

ABSTRACT

Title of Document: SMOKING AND NEUROPHYSIOLOGICAL
MARKERS OF INFORMATION
PROCESSING IN SCHIZOPHRENIA

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The primary aim of this study was to compare patterns of nicotine consumption among patients with schizophrenia and a matched community control sample. Assessments included self-report and biological indexes of nicotine use as well as behavioral measures of smoking topography. Secondarily, this study tested the hypothesis that aspects of nicotine consumption are more closely associated with abnormalities in sensory gating and eye tracking performance among smokers with schizophrenia. Results from 50 patient and 10 healthy control smokers provided some evidence to support the primary hypothesis; biological indexes provided the most robust evidence that patients with schizophrenia extract more nicotine from smoking cigarettes than controls. Both groups demonstrated significant relationships between measures of nicotine dependence and neurophysiological functions. Patterns of results suggest that patients are less able to regulate smoking behaviors or efficiently utilize nicotine to enhance information

processing. Additional factors likely contribute to smoking phenomena observed among patients with schizophrenia.

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PROCESSING IN SCHIZOPHRENIA

By

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Thesis submitted to the Faculty of the Graduate School of the
University of Maryland, College Park, in partial fulfillment
of the requirements for the degree of
Master of Arts
2006

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Table of Contents

Table of Contents	iii
List of Tables	v
List of Figures	vi
Chapter 1: Introduction	1
Tobacco Use and Mental Illness	1
Individual Differences in Smoking Habits	2
Smoking Among Individuals with Schizophrenia	3
Prevalence	3
Smoking Initiation and Cessation	4
Smoking Behavior	7
Neural Systems Underlying Behaviors Related to Nicotine Addiction	9
Nicotine Receptors	9
Nicotine and Reward Systems of the Brain	10
Explaining Smoking Habits in Individuals with Schizophrenia	12
Primary Addiction Hypothesis	14
Antipsychotic Medications	18
The Self Medication Hypothesis	19
Overview	19
The Role of $\alpha 7$ Nicotinic Receptors	20
Symptomatology	22
Cognitive Dysfunction	24
Eye Movement	25
Sensory Gating	27
Chapter 2: The Current Study	32
Summary of Findings to Date	32
Rationale for the Current Study	33
Purpose	35
Chapter 3: Methodology	36
Data Collection	36
Participants	36
Inclusion and Exclusion Criteria	37
Assessments	38
Clinical Evaluations	38
Self-Report Measures of Smoking	39
Physiological Evaluation of Smoking	40
Smoking Topography	41
Neurophysiological Measures	41
Procedures	46
Chapter 4: Analyses	49
Study Aim 1	49
Study Aim 2	50
Chapter 5: Results	51

Sample Characteristics.....	51
Current Smoking Habits	53
Nicotine Dependence	53
Smoking Topography.....	57
Smoking Habits, Nicotine Addiction and Clinical Variables	60
Neurophysiological Markers of Information Processing.....	62
Patients with Schizophrenia.....	62
Healthy Controls	66
Chapter 6: Discussion	70
Smoking Habits and Nicotine Dependence	70
Neurophysiological Functioning.....	78
Smoking and Neurophysiological Markers of Information Processing.....	79
Limitations and Future Directions	87
Concluding Remarks.....	91
References.....	93

List of Tables

1. Smoking History.....	52
2. CRESS Smoking Topography	58
3. Correlations Between Topography Measures	59
4. Smooth Pursuit Eye Movement	67

List of Figures

1. Cigarette Characteristics	53
2. Self-Report Measures of Nicotine Dependence	54
3. Biological Measures of Nicotine Dependence	55

Chapter 1: Introduction

Tobacco Use and Mental Illness

Tobacco smoking is the leading avoidable cause of disease and premature death in the United States (United States Department of Health and Human Services, 1988). Although much attention has been drawn to trends in smoking and smoking related diseases in the general population, increasing evidence suggests that individuals suffering from mental illness are at increased risk for tobacco use and nicotine addiction. Smoking prevalence in the United States general population has consistently been estimated at 22.5% (Lasser, Boyd, Woolhandler, Himmelstein, McCormick & Bor, 2000; Lethbridge-Cejku, Schiller, & Bernadel, 2004). In contrast to the smoking rate in the general population, Lasser et al. (2000) reported that the rate of smoking among respondents with a lifetime diagnosis of psychiatric illness was 34.8%, and among respondents diagnosed with a psychiatric illness in the past month, current smoking rose to 41% ($p < 0.001$ for all comparisons). In fact, individuals suffering from a mental disorder in the past month consumed approximately 44% of the cigarettes smoked by this nationally representative sample (Lasser et al., 2000).

In a seminal study of smoking rates among psychiatric outpatients, Hughes, Hatsukami, Mitchell, and Dahlgren (1986) reported smoking prevalence to be 1.6 times higher among a psychiatric group compared to the population based control group, even after controlling for several confounding variables including age, sex,

marital status, socioeconomic status, and alcohol use. Compared to smoking rates in controls (30%), outpatients with major depressive disorder demonstrated a smoking rate of 49%, which was similar to that of anxiety disorders, 47%. Among outpatients with schizophrenia, smoking prevalence was an astounding 88%. The findings of Hughes et al. exemplify the relationship between nicotine use and mental illness and demonstrate the remarkably high rate of smoking among patients with schizophrenia, which has proven to be a widely replicated finding (de Leon, 1996; de Leon, Dadvand, Canuso, White & Stanilla, 1995; Glynn & Sussman, 1990; Goff, Henderson & Amico, 1992; Hughes et al, 1986; Kelly & McCreadie, 1999; LLerena, de la Rubia, Penas-Lledo, Diaz & de Leon, 2003; Ziedonis, Kosten, Glazer & Frances, 1994).

Individual Differences in Smoking Habits

In light of evidence indicating greater smoking prevalence among individuals with mental illness, Glynn and Sussman (1990) investigated motivational factors behind smoking habits in smokers diagnosed with mental illness and smokers in the general population. The results indicated that both groups reported similar reasons for nicotine use, the most common motivating factors including relaxation, smoking out of habit, or smoking to settle nerves. Thus individuals with mental illness do not appear to report differentiating factors that might contribute to the disparity in rates of smoking. Given the substantially higher rate of smoking among individuals with mental illness, the etiology of smoking behavior needs to be addressed in research, as this observation begs a more comprehensive explanation.

Examination of individual differences in behavioral smoking patterns may provide a methodological framework for research investigating smoking prevalence

among individuals with mental illness. Research suggests that, in general, cigarette smokers may exert a certain amount of control over their pattern of smoking behavior and the manner in which they smoke, such that smoking is most subjectively satisfying. Russell (1980) suggests that smokers may benefit from immediate rewards experienced by periodic smoking to achieve rapid rises or peaks in blood plasma levels of nicotine. Alternatively smokers may benefit from maintaining a high level of nicotine in the blood through frequent and heavier smoking habits. In addition to controlling their pattern and frequency of smoking, smokers can affect their immediate nicotine intake by regulating the intensity (i.e. force and size of the puff), as well as the depth of inhalation, and the time that the smoke is held in the lungs (Russell, 1978; 1980). Consistent with Russell's characterization of individual differences, those with mental illness not only exhibit patterns of smoking that differ from smokers in the general population, but evidence suggests that a diagnosis of schizophrenia further differentiates individuals in terms of smoking prevalence rates, patterns, and behaviors.

Smoking Among Individuals with Schizophrenia

Prevalence

Smoking related fatal disease is more prominent among individuals with schizophrenia than in the general population, and in this patient population smoking has been shown to increase the mortality rate significantly beyond that of nonsmokers with schizophrenia (Brown, Inskip & Barraclough, 2000). Since the Hughes et al. study in 1986, patients with schizophrenia have been demonstrated to smoke at a

higher rate than patients with other psychiatric illnesses and the general population when both inpatient and outpatient status are considered. In 1995, de Leon and colleagues demonstrated that in a state hospital, schizophrenia was associated with twice the risk of smoking compared to patients with other psychiatric illnesses, and replicated this finding in 1996, even when compared to inpatients with other psychiatric illnesses who showed a 67% smoking rate. In this study, de Leon reported a high smoking rate of 85% among the schizophrenia inpatient group. Additional studies of smoking prevalence among individuals with schizophrenia indicate similar smoking rates with values of 70% (Glynn & Sussman, 1990), 74% (Goff et al., 1992), and 68% (Ziedonis et al., 1994) reported.

Elevated rates of smoking among patients with schizophrenia have been demonstrated cross culturally as well. Kelly and McCreadie (1999) studied smoking habits among patients with schizophrenia in Nithsdale, Scotland. In the local general population, 28% were smokers, whereas patients with schizophrenia smoked at twice that rate, with 58% of the patients described as regular smokers. A study of tobacco smoking in a Spanish psychiatric hospital demonstrated that 70% of patients with schizophrenia smoked, which was significantly greater than the rate of 53% found among patients with other psychiatric illnesses (LLerena et al., 2003).

Smoking Initiation and Cessation

A closer examination of factors associated with smoking habits among those with psychiatric illnesses (i.e. rates of smoking initiation and quitting) may distinguish whether smoking among individuals with schizophrenia is a primary characteristic associated with disease vulnerability, or secondary to symptom

presentation and psychiatric diagnosis. Kelly and McCreadie (1999) provide evidence suggesting that the majority of patients with schizophrenia begin to smoke before the onset of illness. Of the smokers with schizophrenia assessed, 90% began to smoke prior to illness onset, where mean age of onset of smoking preceded onset of illness by 11 years. Mean onset of illness was earlier among smokers (27) than nonsmokers (31) with schizophrenia, although the difference was not statistically significant. Interestingly, de Leon, Diaz, Rogers, Browne, and Dinsmore (2002) found that before the age of 20, non psychiatric controls, inpatients with schizophrenia, and inpatients with mood disorder appeared to have similar initiation rates. However, after the age of 20, the initiation rates for patients with schizophrenia were higher than for patients with mood disorder or controls. This difference was not explained by differences in gender, race, or level of education (de Leon et al., 2002a). In addition, de Leon reported that the majority of the individuals with schizophrenia began smoking prior to the onset of illness. Thus, while individuals with schizophrenia may be more likely to begin smoking prior to illness onset, suggesting an association with disease liability, their rates of initiation may not be significantly elevated above those found in other groups prior to the age of 20.

