.11 (0.92)</td>
<td></td>
</tr>
<tr>
<td>CPTHITRTSE</td>
<td>4.792 ± 1.221</td>
<td>5.208 ± 0.908</td>
<td>1.75 (0.11)</td>
<td></td>
</tr>
<tr>
<td>CPTVAR</td>
<td>4.850 ± 1.767</td>
<td>5.942 ± 1.783</td>
<td>1.89 (0.09)</td>
<td></td>
</tr>
<tr>
<td>CPTd'</td>
<td>0.750 ± 0.261</td>
<td>0.808 ± 0.527</td>
<td>0.63 (0.55)</td>
<td></td>
</tr>
<tr>
<td>CPTHITRTISI</td>
<td>0.068 ± 0.032</td>
<td>0.071 ± 0.033</td>
<td>0.38 (0.71)</td>
<td></td>
</tr>
<tr>
<td>CPTHITSEISI</td>
<td>0.029 ± 0.053</td>
<td>0.071 ± 0.095</td>
<td>1.32 (0.21)</td>
<td></td>
</tr>
<tr>
<td>CPTPERS</td>
<td>0 ± 0</td>
<td>0 ± 0</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>CPTHITRTBC</td>
<td>0 ± 0.013</td>
<td>0.006 ± 0.025</td>
<td>0.70 (0.50)</td>
<td></td>
</tr>
<tr>
<td>CPTHITSEBC</td>
<td>0.023 ± 0.057</td>
<td>0 ± 0.051</td>
<td>1.20 (0.26)</td>
<td></td>
</tr>
<tr>
<td>CPTOI</td>
<td>1.540 ± 2.786</td>
<td>2.478 ± 3.068</td>
<td>0.95 (0.36)</td>
<td></td>
</tr>
</tbody>
</table>

Note. CPT = Continuous Performance test Test; CPTB = CPT beta; CPTOmiss = CPT omissions; CPTCommiss = CPY commissions; CPTHITRT = CPT hit reaction time; CPTHITRTSE = CPTHITRT standard error; CPTVAR = CPT variability of standard error; CPTd' = CPT attentiveness; CPTHITRTISI = CPTHITRT inter-stimulus intervals; CPTHITSEISI = CPTHITRTISI standard error; CPTPERS = CPT perseverations; CPTHITRTBC = CPTHITRT block change; CPTHITSEBC = CPTHITRTBC standard error; CPTOI = CPT overall index.

- Could not be calculated due to SE of 0.

\(^a^n = 12\) for all analyses.
The repeated-measures ANOVA revealed no statistically significant differences between nicotine conditions on any of the CPT measures. However several CPT measures showed a trend toward significance and warranted subsequent analysis while controlling for covariates. F scores for the CPT measures primary and covariate analyses are presented in Table 3. As shown in the table there was a statistically significant difference on the CPTOI and CPTHITRTBC between nicotine conditions while controlling for age. The CPTOI is a general indicator of performance on the CPT with scores of 8 or lower indicative of good overall performance. The CPTHITRTBC measures the slope of change in reaction time across the six time blocks. Higher t-scores indicate a slowing of reaction time as the test progressed and represents a loss of vigilance. As table 2 shows, mean scores rose on both measures during the nicotine absent condition. On closer inspection, 2 participants under the age of 26 both had an increase from 0 (nicotine present) to 5.63 (nicotine absent) on the CPTOI while other age related changes were negligible. It is doubtful that any actual significance can be taken from the differences on the CPTOI subscale. Examination of the CPTHITRTBC scores revealed that 4 out of 5 individuals aged 30 or less performed better during the nicotine present condition while only 2 of 7 individuals over the age of 38 showed the same effect. This indicates that smoking prevented a slowing of reaction time as the test progressed in younger participants.

An examination of trend lines from the nicotine presence to the nicotine abstinence condition revealed a worsening of score during the nicotine abstinence condition for all CPT variables except for CPTOmiss which showed no change and CTPPers where no scores were recorded under either nicotine condition. This worsening of scores across all subscales indicates slower reaction times, inconsistent responding, more errors, inattention, impulsiveness, and poorer vigilance under the nicotine absence condition.
Although the size of the effect was smaller, the direction is consistent with literature showing nicotine to improve attention and vigilance.