The elevated smoking rate among individuals with schizophrenia appears to be influenced by continuously increasing rates of smoking initiation, as well as a lack of desire or inability to quit. In the Scottish sample, Kelly and McCreadie (1999) found that 60% of smokers in the local general population expressed the desire to quit smoking, whereas only 26% of the patients with schizophrenia expressed the desire to quit. De Leon (1996) reported that spontaneous quit rate among inpatients with

schizophrenia was less than 10%. Quit rate among inpatients with schizophrenia, inpatients with mood disorders, and among a control comparison group was reexamined in 2002. De Leon, Tracy, McCann, McGary, and Diaz (2002) reported that the odds of smoking cessation among patients with schizophrenia was 0.20 times lower than in controls, and that patients with schizophrenia were less likely to have quit smoking than patients with mood disorder, although the differences were not statistically significant (10% vs 18%). Both groups, however, differed significantly from the control comparison group (43%).

Smoking cessation programs conducted in clinical populations further underscore the implications of nicotine dependence among patients with schizophrenia (El-Guebaly, Cathcart, Currie, Brown & Gloster, 2002). Addington, el-Guebaly, Campbell, Hodgins, and Addington (1998) reported on successful quit rates following treatment of patients with schizophrenia who were chronically heavy smokers. The immediate effects of a manualized group treatment program resulted in a quit rate of 42%, however, follow up after 3 and 6 months demonstrated patients' inability to refrain from smoking with quit rates falling to 16% and 12%, respectively. Similarly, George, Ziedonis, Feingold, Pepper & Satterburg, et al. (2000) reported quit rates as low as 16.7% and 7.4% in patients with schizophrenia taking typical and atypical antipsychotic drugs, respectively, 6 months following the same treatment program. In contrast to the pessimistic findings for treatment among individuals with schizophrenia, Brown and colleagues (2001) reported, among individuals with a history of major depressive disorder, a successful quit rate of 32.5%, which was maintained 12 months following Cognitive Behavioral Therapy for smoking cessation

(Brown, Kahler, Niaura, Abrams & Sales et al., 2001). Thus, in comparison, in half the amount of time, twice the number of patients with schizophrenia failed to quit compared to individuals with depression. Ziedonis and George (1997) attributed the low quit rate of 13% in a group of individuals with schizophrenia undergoing smoking cessation treatment to low motivation to quit upon entry to treatment.

Smoking Behavior

In addition to reporting elevated rates of smoking, several studies have reported findings suggesting that individuals with schizophrenia tend to be heavier smokers as well. Herran and colleagues reported that the frequency of schizophrenic patients consuming 21 cigarettes or more per day (44%) was higher than that observed for non-psychiatric controls (29%) (Herran, de Santiago, Sandoya, Fernandez & Diez-Manrique et al., 2000). Among the patient smokers assessed by Kelly and McCreadie (1999) 68% reported smoking 25 or more cigarettes per day. De Leon et al. (1995) found that the prevalence of heavy smoking, defined by more than 30 cigarettes per day, among state hospital inpatients was 38% among those with schizophrenia, versus 19% in other psychiatric controls.

Other observed smoking behaviors indicative of heavy tobacco use include smoking cigarettes with relatively higher nicotine content, smoking more of the cigarette, and inhaling, or drawing deeper on the cigarette. Lohr and Flynn (1992) reported that patients with schizophrenia tend to smoke cigarettes high in nicotine, and try to smoke them completely (i.e. down to the filter). This is consistent with the findings of Olincy, Young, and Freedman (1997) who reported higher levels of urinary cotinine (a metabolite of nicotine thought to index nicotine dependence) in a

sample of patients with schizophrenia compared with a group of healthy controls matched for smoking history. Although the average number of cigarettes currently smoked per day was not significantly different between groups, cotinine levels in schizophrenic smokers were 1.6 times higher than in non-schizophrenic smokers. Cotinine levels in the patient group were unrelated to antipsychotic or anticholinergic medication status, gender, severity of illness, and unrelated to the time since last cigarette. Thus, Olincy and colleagues concluded that patients with schizophrenia extract more nicotine from each cigarette, presumably through their smoking behavior, such as prolonged inhalation or occlusion of cigarette filters by fingers or lips while smoking.

Overwhelming evidence points to greater smoking prevalence, greater rates of smoking initiation, greater difficulty quitting, and higher rates of heavy smoking among patients with schizophrenia compared to individuals diagnosed with other forms of mental illness and among the general population. Convergent evidence suggests the presence of an underlying mechanism intrinsic to schizophrenia that confers remarkably different smoking patterns and behavior. Evidence from Russell (1980) suggests that the behavioral consequences of smoking patterns sought by smokers and the manner in which individuals choose to smoke are intimately linked with the neurochemical effects of nicotine. In turn, the neurochemical effects of nicotine are based on the physiological and pharmacological properties of a family of cholinergic receptors. In an effort to investigate and understand the mechanisms driving the high rates of smoking and abnormal patterns of smoking behavior among

patients with schizophrenia, the pharmacology and neurobiological effects of nicotine must first be reviewed.

Neural Systems Underlying Behaviors Related to Nicotine Addiction

Nicotine Receptors

As Russell (1978; 1980) suggested, smokers may adjust their style of smoking to elicit specific effects. Perhaps smokers with schizophrenia adjust their style of smoking to target specific nicotinic receptors. Nicotine, extracted from smoking cigarettes, inhalers, from nicotine patches, or from nicotine gum acts primarily at cholinergic receptors in the central nervous system. Nicotinic cholinergic receptors are composed of α subunits, labeled 2 through 9, and β subunits, labeled 2 through 4, combinations of which confer specific pharmacodynamic properties on receptor subtypes (Freedman, Hall, Adler & Leonard, 1995). Each nicotinic receptor subunit is encoded by a different gene (Dalack, Healy & Meador-Woodruff, 1998). Neuronal nicotinic receptors are classified as receptors with either high or low affinity for nicotine; low affinity receptors are less sensitive than high affinity receptors, and therefore require larger amounts of nicotine to be activated, while high affinity receptors can be activated by lower doses of nicotine (Olinicy et al., 1997). The most common high affinity nicotinic cholinergic receptors appear to be composed of $\alpha 4$ and $\beta 2$ subunits (Luetje, Patrick & Seguela, 1990); these binding sites make up approximately 90% of all nicotineric sites in the brain, but are particularly abundant in the striatum and substantia nigra, with lower levels of expression in the hippocampus (McGehee & Role, 1995; Rubboli, Court, Sala, Morris & Chini et al.,

1994). These high affinity receptors tend to be identified by their ability to bind mecamylamine, κ -bungarotoxin, and $^3\text{[H]}$ nicotine (Freedman et al., 1995; Rubboli et al., 1994). The most common low affinity receptors appear to be formed by a pentamer of $\alpha 7$ subunits and are defined by their specific ability to bind α -bungarotoxin (snake toxin), a specific cholinergic antagonist (Seguela, Wadiche, Dineley-Miller, Dani & Patrick, 1993). Located in the midbrain, cortex, hippocampus, and to a lesser extent in the striatum, these so called $\alpha 7$ receptors are further characterized by their rapid desensitization to repeated stimulation by nicotine (Rubboli et al., 1994).

Nicotine and Reward Systems of the Brain

A number of different neural responses to nicotine appear to underlie its reinforcing properties (Balfour, 1994), and thus contribute to the development of nicotine addiction. It is now widely believed that the rewarding effects of nicotine are mediated by the interaction between nicotinic receptors and the DA system in the brain. In particular, the mesolimbocortical dopaminergic projection, consisting of neurons projecting from the ventral tegmental area (VTA) to the nucleus accumbens (NAc), the central nucleus of the amygdala, and the medial prefrontal cortex (mPFC), is implicated in mediating the reinforcing properties of both natural substances and of drugs, such as nicotine (Balfour & Fagerstrom, 1996). Corrigall, Franklin, Cohen, and Clarke (1992) found that systemic administration of nicotine in rats results in the stimulation of nicotinic receptors on mesolimbic DA neurons and the subsequent increase in extracellular concentrations of DA in the NAc. In addition, administration of selective DA receptor antagonists in rats reduced self administration of nicotine

(Corrigall et al., 1992), thus linking behavior to functional pharmacological activity. Furthermore, Nomikos and colleagues (2000) reported that specific stimulation of low affinity $\alpha 7$ nicotinic cholinergic receptors on DA neurons in the VTA resulted in a cascade of neurotransmission, ending with the augmentation of DA activity in the NAc (Nomikos, Schilstrom, Hildebrand, Panagis & Grenhoff et al., 2000). Thus the mesolimbic dopaminergic system is implicated in the reinforcing effects of nicotine, and evidence points to the role of $\alpha 7$ nicotinic receptors in mediating this mechanism.

Excitatory stimulation of the VTA and NAc has been found to play a central role in nicotine addiction. The neural effects underlying nicotine addiction are more complex than the described interaction between nicotine and dopamine, however. Picciotto and Corrigall (2002) suggest a role for both inhibitory and excitatory inputs to DA neurons in the VTA affecting synaptic plasticity. For example, glutamatergic inputs to the VTA may underlie plastic changes in the DA system that lead to the development of addiction. Picciotto & Corrigall (2002) also suggest that nicotine addiction comprises the effects of several other neural systems. The brainstem pedunculopontine tegmental nucleus (PPTg) is an area previously found to be associated with the acquisition of drug taking behaviors and with brain stimulation reward (Olmstead, Inglis, Bordeaux, Clarke & Wallam et al., 1999). Evidence suggests that GABA systems in PPTg may be a key element in nicotine addiction. GABA agonists selectively reduce nicotine self administration in rats (Corrigall, Coen, Zhang & Adamson, 2001), suggesting a dysregulatory mechanism affecting GABA mediated effects. Norepinephrine (NE) and serotonin (5HT) may also be involved in mediating neural mechanisms underlying nicotine addiction. Molecular

evidence indicates interactions between nicotine and NE release and the augmentation of NE activity attenuate self administration of nicotine. While there is no direct evidence for discrete serotonin circuitry in nicotine addiction, nicotine has been found to alter 5HT release and DA neuronal activity may be modulated by 5HT processes (Picciotto & Corrigall, 2002). Thus the neural systems underlying behaviors related to nicotine addiction are vast, comprising the functions of and interactions between several brain structures and multiple neurochemical pathways. An understanding of the effects of nicotine on the brain may provide guidance for researchers investigating the mechanisms underlying smoking behaviors among individuals with schizophrenia.