Table 3: Repeated-measure ANOVA and covariate analysis for CPT raw scores

<table>
<thead>
<tr>
<th>CPT submeasure*</th>
<th>Primary analysis</th>
<th>Covariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPTCommiss</td>
<td>$F(1,11) = 4.55, p = .056$</td>
<td>-</td>
</tr>
<tr>
<td>CPTHITRTSE</td>
<td>$F(1,11) = 3.07, p = .107$</td>
<td>$F(1,10) = 3.81, p = .08^b$</td>
</tr>
<tr>
<td>CPTVAR</td>
<td>$F(1,11) = 3.56, p = .086$</td>
<td>-</td>
</tr>
<tr>
<td>CPTHITRTISI</td>
<td>NS</td>
<td>$F(1,10) = 4.28, p = .065^c$</td>
</tr>
<tr>
<td>CPTHITRTBC</td>
<td>NS</td>
<td>$F(1,10) = 4.96, p = .05^{b*}$</td>
</tr>
<tr>
<td>CPTOI</td>
<td>NS</td>
<td>$F(1,10) = 6.39, p = .03^{b*}$</td>
</tr>
</tbody>
</table>

Note. CPT = Continuous Performance test; CPTB = CPT beta; CPTCommiss = CPT commissions; CPTHITRTSE = CPT hit reaction time standard error; CPTVAR = CPT variability of standard error; CPTHITRTISI = CPTHITRT inter-stimulus intervals; CPTHITRTBC = CPTHITRT block change; CPTOI = CPT overall index. NS = not significant or near significant. - = covariate did not significantly affect the $p$ value.

*a n = 12 for all analyses.

*b age as covariate.

ceducation as covariate.

*p < .05

Change in indicators of inattention, impulsivity, and vigilance

As mentioned previously CPT subscales can be grouped to form indicators of inattention (CPTOmiss, CPTCommiss, CPTHITRT, CPTHITRTSE, CPTVAR, CPTd', CPTPERS, CPTHITRTBC, CPTHITSEBC, CPTHITRTISI, and CPTHITSEISI)
impulsivity (CPTCommiss, CPTHITRT, and CPTPERS) and vigilance (CPTHITRTBC and CPTHITSEBC). The age and sex-corrected t scores for each relevant subscale were added together to represent their respective indicators, and analyses were conducted to compare these indicators across nicotine condition. Covariate analysis was performed if indicated.

The repeated-measures ANOVA revealed no statistically significant differences between nicotine conditions on any of the CPT indicators. There was a near significant difference for the impulsivity indicator $F(1,12) = 3.33, p = .095$. As was the case with the CPT subscale raw scores, Figure 2 illustrates poorer performance in the nicotine abstinence condition for all three indicators.

Figure 2: CPT Factor Changes
CHAPTER IV

DISCUSSION

This study examined the effects of acute nicotine abstinence on measures of attention and verbal memory. The literature has shown deficits in these areas to correlate with poor social functioning in schizophrenic patients. Further, the overwhelming majority of evidence has shown nicotine to mitigate deficits in these areas in diagnosed patients, but this has not been as reliably demonstrated in non-diagnosed populations. The main findings of this study were: 1) consistent with previous findings the FTND scores correlated with number of cigarettes smoked per day and carbon monoxide level at the nicotine present condition; 2) a significant effect of nicotine condition on RVLTTT when controlling for sex, $F(1,11) = 4.96$, $p = .05$, and when controlling for cig/day, $F(1,11) = 7.41$, $p = .020$; 3) An examination of trend lines from the nicotine presence to the nicotine abstinence condition revealed a worsening of score during the nicotine abstinence condition for variables RVLTV, RVLTTT and RVLTVII (memory retrieval), and an improvement in scores for the RVLTLCOREC and RVLTRECDISR (memory storage); 4) a statistically significant difference on the CPTOI and CPTHITRTBC between nicotine conditions while controlling for age, $F(1,10) = 6.39$, $p = .03$ and $F(1,10) = 4.96$, $p = .05$ respectively; 5) An examination of trend lines from the nicotine presence to the nicotine abstinence condition revealed a worsening of score during the nicotine abstinence condition for all CPT variables except for CPTOmiss which showed no change and CPTPers where no scores were recorded under either nicotine condition. Poorer performance in the nicotine abstinence condition was also observed for all three CPT indicators – inattentiveness, impulsivity and vigilance.