Explaining Smoking Habits in Individuals with Schizophrenia

Several theories have been formulated and examined in explaining the apparent association between smoking behavior and schizophrenia. Chronic hospitalization and the use of smoking as a “behavioral filler” to alleviate boredom presents the simplest explanation for the association. While this may contribute to the maintenance of smoking behavior to an extent, several lines of evidence have ruled out the effects of institutionalization as a primary contributing factor to the high prevalence rates of smoking. As mentioned, high rates of smoking are not limited to inpatients or the chronically ill; elevated rates of smoking are found consistently among both inpatients and outpatients with schizophrenia. In addition, patients with schizophrenia share environmental influences with patients hospitalized for other disorders, such as chronic mood disorders, as was examined by de Leon et al. (2002a), but, comparatively, still demonstrate elevated smoking rates. Furthermore,

smoking among patients with schizophrenia often appears to precede the onset of illness, prior to hospitalization.

Williams and Ziedonis (2004) suggest that biological factors associated with genetic or neurobiological mechanisms contribute to the higher rates of smoking in the mentally ill. Indeed, genetic evidence points to the relationship between smoking and schizophrenia. The findings of Lyons and colleagues (2002) indicate elevated rates of both nicotine dependence and unsuccessful smoking quit attempts among unaffected co-twins of patients with schizophrenia. The odds of being a regular smoker were 3.7 times greater among co-twins of schizophrenic probands than the odds of being a regular smoker among twin pairs in which neither has schizophrenia (Lyons, Bar, Kremen, Toomey & Eisen et al., 2002). This finding not only highlights the presence of extreme smoking behaviors in the absence of florid psychosis, but it also supports the existence of a familial vulnerability underlying the use of nicotine in schizophrenia.

Efforts to explain smoking behavior among individuals with schizophrenia must account for findings suggesting an elevated risk for nicotine use among those possessing a latent liability for schizophrenia. Following this mode of conjecture, three primary hypotheses have emerged as models of investigation in examining the neurobiological link between smoking and schizophrenia. (1) Individuals with schizophrenia may be more likely to use substances (i.e. drugs and alcohol), such that an underlying vulnerability to substance use in general results in elevated rates of nicotine use, and aspects of the disease make quitting smoking less desirable or more difficult; (2) nicotine is used to alter the effects of neuroleptic medications; (3)

smoking behaviors may modulate the symptoms or deficits (e.g. cognitive deficits) associated with the illness (Dalack et al., 1998), thus implicating nicotine use as self medication.

Primary Addiction Hypothesis

Current evidence lends support for the hypothesis that behavioral patterns and rates of smoking among individuals with schizophrenia reflect aspects of the underlying neuropathology associated with the disease. The primary addiction hypothesis proposes that nicotine use is representative of an effort to facilitate neural substrates that mediate positive reinforcement and reward (Chambers, Krystal & Self, 2001). However, the ability of nicotine to produce reinforcing effects is shared by other drugs of abuse, and common substances of abuse among individuals with schizophrenia in addition to nicotine include alcohol, cannabis, cocaine, and amphetamines (Dixon, Haas, Weiden, Sweeney & Frances, 1991). Evidence of co-occurring substance use among individuals with schizophrenia may suggest that nicotine is just one example among several substances of abuse and dependence. A vulnerability to substance abuse and addiction among individuals with schizophrenia may be explained by shared specific neurobiological substrates.

The mesolimbocortical DA system is implicated in the pathophysiology of addiction as well as schizophrenia. As previously indicated, animal models of the neurocircuitry of addiction indicate that the mesolimbic DA system is a major neural substrate for the reinforcing effects of psychostimulants; as such, substances such as ethanol, nicotine, and cannabinoids cause an increase in DA release in the nucleus accumbens (NAc) via DA neurons in the VTA (Balfour & Fagerstrom, 1996;

Chambers et al., 2001). The primary addiction hypothesis also incorporates evidence of neuropathology in neural networks that integrate mesolimbic DA in the NAc with both cortical and hippocampal inputs. Chronic nicotine administration is associated with increased DA release in the prefrontal cortex (PFC); the PFC also regulates DA cells in the VTA (Nomikos et al., 2000). NAc neurons have also been shown to integrate excitatory signals from the PFC and hippocampus, as well as DA input from the VTA (Chambers et al., 2001).

Subcortical and cortical regions of DA release are important sites of dysregulation in schizophrenia (Egan & Weinberger, 1997). Positive symptomatology (i.e. hallucinations and delusions) is thought to emerge from dopaminergic hyperactivity in the mesolimbic, or temporal-limbic, area of the brain. Mesolimbic hyperactivity is, in turn, linked to hypoactivity of DA neurons projecting to the frontal cortex. Hypofrontality is commonly associated with cognitive dysfunctions as well as negative symptomatology, such as anhedonia, amotivation, and asociality; such behavioral deficiencies may be thought of as manifestations of dysfunctional reward pathways and hypodopaminergic functioning in the mesocortical DA system (Smith, Singh, Infante, Khandat & Kloos, 2002).

According to the primary addiction hypothesis, the activation of nicotinic receptors by cigarette smoking is speculated to be an attempt to remediate a disturbance in the reward pathways of the brain affecting both the cortical and subcortical DA systems, particularly in the ventral striatum (Dalack et al., 1998). Findings from Nomikos et al. (2000) providespeculation that a deficiency specifically related to $\alpha 7$ nicotinic receptor function may play a role in the impairments in the

mesocortical pathway of the reward system. Animal models of the imbalance between cortical and subcortical DA indicate an association with increased sensitivity to the reinforcing effects of psychostimulants. Chambers et al. (2001) posit that, in schizophrenia, alterations in the hippocampal and PFC DA projections to the NAc may result in hyperresponsive drug stimulated DA release. Thus, dysfunctional integration of cortical, hippocampal, and DA signals may augment the activity of the reward circuitry and alter an individual's propensity towards addictive behavior (Chambers et al., 2001). Perhaps this dysfunction would relate to both the initiation and maintenance of such behavior.

In summary, it was shown that the pathophysiology of schizophrenia appears to overlap with findings from substance use in terms of various pharmacological and neural mechanisms underlying the reward system. It is commonly found that individuals with substance abuse disorders demonstrate high rates of smoking, similar to individuals with schizophrenia, and that individuals with schizophrenia tend to abuse alcohol and drugs more frequently than the normal population (Selzer & Lieberman, 1993). However, when considering nicotine use within the context of the primary addiction hypothesis, it is important to note that the body of research on substance use disorders indicates a lack of diagnostic differences in patterns of substance use, whereby substances used among individuals with schizophrenia is not only similar to those found with respect to other psychiatric diagnoses, but also reflects substance use patterns in the general population (Blanchard, Brown, Horan & Sherwood, 2000). In a review of substance use disorders in schizophrenia, Blanchard et al. (2000) indicate that demographic characteristics such as gender and age

represent the most reliable predictors of substance use, not diagnosis. In contrast, prevalence studies of smoking among psychiatric populations indicate elevations in the rates of nicotine use among patients with schizophrenia even after controlling for demographic variables such as age, gender, race, or socioeconomic status (Hughes et al., 1986; de Leon et al., 2002a).

Furthermore, the literature does not support a clear pattern of substances used among individuals with schizophrenia, which might otherwise be predicted if overlap in specific neurobiological substrates is assumed to dictate the incidence of substance use disorders. However, a prevalence study of smoking in a psychiatric hospital by de Leon et al. (2002b) reported that a diagnosis of schizophrenia had an effect in predicting current smoking independent of alcohol and drug history in a logistical regression analysis. In addition, although rates of substance use are elevated among individuals with schizophrenia, the prevalence of substance abuse is much lower than that of tobacco use. Nicotine dependence is, in fact, the most common substance use disorder among individuals with schizophrenia (Ziedonis & George, 1997). Thus, in contrast to findings of substance use in schizophrenia, nicotine may be independently related to schizophrenia beyond demographic variables and rates of substance use in general.

Taken all together, there appears to be little evidence to suggest that the proposed neurobiological underpinnings for substance use and addiction is the most relevant method to explain the remarkably elevated rates of cigarette smoking and smoking behavior among individuals with schizophrenia. While the neurobiological substrates of substance use and addiction may be pertinent as contributing factors to

the maintenance of smoking behavior, the high rates of smoking among individuals with schizophrenia cannot be completely explained by a neuropathological propensity towards substance use or addiction. Nicotine should therefore be investigated as a substance of use in its own right. Alternative hypotheses relating the specific neurobiological properties of nicotine to those underlying schizophrenia may be more relevant to explain the pattern of smoking behavior characteristic of individuals with the disease.

Antipsychotic Medications

A second hypothesis explaining the extreme smoking rates among individuals with schizophrenia proposes that high doses of nicotine are used to counter the effects of antipsychotic medications. Smoking can increase the rate at which neuroleptic medication is metabolized (Ereshefsky, Jann, Saklad, Davis, Richards & Burch, 1985), and may thereby reduce the potential negative side effects associated with antipsychotic drugs. In addition, Dawe, Gerada, Russell, and Gray (1995) demonstrated that administering 5mg of the antipsychotic drug haloperidol to normal smokers results in increased nicotine use. McEvoy, Freudenreich, Levin, and Rose (1995) demonstrated a similar finding in patients with schizophrenia. These findings may be explained by the fact that blockage of DA receptors by haloperidol decreases DA mediated reward and thereby results in a compensatory increase in nicotine intake in an attempt to maintain levels of subjective reward (Dawe et al., 1995). Again, nicotine use may represent an effort to overcome certain effects of antipsychotic drugs.

Contrary to these findings, however, McEvoy and Brown (1999) reported that first episode schizophrenia patients with less than 30 days' previous lifetime exposure to antipsychotics did not differ from chronic patients in their smoking behaviors. In addition, Goff et al. (1992) reported a temporal disjunction between smoking and neuroleptic exposure. In an outpatient sample of patients with schizophrenia, smoking initiation occurred, on average, 8 years before starting antipsychotic drug treatment. Likewise, Kelly and McCreadie (1999) reported that 90% of patient smokers began smoking, on average, 11 years prior to the onset of the disease. Together, these findings suggest that antipsychotic medications cannot fully explain the high prevalence rate of smoking among individuals with schizophrenia. In particular, this hypothesis does not address the initiation of smoking behavior prior to illness onset.