Verifying smoking or smoking abstinence via CO level and administering the FTND and documenting cigarettes smoked per day (cig/day) to determine level of addiction is
common place in nicotine research with humans; however, only a few of these studies have reported information about the relationship between these variables. Payne et al. (1994) reported positive correlations between FTND and CO level, Jacobsen et al. (2005) between FTND and cig/day, and Steinberg et al. (2005) reported FTND was positively correlated to both CO level and cig/day. The current study bolstered these studies by finding very strong correlations between these three variables.

The current study revealed that nicotine had a significantly greater effect on females RVLT total scores (RVLTTT) than on the same scores in males. There is some literature to support that nicotine effects are different based on sex. Trimmel and Wittberger (2004) found nicotine had a larger effect in females on tests of attention and vigilance. Razani et al. (2004) reported sex was a significant covariate for nicotine effects on WCST categories and % concept-level responses. However, Jacobsen et al. (2005) reported no sex differences in the effect of nicotine on the CPT. While no conclusions can be drawn from the current findings, sex differences in nicotine effects on constructs would not be surprising due to sex differences in nicotine metabolism (Le Houzec, 2003).

The current study also found that nicotine exerted more of an effect on RVLTTT scores in heavy smokers than in light smokers. This is not a surprising finding in that heavy smokers more closely resemble, in terms of number of cigarettes smoked, smoking topography, and possible shared neurobiological abnormalities, diagnosed populations where nicotine effects are more easily seen. This would also be expected given the literature that supports low affinity $\alpha$-7 receptor involvement which requires a higher dose of nicotine to depolarize. Although due to delivery mechanism exact dose is difficult to determine, Le Houzec (2003) does report that nicotine yield per cigarette is about 1.0mg independent of FTC yield reports. So the greater effect of nicotine in heavy smokers is consistent with controlled dose studies such as Poltavski and Petros (2005)
that show dose-dependent effects on verbal recall. Further, if heavy smokers are smoking to mitigate neurobiological differences while light smokers smoke for other reasons related to reinforcement, anxiety reduction, etc., Poltavski and Petros (2006) assertion is that we would expect to see less improvements as a result of nicotine in those whose performance is already optimized. This subset of non-diagnosed smokers who may have a genetic and neurobiological make up similar to diagnosed populations may add to the variability seen in smoking behaviors (Kumari and Postma, 2005), which adds to the difficulty in interpreting the results of nicotine research.

The trend lines showing different effects of nicotine on storage and encoding memory are of interest, and consistent with our literature that pointed to a lack of consistent findings of an effect of nicotine on memory. Consistent, in part, with the trend reported in the current study, Mangan (1983) showed that nicotine improved long-term memory but had no effect on short term memory on a word list task. Warburton et al. (1992) found an effect of nicotine in smokers on both immediate and delayed recall. However, upon closer inspection of the data reported, the effect was far from universal as 6 out of 14 and 6 out of 13 participants either failed to show improvement or showed a decrement in performance on the immediate and delayed recall tasks, respectively. Still other studies showed no effect of nicotine on verbal memory in smokers (Harris et al., 2004; Smith et al., 2006). Newhouse, Potter, and Singh's (2004) claim that nicotine effects on memory, acquisition, encoding, storage, and retrieval in normal smokers is a result of nicotine's attentional effects on the front end appears to be in question. Levin, et al. (2006) assert that nicotine effects on memory are less frequently seen in humans, and are more clearly seen in rat studies (e.g. Rezvani and Levin, 2001; Levin, 1992). The most consistent finding in human research in this area is that nicotine has a positive effect on spatial memory in diagnosed patients and a detrimental effect on spatial

In the current study a significant effect of nicotine was found on the CPT overall index (CPTOI) and CPT hit rate block change (CPTHITRTBC) when controlling for age. Upon closer inspection it appeared that the effect was on preventing a slowing of reaction time in younger participants. This result at least partially confirms previous findings. Of more importance, I believe, is the finding of no statistical difference in this population but trend lines all in the predicted direction, i.e. nicotine improving vigilance, inattention, and impulsivity.