The Self Medication Hypothesis

Overview

Evidence from a variety of research domains converge on the importance of nicotinic receptors in the pathophysiology of schizophrenia. Specifically, compelling links have been demonstrated between $\alpha 7$ nicotinic cholinergic receptors and schizophrenia related phenomenology including cognitive and neurophysiological deficits involving visual attention, memory, eye movements, and sensory gating. Deficits in oculomotor functioning and in sensory gating mechanisms have been well documented among individuals with schizophrenia as well as among unaffected relatives of schizophrenia probands (Baron, 2001); these phenomena have thus been proposed as biological endophenotypes of schizophrenia, that is, specific neurobiological phenotypes presumed to represent the direct effects of genes

associated with the disease (Freedman, Coon, Myles-Worsley, Orr-Urtreger & Olincy et al., 1997). There is compelling evidence to suggest a link between biological endophenotypic markers and an underlying vulnerability for smoking in schizophrenia. Researchers have suggested the self medication hypothesis to explain the relationship between smoking habits and schizophrenia. This hypothesis posits that the high smoking prevalence rate and the patterns of smoking behavior may represent an effort to remediate, or self medicate, basic symptoms and cognitive dysfunctions associated with pathophysiological processes that characterize the disease.

The Role of $\alpha 7$ Nicotinic Receptors

Regulation of nicotinic receptors appears to be abnormal among individuals with schizophrenia. Post mortem studies indicate that, normally, humans exhibit a dose dependent increase in neuronal high affinity nicotinic receptors ($^3\text{[H]}$ nicotine labeled receptors) in the hippocampus and thalamus, indicating a role of high affinity nicotinic receptors in tolerance and addiction to nicotine (Breese, Marks, Logel, Adams & Sullivan et al., 1997). However, post mortem brain studies of smokers with schizophrenia demonstrate reduced high affinity nicotinic receptor levels, unrelated to neuroleptic treatment, when compared to control smokers, which may be associated with the rate of smoking and nicotine addiction in this population (Breese, Lee, Adams, Sullivan & Logel et al., 2000). Further evidence suggests that an underlying mechanism common to both schizophrenia and smoking involves a specific dysfunction of the $\alpha 7$ nicotinic cholinergic receptor (Martin, Kem & Freedman, 2004). $\alpha 7$ nicotinic receptors have been found to be instrumental in governing

sensory gating mechanisms and memory function at the neuronal level in the hippocampus, and are present in the ventral lateral geniculate nucleus (vLGN), which is proposed to play a role in the generation of smooth pursuit eye movements (Freedman et al., 1995; Denny-Brown & Fisher, 1976). Such deficits, which will subsequently be discussed at greater length, are likely to represent dysfunctions fundamental to the disease process and related to disease vulnerability.

The role of the $\alpha 7$ nicotinic receptor in the pathophysiology of schizophrenia has been upheld by a genome wide linkage analysis of multiaffected families indicating that the P50 auditory sensory gating deficit is genetically linked to the locus of the $\alpha 7$ nicotinic receptor gene (Freedman et al., 1997). In addition, evidence in postmortem brain tissue indicates that schizophrenia appears to be associated with decreased numbers of hippocampal $\alpha 7$ nicotinic receptors, apart from generalized loss of cell density, and unrelated to smoking behavior (Freedman et al., 1995). Abnormalities in the expression and regulation of $\alpha 7$ nicotinic receptors have also been indicated by decreased receptor binding in the reticular nucleus of the thalamus (Court, Spurden, Lloyd, McKeith & Ballard et al., 1999), the cingulate cortex (Marutle, Zhang, Court, Piggot & Johnson et al., 2001), and reduced $\alpha 7$ subunit levels in the frontal lobe regions among individuals with schizophrenia (Guan, Zhang, Blennow & Nordberg, 1999).

The self medication hypothesis, based on these relationships, asserts that nicotine administration via tobacco use may temporarily restore altered nicotinic receptor functioning, leading to improved cognitive functioning among individuals with schizophrenia. The reduction in nicotinic receptor functioning may likely be

linked to the heavy consumption of nicotine associated with schizophrenia. Olincy et al. (1997) propose that this pattern of heavier, more intensive smoking may be an attempt to activate $\alpha 7$ nicotinic receptors, which, due to the low affinity for nicotine, require larger amounts of nicotine for activation. The effects of nicotine on schizophrenia related symptomatology will subsequently be discussed.

Symptomatology

Patients with schizophrenia may be more likely to exhibit behaviors associated with heavy smoking in order to maintain high levels of nicotine in the blood. Given the ability of nicotine to modulate neurochemicals (i.e. dopamine, glutamate) linked to the generation of schizophrenic symptomatology, several studies have evaluated the association between smoking and changes in positive and negative symptoms. However, the relationship between smoking and symptoms is difficult to delineate. For example, among individuals with chronic schizophrenia, Ziedonis et al. (1994) found higher ratings of positive symptoms among smokers compared to nonsmokers and the lowest number of negative symptoms among those who smoked heavily. In contrast, Hall, Duhamel, McClanahan, Miles & Nason et al. (1995) reported an association between fewer negative symptoms and nonsmoking. Furthermore, Goff et al. (1992) reported higher positive and negative symptoms in smokers compared to nonsmokers while Dalack and Meador-Woodruff (1996) found an association between nicotine withdrawal and exacerbation of symptoms.

Studies addressing temporally linked nicotine related changes in schizophrenic symptomatology have attempted to clarify these findings. Dalack, Becks, Hill, Pomerleau, and Meador-Woodruff (1999) reported the results of a double

blind cross over paradigm where acute abstinence from cigarette smoking was replaced by either active or placebo nicotine patch. In contrast to the conclusion drawn by Dalack and Meador-Woodruff (1996), no sustained change in positive, negative, or mood symptoms was found. To investigate the effects of varying levels of nicotine on symptoms, Smith et al. (2002) conducted a randomized double blind cross over study using both high nicotine (1.9 mg) and denicotinized (0.1 mg nicotine) cigarettes. After smoking both cigarettes, negative symptoms decreased, as indicated by lowered scores on the SANS and the negative symptom factor of the PANSS. There were no effects, however, on PANSS positive symptoms, depression, or anxiety. The denicotinized cigarettes increased nicotine levels only 11% of the increase produced by the high nicotine cigarette, but appeared to affect negative symptoms nonetheless. This action may be due the pharmacological effects of the small amount of nicotine present, but could also be due to the behaviorally conditioned stimulus cues from the act of smoking, thereby generating effects similar to the cigarettes with high nicotine content.

The findings of Smith et al. (2002) may be interpreted as demonstrating a preferential effect of nicotine on neural mechanisms associated with negative symptomatology. However, the precise mechanism of action was not able to be defined and the conclusion drawn not strongly supported. In summary, research investigating the relationship between nicotine and positive and negative symptoms appear to be conflicting and difficult to interpret. Research attempts to characterize the relationship between nicotine use and other schizophrenia related

symptomatology, such as neurocognitive deficits, have proven to be more informative.

Cognitive Dysfunction

The self medication hypothesis posits that individuals with schizophrenia smoke cigarettes to alleviate a neurobiological abnormality associated with dysfunctional cognitive processes. In an effort to characterize this relationship, investigations have examined the effects of controlled nicotine administration on cognitive deficits such as attention and memory in a laboratory setting. Depatie and colleagues reported that laboratory administration of nicotine via transdermal patch improved a measure of sustained attention (CPT-IP hit rate) in smokers with schizophrenia but not in the smoking nonpsychiatric controls, although both groups demonstrated a similar effect of nicotine on a signal detection measure (Depatie, O'Driscoll, Holahan, Atkinson & Thavundayil et al., 2002). In comparison, Rezvani and Levin (2001) found that the transdermal administration of nicotine improved sustained attention by decreasing errors and response variability on the Conners' CPT task in both healthy non-smoking individuals and medicated smokers with schizophrenia, although the effects of nicotine administration in this study were not compared between groups. Furthermore, Rezvani and Levin (2001) reported a dose related reduction in CPT response variability in the schizophrenia group as well as attenuated deficits during a delayed match to sample working memory task. Similarly, George and colleagues suggested a beneficial effect of nicotine on a task of visuospatial working memory in schizophrenic smokers not found in non-psychiatric smoking controls (George, Vessicchio, Termine, Sahady & Head et al., 2002). These

results suggest that nicotine improves cognitive deficits, such as in attention and working memory, and may be more beneficial in remediating deficits on task performance in smokers with schizophrenia than in non-psychiatric smoking controls.

Depatie and colleagues (2002) reported that the additional beneficial effects of nicotine on smooth pursuit eye movement and antisaccadic eye movement performance were correlated with the effects of nicotine on sustained attention only in their schizophrenia patient group and not among the controls, thus suggesting a link between the pharmacological impact of nicotine, oculomotor, and attentional processes, specific to schizophrenia. The association between these functions implicates the roles of the mesocortical DA system and structures in the frontal cortex as important sites underlying a common neural mechanism (Depatie et al., 2002). Thus, evidence of nicotine use and cognitive impairments among individuals with schizophrenia support the hypothesis that nicotine is used to alleviate neurobiological dysfunctions associated with disease processes.

Eye Movement

Individuals with schizophrenia frequently demonstrate impaired smooth pursuit eye movements, lower pursuit gain, and deficient antisaccade oculomotor performance when compared to nonpsychiatric controls. In addition, eye movement dysfunction is found in approximately 34% to 58% of relatives of schizophrenic probands, compared to 5% to 13% of relatives of individuals with other psychiatric illnesses, and approximately 8% in the general population (Clementz & Sweeney, 1990). Eye movement dysfunction is therefore investigated as one behavioral marker of risk (endophenotype) for schizophrenia. Smooth pursuit eye movement

abnormalities have also been shown to be temporarily corrected by laboratory nicotine administration. As mentioned, Depatie et al (2002) reported an association between improvements in performance on tests of sustained attention, smooth pursuit eye movement (peak gain), and antisaccadic eye movements with nicotine administration among individuals with schizophrenia. In another study, nicotine, via nasal spray, was shown to increase eye acceleration during initiation of the smooth pursuit response and pursuit gain during sustained visual tracking in patients with schizophrenia but not in healthy controls. The lack of significant effect of nicotine on controls' performance was not due to performance ceiling effects; in fact, after nicotine administration, patients' initiation of smooth pursuit exceeded that of the control group (Sherr, Myers, Avila, Elliot, Blaxton & Thaker, 2002). Avila and colleagues proposed that enhanced initiation performance may be related to nicotine induced improvements in the predictive component of the pursuit response (Avila, Hong & Thaker, 2002).