Common criticisms of studies investigating the acute effects of nicotine are small sample and effect sizes. Kleykamp, et al. (2005) suggest that modest effect sizes on cognitive measures coupled with small samples sizes in studies involving never smokers may result in an increased probability of type II error. However the authors also suggest that these small effect sizes may be telling us that cognitive effects may not be a significant factor in the initiation of smoking by healthy adults. However effect and sample size do not appear to be as important factors when looking at nicotine effects in smokers and individuals with diagnoses related to cognitive impairment and people demonstrating pre-diagnostic or mild cognitive impairment (MCI). Harte and Kanarek (2004) state that we most consistently see increased performance on the CPT in deprived smokers. Bekker, et al. (2005) suggests using only smokers when asking questions about smokers, because nicotine effects in non-smokers may not generalize due to neurobiological abnormalities in smokers. Newhouse, et al. (2004) also suggest neurobiological differences between non-smokers and smokers.

The literature also points to differential effects of nicotine between non-diagnosed and clinical populations. Differential effects of nicotine on cognition in normal and cognitively impaired populations are of particular interest since these may point to
reasons for the differential prevalence of smoking between these two populations. Both Poltavski and Petros (2006) and Newhouse, et al. (2004) assert that nicotine optimizes performance, and when performance is already optimized, results in a decrement in performance. Poltavski and Petros (2006) make the claim, that I'm making here, that it is reasonable to expect less improvement or even deficits in participants whose performance is already optimized. The way to look for improvement in those already optimized individuals is to increase task difficulty (Newhouse et al., 2004).

Strengths and weaknesses of current study

Using standardized and psychometrically sound assessment instruments that measured clinically meaningful constructs was a significant strength of this study. The constructs measured were not chosen because it was believed that these would most easily show nicotine effects, nor were they chosen because of the large literature surrounding them: they were chosen because they were correlated with impaired behaviors in schizophrenic patients that severely impact their ability to function. Standardized administration of the instruments by a single trained rater added to the strength of the instruments used.

Another strength of the study was the study design. The study employed a counterbalanced (crossover) repeated-measures design, where participants were randomly assigned to which nicotine condition they would participate in first. This design controlled for order effects related to nicotine condition (abstinence or free-smoke), possible effects of time, and any practice effects related to the dependent variables. In a small sample size study sound design is even more important.

Choosing smoking as the delivery mechanism can be viewed as a strength and a weakness of the study. It is considered a weakness due to the inability to control the exact dose of nicotine delivered and therefore being unable to ascertain any dose
dependent effects. However, using controlled delivery mechanisms such as patch, gum, nasal spray, subcutaneous or i.v. may not deliver the dose rapidly enough to depolarize the \( \alpha-7 \) receptors thought to be responsible for the effects of nicotine on cognition without first desensitizing these same receptors. Further Bekker, et al. (2005) state, while discussing reasons for mixed results on dose-dependent effects, that plasma concentrations in transdermal admin varies just as greatly as in smokers, inter-individual differences, body weight, gender, absorption rate all contribute to error variance and may mask effects. Likewise Le Houzec (2003) reports variation in absorption rate when nicotine is delivered via gum. The inter-individual differences mentioned by Bekker, et al. (2005) exist regardless of delivery mechanism. Also, a presumed source of variance, the type or brand of cigarette smoked, Le Houzec (2003) reports not to be as much of a source of variation as frequently referenced. He reported that regardless of Federal Trade Commission (FTC) nicotine yield estimates for cigarettes, that the average smoker yields 1.0 mg (range .97 – 1.39) from a single cigarette. This does not, of course, mitigate differences in smoking topography observed between most notably diagnosed and non-diagnosed populations.

As a strength, smoking ad libitum allows us to see if nicotine as self-administered impacts vigilance and verbal memory. And the immediacy of delivery allows us to confidently assume that the low-affinity \( \alpha-7 \) receptors were activated.

One obvious weakness, and one that is pervasive in this line of inquiry, is the low sample size. Even though pre-study power analysis suggested that a sample size as low as 9 may be large enough to detect an effect, a larger sample size would allow more confident comments to be made about this study. Levin et al. (1998) reported effects of nicotine on the CPT in normals with a sample size of 11. However other studies that have reported nicotine effects on the CPT in normal smokers have had larger samples,
and those studies with small samples reporting an effect of nicotine on the CPT have been with diagnosed populations (White and Levin, 1999; Levin, Wilson, et al., 1996). Not only does this study highlight the importance of effect sizes, but it points to a need to pay attention to effect size differences between populations. Not only may this be instructive for determining different etiologies of smoking between populations, but it informs researchers to use effect sizes relevant to the population under investigation when conducting pre-study sample size estimates.