A limitation to this study is the potential confounding effects of overnight nicotine abstinence. However, further research has provided evidence to support the claim that the normalization of eye movement deficits is due to the pharmacological effects of nicotine and that improvement is not a compensatory reaction related to recovery from nicotine withdrawal. Avila, Sherr, Hong, Myers, and Thaker (2003) studied the effect of nicotine nasal spray on leading saccades during smooth pursuit eye movements in smoking and non-smoking schizophrenic and healthy control groups. Nicotine reduced the number of leading saccades in the both patient groups so as to eliminate baseline differences in performance between patients and controls.

Taken together, these studies suggest that oculomotor dysfunction is closely tied to neuropharmacological mechanisms associated with neuronal nicotinic receptors and that these findings can be closely linked to the pathophysiology of schizophrenia.

Sensory Gating

Meehl hypothesized that schizotaxia, the inherited predisposition to schizophrenia, is likely to involve increased neuronal sensitivity to sensory stimuli (Meehl, 1962). The experiential consequences of such sensory “flooding” in individuals with schizophrenia may include deficits in attention, experience of sensory overload, thought disorder, and possibly the experience of auditory hallucinations (Leonard, Adler, Benhammou, Berger & Breese et al., 2001; Lyons et al., 2002; Williams & Ziedonis, 2004). It has been speculated that impaired sensory gating, the inability to accurately or efficiently process sensory information, may reflect a state of neuronal hyperarousal, in which neurons are hyperexcitable and oversensitive to sensory input. Defects in inhibitory neural pathways may underlie such abnormalities. As a result, neurons are unable to respond differentially to various inputs (Braff & Geyer, 1990; Adler, Pachtman, Franks, Peceovich & Waldo et al., 1982). Sensory gating mechanisms can be observed and quantified in the laboratory using electrophysiological and neurophysiological testing paradigms. These include the electrophysiological P50 auditory gating response and prepulse inhibition (PPI) of the startle response. Patients with schizophrenia have demonstrated impairments on both types of measure (Braff & Geyer, 1990).

Sensorimotor gating, as measured in the prepulse inhibition paradigm, is quantified by electromyographic activity of facial muscles linked to the eye blink

startle response to auditory stimuli. Normally, startle responses show habituation in response to repeated stimuli. In the PPI paradigm, a weak prestimulus induces an inhibition of startle in response to a subsequently presented test stimulus. Among individuals with schizophrenia, absence of inhibition of the startle response indicates a defective inhibitory neural process. It is hypothesized that loss of central inhibitory mechanisms is linked to the reciprocal functional relationship between cortical and subcortical dopaminergic activity, which has been identified as a common mechanism of dysfunction in schizophrenia (Braff & Geyer, 1990). The P50 gating paradigm is a widely used electrophysiological measure for testing the integrity of inhibitory circuits. In this paradigm, an auditory conditioning stimulus is first presented and the evoked cortical P50 waveform is measured. A second auditory test stimulus is presented and a decremented evoked response is expected, as inhibitory mechanisms activated by the conditioning stimulus attenuate the secondary reaction (Adler et al., 1982). Inhibition of the second response is measured by the ratio of the test response to the prior conditioning stimulus. Using this electrophysiological paradigm, Adler, Hoffer, Wiser & Freedman (1993) localized the effect of repeated sensory stimulation, represented by the P50 waveform, to originate in the medial temporal lobe, in and near the hippocampus. Thus, the P50 gating phenomenon represents the ability of the hippocampus to filter out extraneous background information and to focus attention on newer, more salient stimuli (Adler et al., 1993).

Individuals with schizophrenia typically demonstrate a diminished gating response to auditory stimuli. Adler et al. (1982) quantified the disparity in P50 responsivity between individuals with schizophrenia and non-psychiatric controls,

demonstrating 10% versus 86.1% inhibition respectively. The latency of the response was also shorter in the patient group compared to controls. A shorter latency in the patient group suggests that subcortical transmission of the response occurs over more excitable neuronal pathways, thus supporting the hypothesis that a lack of inhibitory input results in neuronal hyperactivity and oversensitivity (Adler et al., 1982).

Consistent with the concept of the endophenotype, Waldo and colleagues demonstrated that patterns of abnormal responses to sensory stimulation are directly linked to familial liability to schizophrenia (Waldo, Carey, Myles-Worsley, Cawthra & Adler et al., 1991). In examining the co-distribution of sensory gating deficits and schizophrenia in multi-affected families, Waldo et al. reported poorer sensory gating with increasing familial proximity to an affected family member. As biological markers of the genetic liability for schizophrenia, sensory gating deficits, like oculomotor deficits demonstrated from eye movement data, may be present apart from overt clinical manifestations of the disease (i.e. positive and negative symptoms). The sensory gating mechanism, associated with a genetic liability to schizophrenia, is also genetically linked to the locus of the $\alpha 7$ nicotinic receptor on chromosome 15q14. The hippocampus, the site of origination of the P50 response, is noted to be rich in $\alpha 7$ nicotinic cholinergic receptors. The relationship between sensory gating dysfunction and nicotinic receptors, particularly the $\alpha 7$ subtype, thus has strong implications for determining the pathophysiology and etiological underpinnings of schizophrenia (Freedman, et al., 1997).

Further characterization of the link between smoking and schizophrenia has been investigated by testing the effects of nicotine on deficient auditory sensory

gating. Adler et al. (1993) compared the effect of nicotine between smokers with and without schizophrenia. Similar to previous findings, at baseline controls showed a 94.7% decrement in the P50 response, while patients showed only a 17.9% decrement. Patients and controls showed markedly different responses to smoking. Although the control group demonstrated almost complete suppression of the P50 response in the smoking and nonsmoking conditions, patients showed a significantly lower P50 response in the smoking trial compared to the nonsmoking trial. In the smoking trial, the mean P50 ratio was significantly lower in the patient group than in the comparison group. In addition, there was a linear correlation between the P50 ratio before and after smoking in the patient group but not in the control group. Together, these results suggest that nicotine has an effect on auditory sensory gating in smokers with schizophrenia that is not found among smokers in the general population.

A limitation of the study was the effects of medication and the possible confounding effects of acute nicotine withdrawal, as subjects underwent an overnight smoking abstinence. However, prior research supports the conclusion that the normalization of the P50 gating response in smokers with schizophrenia was due to the neurobiological effects of nicotine administration. Adler, Hoffer, Griffith, Waldo, and Freedman (1992) studied relatives of individuals with schizophrenia who had previous evoked potential recordings that showed diminished gating of the P50 wave. None of the subjects were being treated with medications and none had smoked cigarettes or abused alcohol. As in patients with schizophrenia, oral nicotine administration produced a transient improvement of P50 gating in the relatives, which

was not due to relief from nicotine withdrawal or medication effects. Instead this study provides evidence for the normalization of a familial neurophysiological deficit associated with schizophrenia and the role of the nicotinic receptors in regulating schizophrenia related neurophysiological functions.

Chapter 2: The Current Study

Summary of Findings to Date

The prevalence of smoking among individuals with schizophrenia is estimated between 70 and 90%, a rate remarkably above the rate found among individuals diagnosed with other mental illnesses and among the general population. This finding is consistent across treatment settings and has been demonstrated internationally. The pronounced rates of smoking among individuals with schizophrenia appear to be due to increased rates of initiation and the lack of desire or inability to quit. In addition, smoking behavior in this population typically starts well before the onset of the disease, and is found more commonly among family members of individuals with schizophrenia than in the general population. Nicotine dependence appears to be related to underlying symptoms and deficits of schizophrenia as well as a familial vulnerability to the disease.

Patterns of smoking behavior, genetic findings, and clinical manifestations of schizophrenia appear to converge on the functioning of nicotinic acetylcholine receptors in the brain. Neurobiological mechanisms appear to relate more specifically to nicotine than substances of abuse in general, and the initiation of smoking behavior does not coincide with illness onset or the initiation of antipsychotic medication treatment. The self medication hypothesis posits that individuals with schizophrenia use nicotine with great frequency and smoke heavily in an effort to remediate an underlying neuronal dysfunction. Nicotine has been shown to normalize cognitive

and neurophysiological deficits among individuals with schizophrenia and their family members. Deficits in sensory gating and ocular motor dysfunction have been described as endophenotypes, biological markers of risk for schizophrenia, and have been genetically linked to the $\alpha 7$ nicotinic receptor gene locus on chromosome 15q14. Thus a vulnerability for extreme smoking patterns among individuals with schizophrenia suggests a special relationship between nicotinic receptor functioning and both genetic and neurobiological underpinnings associated with the disease.

Rationale for the Current Study

Despite the significant contributions the literature has made to understanding the relationship between smoking habits, nicotine dependence, and schizophrenia, additional research is warranted. First, smoking habits in previous studies have been simplistically assessed. Prior research has relied on using a self report measure of nicotine use in isolation, making it difficult to assess levels of nicotine use, and limiting researchers' ability to determine if patients with schizophrenia are in fact heavier smokers. Some studies have used only self-reported packs or number of cigarettes smoked per day as a measure of level of nicotine dependence. Nicotine intake is not, however, adequately represented by daily cigarette consumption or a calculation of nicotine yield, as has been done in previous studies. Rather actual nicotine intake is a function of the way cigarettes are puffed, the extent to which each puff is inhaled, and the rate of puffing per cigarette (Russell & Feyerabend, 1978). Most studies have neglected to use biological measures of nicotine consumption to test the validity of self reported nicotine use and few studies, to date, have

systematically examined smoking topography in individuals with schizophrenia in comparison to smokers in the general population.

Second, the suggested link between smoking behavior and neurophysiological deficits is based on indirect evidence. The research cited has primarily assessed the effects of nicotine as nicotine is administered in a controlled laboratory setting. Yet neither methods of nicotine administration (i.e. transdermal patch, nasal spray, gum) nor amount of nicotine delivered has been standardized and thus vary among studies. According to Russell (1978; 1980), smokers may control the amount of nicotine intake such that the effects of smoking are subjectively satisfying. Studies have not taken these individual differences (i.e. tolerance) into account when assessing the effects of nicotine. Furthermore, while prior research has focused on the effects of nicotine administration, the relationship between smoking and neurophysiological and cognitive impairments has been assessed to a lesser extent.

Third, the specificity of these relationships to smokers with schizophrenia, compared to smokers in the general population, has not been established. While some studies have shown that nicotine can affect cognitive and neurophysiological functions in non-schizophrenic individuals, a clear and comprehensive comparison of the relationship between smoking habits and these processes is warranted. Demonstration of associations between impaired neurophysiological functions previously shown to be improved by nicotine and patients' smoking habits would provide additional support for the hypothesis that smoking is a form of self medication to alleviate underlying neurobiological dysfunction among individuals with schizophrenia.

Purpose

The purpose of the current study was to (1) provide a rigorous comparison of smoking habits between smokers with schizophrenia and smokers in the general population using a number of behavioral, physiological, and biochemical measures of smoking topography and nicotine dependence, and (2) to compare how smoking behaviors are differentially related to neurophysiological functioning between groups using measures shown previously to be affected by nicotine. We tested the hypothesis that individuals with schizophrenia demonstrate greater nicotine dependence and more severe smoking topography than a comparison group of non-psychiatric controls. We also aimed to describe sensory gating and eye tracking functions in smokers with schizophrenia relative to non-psychiatric smoking controls. Preliminary results by Sherr et al. (2002) suggest that there is a negative association between some aspects of neurocognitive performance and indices of nicotine addiction among individuals with schizophrenia. We hypothesized that smoking topography and indices of nicotine dependence are related to measures of neurophysiological impairment among smokers with schizophrenia and are less related among smokers in the general population. This finding would suggest that schizophrenic and non-schizophrenic smokers differentially benefit from the pharmacological effects of nicotine and would thereby support the hypothesis that smoking among individuals with schizophrenia represents an attempt to correct an inherent neurobiological defect associated with the pathophysiology of, and latent liability to, the disease.

Chapter 3: Methodology

Data Collection

The current study employed both case control comparisons and within group analyses using patients with schizophrenia and healthy community controls. The project took place within the context of a larger ongoing study at the Maryland Psychiatric Research Center (MPRC). Data had been collected on a sample of 64 patients with schizophrenia, in accordance with the University of Maryland-Baltimore Institutional Review Board guidelines, and were available for analysis. Additional participants were recruited for the purposes of both the current study and the ongoing protocol at the MPRC investigating the relationships between smoking, nicotine dependence, and schizophrenia.

Participants

The patient participants were individuals with a DSM-IV diagnosis of schizophrenia or schizoaffective disorder attending inpatient and outpatient programs at the Maryland Psychiatric Research Center (MPRC). MPRC patients are typically referred from area state hospitals, community mental health clinics, and private psychiatrists. The patient group was composed only of current smokers. Patient participants were maintained on their current medications.

The MPRC Intervention Research Center (IRC) has an ongoing community recruitment program from which healthy volunteers for the proposed study were drawn. Control subjects are typically recruited from the greater

Baltimore/Washington D.C. metropolitan area using newspaper advertisements.

Potential IRC normal control subjects completed an initial telephone screen. Subjects whose initial telephone screen indicated an absence of serious medical illness, personal and family histories of psychiatric illness, or alcohol and drug abuse were invited to undergo further assessments. Only community members who currently smoke and met inclusion and exclusion criteria were actively recruited to participate.

Inclusion and Exclusion Criteria

Participants between the ages of 18 and 55 were eligible to participate.

Smokers included individuals who smoke at least one cigarette daily. Patients with a DSM-IV diagnosis of schizophrenia or schizoaffective disorder were included.

Community subjects with no personal history of psychiatric illness, according to DSM-IV criteria, and no family history of psychotic illness, according to Family History Research Diagnostic Criteria (FH-RDC) were considered eligible.

Subjects with neurological illnesses (e.g. seizure disorders), mental retardation, or a history of drug or alcohol dependence (according to DSM-IV criteria) were excluded. Individuals with chronic obstructive lung disease and/or pulmonary emphysema or preexisting clinically significant cardiovascular disease, or recent myocardial infarction (within the past year) were excluded. Patients exhibiting severe tardive dyskinesia were excluded. Pregnant women were not eligible to participate.

Community participants meeting DSM-IV criteria for an Axis I disorder were excluded with the exceptions that individuals meeting criteria for a past, single episode of major depression, ending a minimum of one year before the study, or

individuals with a history of substance abuse ending at least 6 months before the study were included.

Assessments

Clinical Evaluations

Structured Clinical Interview for DSM-IV (SCID; First, Spitzer, Gibbon & Williams, 1997): Masters and doctoral level trained clinicians from the MPRC Schizophrenia Related Disorders (SRD) Program assessed community participants for Axis I disorders using the SCID. Rater agreement on the SCID is adequate with kappas greater than 0.60 (Williams, Gibbon, First, Spitzer & Davies et al., 1992).

Family History Research Diagnostic Criteria (FH-RDC; Andreasen, Rice, Endicott, Reich & Coryell, 1986): SRD clinicians used the FH-RDC to screen community subjects for a family history of psychosis. To increase the sensitivity for Axis I diagnoses, especially schizophrenia, extensive probe questions were added to obtain additional information regarding each of the assessment items (e.g. hallucinations, delusions).

Patient Clinical Assessments: Patient clinical assessments were conducted by trained MPRC Intervention Research Center (IRC) psychiatrists. The MPRC IRC assessment battery includes demographic and medication history, SCID diagnosis, Brief Psychotic Rating Scale (BRPS), Scale for the Assessment of Positive Symptoms (SAPS), Schedule for the Deficit Syndrome (SDS), Involuntary Movement Scale, Premorbid Adjustment Scale, Level of Functioning Scale, Quality of Life Interview, and a Neuropsychological Summary. Diagnostic information on each patient was

reviewed in a best estimate diagnosis meeting. A senior psychiatrist chaired the meeting and the clinician who conducted the structured interviews presented each case.

Self-Report Measures of Smoking

Several self report questionnaires were utilized during the assessment for the MPRC protocol in order to measure multiple aspects of smoking history, motivation, habits, and dependence. Only certain pre-selected questionnaires were used for the current study in order to assess smoking history and current level of nicotine dependence. These are discussed below.

Cigarette Brand Form: Participants were asked about their usual cigarette brand and information on cigarette size (e.g. regular, 100's), tar-nicotine level (e.g. lights, mediums), filter (i.e. filtered vs. unfiltered), and menthol content.

Fagerstrom Test for Nicotine Dependence (FTND; Heatherton, Kozlowski, Frecker & Fagerstrom, 1991): The FTND is a widely used measure of behaviors related to physiological nicotine dependence. The questionnaire consists of 6 self report items pertaining to amount of time to first cigarette of the day, difficulty refraining from smoking, increased smoking in the morning, and the most difficult cigarette of the day to give up. The FTND yields a global score ranging from 0 to 10. A FTND score of 6 or higher identifies subjects with high nicotine dependence (Fagerstrom, Kunze, Schoberberger, Breslau & Hughes et al., 1996). The FTND has adequate internal consistency (coefficient $\alpha = 0.61$; Heatherton et al., 1991) and has been shown to correlate with cigarette pack years, number of smoking related

physical symptoms, exhaled carbon monoxide level, and cotinine level (Burling & Burling, 2003).

Smoking History Questionnaire and Nicotine Dependence Symptoms Scale (NDSS): The Smoking History Questionnaire and NDSS were developed in conjunction with nicotine and tobacco research being conducted at the National Institute on Drug Abuse (NIDA). Questions address smoking behavior patterns (i.e. frequency of smoking), smoking history (e.g. age at which regular smoking was initiated), and history of quit attempts. The NDSS yields a numerical score that indexes level of nicotine dependence. There is currently no available published information on the reliability or validity of these scales.

Physiological Evaluation of Smoking

Laboratory measures for the current study included plasma cotinine levels and pre/post smoking changes in plasma nicotine levels (nicotine boost). Cotinine was used as a global biological index of nicotine addiction (Galeazzi, Daenens & Gugger, 1985); cotinine levels are fairly stable in the blood and urine of smokers over time (Benowitz, 1999) and is thus useful as an indicator of habitual smoking. Pre- and post-smoking blood samples required a total of 5-6 ml of blood to be drawn by a certified SRD nurse. The post-smoking blood draw occurred 5 minutes after the participant finished smoking. This corresponds to the average time to peak nicotine levels in the blood. Blood samples were stored in a refrigerated and secure container until shipped to a commercial lab for analysis.

Smoking Topography

Smoking topography, the manner in which individuals smoke, was assessed using a commercially available hardware/software package: Clinical Research Support System (CRESS) (Plowshare Technologies, Baltimore, Maryland). To obtain measures of topography, a cigarette (the subject's own brand) was smoked through a mouthpiece connected to a pressure transducer. The analog signal was converted to a digital output and presented to a computer-based analysis system. Puff volume, puff duration, maximal puff velocity, and inter-puff interval were computed. The time to smoke the cigarette and the number of puffs per cigarette were also recorded. Raw data were collected and stored on the system hard drive automatically for each subject. The cigarette holders were sterilized between each use. The CRESS system was calibrated prior to each use with a syringe that draws 20, 30, 40, and 50 mL, which are in the range of human puff volumes reported in the literature. The CRESS system has been used in several studies of smoking topography in normal volunteers and has been shown to yield reliable results (interclass coefficients for CRESS parameters > 0.65 across testing occasions) with biochemical and physiological changes similar to those observed for smoking when not using the CRESS system (Lee, Malson, Waters, Moolchan & Pickworth, 2003).

Neurophysiological Measures

Sensory gating was measured using two paradigms: (1) an auditory evoked potential paradigm, P50 gating and (2) a pre-pulse inhibition paradigm (PPI), measuring sensorimotor gating of the acoustic startle response. Eye movement

functions were also assessed. Neurophysiological testing took place in the MPRC's event related potentials laboratory and the MPRC's oculomotor laboratory.

P50 Auditory Evoked Potentials: The procedures for event related potential (ERP) testing consists of the application of electrodes to the scalp and face, the performance of a simple task while electroencephalography (EEG) is acquired, removal of electrodes, and clean up. Each location for the electrode sites was cleaned with alcohol and a mild abrasive to slough off dead cells and the electrodes were applied with water soluble electrode gel. The subject was seated in a comfortable chair in an enclosed, sound-attenuated room under controlled lighting conditions. Participants were instructed to keep their eyes open and listen to paired click stimuli through headphones. Auditory stimuli were generated by a programmable sound module (Neuroscan) under software control (Neuroscan STIM) and delivered to an audio amplifier adjusted to a sound intensity of 75dB for the participant. In this paradigm, auditory clicks were delivered in pairs with a 500ms inter-click interval, at a rate of 1 pair every 10 seconds until 150 pairs were presented. Practice blocks and blocks where ERP data were collected lasted approximately one hour.