Another problem related to the small sample size is the need to conduct multiple ANOVA’s and covariate analyses. Conducting multiple ANOVA’s increases the probability of making a Type 1 error, which as it turned out, wasn’t a problem in this study. This problem was made a bit less threatening by utilizing the three factors on the CPT (impulsivity, inattentiveness, and vigilance) which were derived from multiple subscales. Also, having t-scores that accounted for age and sex helped. With the RVLT, the RVLT total score was derived from 5 separate trials which helped decrease the likelihood of Type 1 error; however it was still a concern on the other RVLT scores.

Summary and future direction

Admittedly drawing conclusions from a low sample study with few statistically significant findings is a perilous task. But the direction of the effect on attention is consistent with the literature as is the mixed results found on the memory task. A less robust finding in a non-diagnosed population than is typically found in diagnosed populations is suggestive of different reasons for smoking between the populations. Population, effect size, assessment tool, and smoking status are all variables that garner much attention when conducting research in this area.

When considering future research, low sample size is a pervasive problem in this line of research for a reason; it is hard for smokers to stop for any given time. Of course this
is not surprising given the research showing how addictive cigarette smoking is. Future studies aimed at assessing acute abstinence in smokers need to take control of this factor and pair their research to smoking cessation programs or employ successful smoking cessation strategies. In the current study the PI offered rudimentary advice (drink water, chew gum, exercise, avoid caffeine, etc) to participants to help abstain from smoking but more is warranted. Tidey, et al. (1999) and Roll, et al. (1998) demonstrated that contingency management approaches to smoking cessation can be as effective in persons diagnosed with schizophrenia as it is in non-diagnosed populations. Sacco, et al. (2005) reported using 20:1 ratio of contingent reinforcement to achieve 90% over night abstinence in both schizophrenic and control smokers. Ziedonis, Williams, and Smelson (2003) have also reported success in conducting smoking cessation groups in diagnosed populations.

Finally, future studies should be able to better isolate individual differences that may relate to nicotine effects. Pre-study testing to determine low attention and mildly cognitively impaired groups, as well as those with auditory inhibition abnormalities and visuospatial deficits would help determine how these factors impact nicotine effects. We are more confident about genetic markers that may indicate α-7 deficits that may be at the core of nicotine’s affect on attention and memory. Cheek swab genetic samples and subsequent analyses are widely available and affordable, making them easier to include in research protocols.

As existing methodologies undergo continued refinement, and neuroimaging and pharmacological technologies improve, so will our ability to more confidently draw conclusions about the relationship between smoking, receptor deficits, psychological pathology, and social functioning.
REFERENCES


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Date: March 18, 2004

To: Lisa Baker, Principal Investigator
   David Ayer, Student Investigator for dissertation

From: Mary Lagerwey, Ph.D., Chair

Re: HSIRB Project Number: 04-02-09

This letter will serve as confirmation that your research project entitled "The Effects of Acute Nicotine Abstinence on Vigilance and Verbal Working Memory in Schizophrenic vs. Normal Populations" has been approved under the full category of review by the Human Subjects Institutional Review Board. The conditions and duration of this approval are specified in the Policies of Western Michigan University. You may now begin to implement the research as described in the application.

Please note that you may only conduct this research exactly in the form it was approved. You must seek specific board approval for any changes in this project. You must also seek reapproval if the project extends beyond the termination date noted below. In addition if there are any unanticipated adverse reactions or unanticipated events associated with the conduct of this research, you should immediately suspend the project and contact the Chair of the HSIRB for consultation.

The Board wishes you success in the pursuit of your research goals.

Approval Termination: February 18, 2005
March 17, 2004

David W. Ayer, M.A., IRB Administrator/Research Coordinator
Centerstone
1101 5th Avenue North
Nashville, TN 37208

Centerstone IRB # 2004.003: "The effects of acute nicotine abstinence on vigilance and verbal working memory in those diagnosed with schizophrenia vs. those who carry no psychiatric diagnosis." Final approval

Mr. Ayer,

Following receipt of your March 15, 2004 letter indicating the committee's recommended changes have been made, the Chair has granted final approval of your study.

Please note that approval is granted from the date of initial review, March 11, 2004. Any further changes to the protocol and/or consent form should be presented to the Committee for approval before any implementation of the changes. While the Centerstone research staff will make every attempt to notify the investigator before their continual review is due, it is ultimately the investigator's responsibility.

Final Approval: March 11, 2004 Expiration Date: March 11, 2005

Respectfully,

[Signature]

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