Event related potential EEG recordings were amplified, filtered, and digitized using a commercially available electrophysiological recording system (Neuroscan Acquire and Synamp). Auditory evoked potentials were obtained and averaged from the paired click stimuli. S1 denotes the average response from the first click and S2 from the second click. P50 amplitude and latency measurements were compiled from averages obtained from electrode position CZ. For the S1 response, P50 was defined as the largest positive wave occurring within a 35 to 70ms interval following the

stimulus. Amplitude was measured from the trough of the preceding wave to the P50 peak. Measurement of the response to the second click (S2) was limited to a latency window 10ms before or after the S1 P50 latency. Gating of the P50 response was quantified by the ratio of the amplitude of the second response to the first response. Disrupted gating was defined as a S2/S1 ratio that exceeded 0.50 (Freedman, Adler, Myles-Worsely, Nagamoto & Miller et al., 1996).

Pre-Pulse Inhibition of the Acoustic Startle Reflex: Measures of prepulse inhibition (PPI) were obtained by monitoring eye blinks using electrodes placed around the eyes. Electromyographic (EMG) activity was recorded with two disk electrodes, one placed 1 cm lateral to and slightly below the lateral canthus, and the other 1 cm medio-inferior to the lateral electrode. A ground electrode was placed on the forearm. Each session began with a 4 minute acclimation period with 70 dB static white noise, presented through headphones, which was present throughout the session. Each session consisted of two conditions: the pulse alone trials with 116 dB while noise lasting 40 ms, and the pre-pulse trials that included a 20 ms 85 dB white noise pre-pulse. The following pre-pulse inter-stimulus intervals (ISI) were tested in the patient group: 30, 45, 60, 75, 90, 120, 180, 240, and 500 ms. Only an inter-stimulus interval of 120 ms was utilized to measure pre-pulse inhibition among the controls. Pre-pulse trials were presented 6 times at each ISI and the pulse alone trial was presented 12 times. Trials were divided into 3 blocks, each consisting of 4 pulse alone trials and 2 pre-pulse trials for each ISI. The trials within each block were pseudo-randomized. The full session was estimated to take approximately 22 minutes.

Participants were instructed to relax and sit comfortably in an armchair while data were collected. .

The auditory stimuli were generated by a PSYLAB Stand Alone Monitor unit and a Psylab Noise/Tone Generator (Contact Precision Instruments, Cambridge, MA). Sound pressure from the headphones was measured with a Sound Level Meter (Model 2700, Quest Technologies, Oconomowoc, WI) and an earphone coupler (Model EC-9A, Quest Electronics). Eye blink EMG response was measured using a Grass model AC Amplifier (model 1CP511, Astro-Med, Inc) and was acquired and digitized using commercially available hardware and software (BioPac analogue-to-digital converter and Aqcknowledge software, Gloeta, CA) EMG records were imported into data analysis software.

The primary measure of PPI was the blink response area of the EMG startle response. Trials were not included if a response occurred within the pre-pulse interval, if the response latency was less than 20ms, if the peak response fell outside of a 20-120 ms range following the pulse, or the distance of the response latency and peak response latency was 90 ms or more apart. Non-responders were defined as subjects who responded to less than 50% of the first 8 pulse alone trials. These participants were identified and removed from analyses. Inhibition of the startle response was measured, in the patient group, as the ratio of pre-pulse to no pre-pulse response area. In the control participants, inhibition of the acoustic startle response was measured as percent inhibition. This is calculated as the ratio of the difference in the peak amplitudes between a pulse alone trial and a pre-pulse trial to the peak amplitude in the pulse alone trial.

Eye Tracking: Visual acuity was tested grossly using a Snellen Rating chart. Individuals with uncorrected acuity worse than 20/200 were excluded. Ocular motor testing was performed in a sound muffled, windowless testing room. A chin rest and head abutment were used to stabilize the head approximately 28 inches from the visual display, which was presented on a 20 inch monitor. Eye movement data were collected using an infrared technique (Applied Sciences Laboratory, 210 model or equivalent). Blinks were monitored using electro-oculography (EOG). Head movement data was collected using an induction coil in a magnetic field and Grass 7 DC amplifier. The analogue data was then digitized using a 16 bit analogue to digital converter and stored for off line analysis. The data acquisition system has a sampling rate of 333Hz with a time constant of 4msec. The target system consisted of a 20 inch flat screen VGA monitor, which displayed the target (a cross in a box of 0.15 x 0.15 degrees) driven by an IBM compatible PC. The target velocity was presented as angular velocity. The photometric contrast of target to background was 2.1 log units.

A ramp-mask-ramp (RMR) procedure was used to examine pursuit performance during visually guided and memory guided pursuit tasks (Thaker, Ross, Cassady, Adami & LaPorte, et al., 1998). Participants were instructed to follow the moving target presented on the computer monitor, even when becoming briefly invisible (masked). Two primary measures of eye movement were assessed. First, closed loop pursuit gain (eye velocity/target velocity) during sustained visual tracking, is a measure of eye movements based on retinal motion (motion of the target image on the retina) and extraretinal motion (motion signals based on an internal representation of previous target and eye velocity information). Second, predictive

pursuit gain was measured during target masking, and is thus based on extraretinal motion processing (Thaker, Ross, Buchanan, Moran & Lahti et al., 1996; Thaker et al., 1998). Work by Thaker and colleagues suggests that the ability to generate and/or store extraretinal motion information is the primary contributing factor to poor visual tracking in individuals with schizophrenia. This is represented by low predictive pursuit gain (Thaker, Ross, Buchanan, Adami & Medoff, 1999; Avila et al., 2002). Two types of predictive pursuit gain were measured. Predictive peak gain was obtained when a target mask occurred at the beginning of a ramp, and residual predictive pursuit gain was obtained when a mask interrupted a smooth pursuit eye movement tracking a visual target in the middle of a ramp.

Procedures

Prior to testing, participation in previous protocols was confirmed, and which neurophysiological tasks had been completed prior to the current assessment was ascertained. On the day of study enrollment, subjects first met with an investigator (A. Saperstein or M. Avila) who explained the study procedures. For subjects who could not read, the consent form was read to them in its entirety. Questions regarding procedures, potential risks, and benefits were discussed. The investigator then obtained written consent after explaining the procedures. For patient participants, a non-investigator clinician performed an evaluation of capacity to sign consent.

Following consent all participants took part in smoking assessments which encompassed measures for the current study as well as additional measurements for the larger MPRC protocol, of which the current study is a part. Participants were not asked to refrain from smoking prior to the smoking assessments; participants were

asked to determine at what time they last smoked a cigarette. Procedures for the smoking assessments were as follows: (1) The participant completed a Cigarette Brand Form and the Questionnaire for Smoking Urges (QSU). (2) A certified SRD nurse obtained a pre-smoking blood sample. This included one 3-4 mL tube for cotinine and pre-smoking plasma nicotine assays and one 5-6 mL tube to conduct analyses related to peripheral nicotinic receptor density and nicotinic receptor subunit genes. The patient participants were asked to provide a simple measure of baseline exhaled carbon monoxide (CO). (3) Smoking topography measures were obtained during an ad libitum smoking session. The time at which the first puff was taken and the time when the cigarette was finished, as indicated by the subject, were recorded. (4) There was a 5 minute delay to allow nicotine to reach peak levels in the blood. During this time, additional questionnaires were completed, including the FTND, NDSS, and the Smoking History Questionnaire, which includes the Stages of Change Questionnaire. (5) A second blood sample was drawn to measure post-smoking plasma nicotine and cotinine levels; a post-smoking exhaled CO measurement was obtained from the patient participants. (6) The participants completed the post-smoking QSU and any other questionnaires that were not completed during the 5 minute interval. The entire procedure took approximately one and a half hours to complete.

Following the ad libitum smoking session, participants were allowed to resume their normal smoking habits. However, all participants were asked to refrain from smoking for a period of at least 30 minutes before the neurophysiological tasks were completed. These included the P50 gating paradigm, the PPI task, the eye

movement tasks, and additional cognitive measures obtained for the larger protocol, including the CPT-IP and a non-verbal memory task. Depending on the participants' preference, or to what extent tasks had been completed as a part of previous protocols, these assessments were completed within the same day, or in a follow up session. The P50 testing took approximately 1 hour to complete, the PPI task was completed within approximately 30 minutes, and the eye movement testing took approximately 1 hour and 30 minutes to complete.

Chapter 4: Analyses

Study Aim 1

Patients with schizophrenia and non-psychiatric controls were compared to address the two specific aims of this study: (1) to provide a rigorous comparison of smoking habits and neurophysiological functions between smokers with schizophrenia and smokers in the general population and (2) to compare how smoking and neurophysiological functions previously shown to be affected by nicotine are differentially associated among individuals with schizophrenia and healthy controls who smoke.

In the following chapter, sample characteristics of the patient and control groups are first presented, including comparisons for demographic information as well as for smoking history. Descriptive information with regard to the type of cigarettes smoked and current smoking habits is then provided for both groups. In reference to the first study aim, three hypotheses are tested. First, group comparisons using analysis of variance (ANOVA) are presented to test the hypothesis that smokers with schizophrenia exhibit greater levels of nicotine dependence, as indicated by self-report measures and biological indexes of nicotine consumption. Second, ANOVA is used to test the hypothesis that smokers with schizophrenia demonstrate more extreme smoking behaviors on measures of smoking topography. Effect size comparisons for self-report and biological indexes of nicotine dependence and smoking topography are also presented. Additional analyses are included to describe the relationships within the patient group between degree of symptomatology,

medication, and characteristics of nicotine use. Third, the results of sensory gating and eye tracking tasks are presented for patients and controls. ANOVA and effect size comparisons are shown for the eye tracking data to test the hypothesis that patients with schizophrenia demonstrate impaired smooth pursuit eye movements compared to healthy controls. Alterations to sensory gating study paradigms as well as differences in the methods used to quantify the main outcome variables precluded the use of direct statistical comparisons between groups for these measures. Within group analyses for sensory gating functions are presented as indicated below.

Study Aim 2

In reference to the second study aim, the results of correlational analyses and regression are utilized to characterize the associations between neurophysiological functions and smoking related measures within the patient and control groups. Pearson correlations are presented to describe the magnitude and direction of the associations between neurophysiological functions and smoking related measures in separate analyses for patients and controls. In these analyses, measures representing nicotine consumption and dependence and measures of smoking topography were included with continuous measures of neurophysiological performance. For those measures found to be associated with smoking behavior and nicotine exposure in each group, regression analyses are presented to describe the proportion of variance in smoking measures of interest explained by related neurophysiological performance. We thereby test the hypothesis that patients with schizophrenia demonstrate a more robust association between measures of nicotine use and neurophysiological measures of information processing when compared to healthy controls.

Chapter 5: Results

Sample Characteristics

To examine the study hypotheses, smoking and neurophysiological data were collected for 64 smokers with DSM-IV diagnosed schizophrenia or schizoaffective disorder and 10 smoking comparison subjects from the general population. The patient group consisted of individuals recruited from both inpatient and outpatient units at the Maryland Psychiatric Research Center. Six patient smokers were excluded from analyses based on either the age criterion ($n = 5$) or significant missing self-report and physiological data ($n = 1$). To better match the patient and control groups on smoking history, analyses were further limited by excluding patients with smoking years outside of the control group range ($n = 8$). Smoking years was defined as the difference between subjects' age at the time of testing and the age of smoking initiation (i.e. smoking one cigarette per day). Limiting analyses to patients with smoking years within the control group range had little effect on sociodemographic characteristics for the patient group. The final sample of patient smokers ($N = 50$) had a mean age of 38.76 ± 8.56 years and mean smoking years of 22.96 ± 8.46 . This group was characterized as 64% Caucasian, 36% Black, 26% female, and 74% male. The control group ($N = 10$) was characterized by a mean age of 40 ± 12.20 years, 22.30 ± 13.56 smoking years, and was 50% Caucasian, 50% Black, 50% male, and 50% female.

Groups were statistically comparable in terms of all sample characteristics with no significant differences for age, $F(1, 58) = 0.15, p = 0.69$, smoking years, $F(1, 58) = 0.04, p = 0.84$, race $\chi^2(1, N = 60) = 0.69, p = 0.41$, or gender $\chi^2(1, N = 60) = 2.29, p = 0.13$. Patients and controls also did not significantly differ on mean age of smoking initiation, $F(1, 58) = 0.449, p = 0.51$, or reported age of regular tobacco use, $F(1, 58) = 1.14, p = 0.29$. Smoking history variables are summarized in Table 1.

Table 1. Smoking History

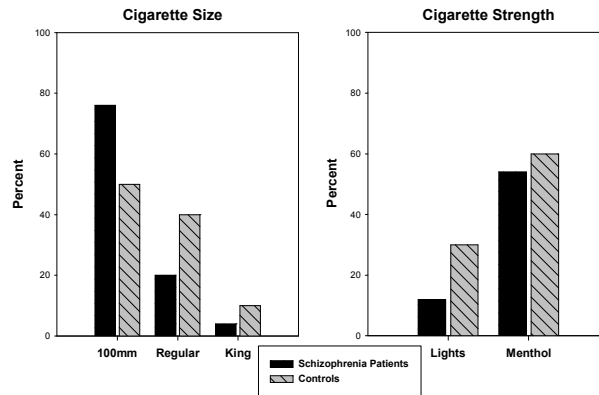
	Age at Smoking Initiation	Age at Regular Smoking	Smoking Years
	Mean (SD)	Mean (SD)	Mean (SD)
Patients	16.55 (4.46)	18.34 (4.07)	22.96 (8.46)
Controls	17.7 (7.21)	20.00 (6.29)	22.3 (13.56)

Among those who reported a history of quit attempts, patients ($n = 31$) reported twice as many lifetime quit attempts as controls ($n = 7$), with means of 4.35 ± 9.13 for patients and 2.28 ± 1.49 for controls, although this difference was not statistically significant, $F(1, 36) = 0.35, p = 0.56$. However, there was a trend towards significance, $F(1, 34) = 3.35, p = 0.076$, for controls to report, on average, abstinence from cigarette use (49.35 ± 74.98 weeks) for a longer duration than patients (18.12 ± 28.07 weeks) for any single quit attempt. The majority of participants (50 patients, 9 controls) were able to provide information about the smoking history of their first-degree family members as well. Relatively equal percentages of participants between groups reported a family history of smoking with 94% of patients and 88.9% of controls reporting either past or present smoking among biological parents and siblings $\chi^2(1, N = 59) = 0.32, p = 0.57$.

Current Smoking Habits

The Cigarette Brand Form was utilized to gather descriptive information about the type of cigarettes participants typically smoke with respect to cigarette strength, whether cigarettes are filtered or non-filtered, menthol or non-menthol, and size. These data are summarized in Figure 1. The patients and control groups did not statistically differ in the types of cigarettes smoked with regard to both cigarette size and strength. All controls and all but one patient reported smoking filtered cigarettes.

Figure 1. Cigarette Characteristics



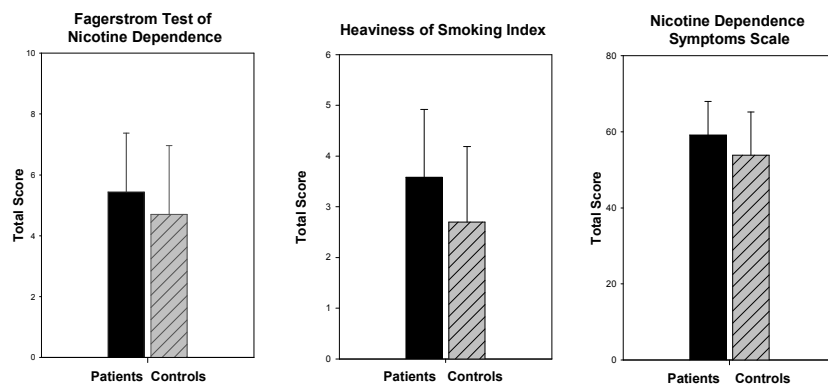
Additional data regarding participants' daily smoking habits were obtained from the Smoking History Questionnaire. On average, patients reported smoking a greater number of cigarettes per day than controls, with mean values of 20.06 ± 9.62 and 15.3 ± 12.73 respectively. ANOVA demonstrated that this difference was not statistically significant, $F(1, 58) = 1.83$, $p = 0.18$, with an effect size in the small range ($d = 0.42$).

Nicotine Dependence

Level of self-reported nicotine dependence was examined using the Fagerstrom Test for Nicotine Dependence (FTND) and the Nicotine Dependence Symptoms Scales (NDSS). Mean total scores were compared using ANOVA to test the hypothesis that

patients with schizophrenia would exhibit greater levels of nicotine dependence than smokers in the general population. In both groups, the self-report measures were significantly correlated, $r = 0.67$ ($p < 0.05$) in the control group, and $r = 0.39$ ($p < 0.01$) in the patient group. Furthermore, both measures were significantly correlated with cigarettes per day. Results for self-reported level of nicotine dependence are depicted in Figure 2 below. ANOVA revealed no significant group differences for

Figure 2. Self-Report Measures of Nicotine Dependence

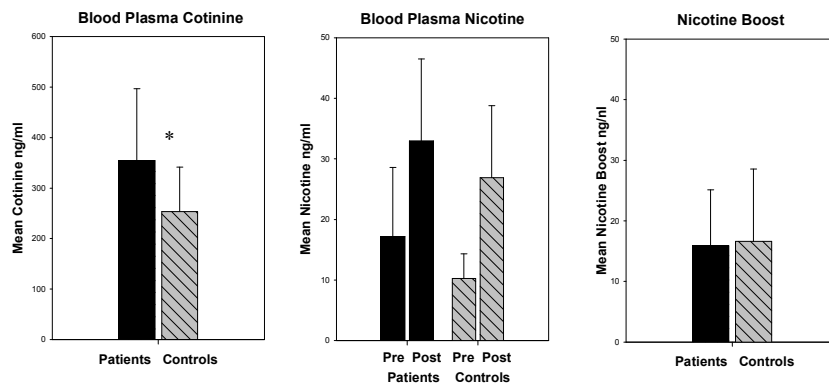


total scores on the FTND, with means of 5.44 ± 1.93 and 4.70 ± 2.26 for patients and controls respectively, nor did ANOVA yield significant groups differences between patients (59.14 ± 8.86) and controls (53.80 ± 11.38) for NDSS total scores. Effect size comparisons yielded effect sizes in the small range for the FTND ($d = 0.35$) and in the medium range for the NDSS ($d = 0.52$).

Prior research utilizing the FTND has suggested that two FTND items reflect nicotine dependence best (de Leon, Diaz, Becona, Gurpegui & Jurado et al., 2003; Diaz, Jane, Saltoe, Pardell & Salleras et al., 2005). Item 1 (the time to the first cigarette of the day) and Item 4 (the number of cigarettes smoked per day) are summed together to create a composite called the Heaviness of Smoking Index (HSI; Heatherton, Kozlowski, Frecker, Rickert & Robinson, 1989). The HSI was calculated,

post-hoc, for each group and compared using a one-way ANOVA. Patients demonstrated a higher score (3.58 ± 1.34) than controls (2.70 ± 1.49); although the difference in HSI was not statistically significant at the 0.05 level, $F(1, 58) = 3.46$, $p = 0.068$, the effect size ($d = 0.62$) was in the medium range. To supplement self-report measures of nicotine dependence, biological indexes of nicotine use were obtained and compared between groups to further test the hypothesis that patients with schizophrenia evidence greater levels of nicotine consumption than controls. These data are represented in Figure 3. Blood plasma cotinine was analyzed in two blood samples (before and after ad libitum smoking) and averaged together to create a composite measure. Mean cotinine levels were significantly different, $F(1, 55) = 4.63$, $p = 0.04$, between patients ($354.36 \text{ ng/mL} \pm 142.58$) and controls ($253.00 \text{ ng/mL} \pm 88.73$) with an effect size ($d = 0.85$) in the large range.

Figure 3. Biological Measures of Nicotine Dependence



Biological measures of nicotine use also included pre- and post-smoking blood plasma nicotine levels. In both groups, pre-smoking levels of nicotine were negatively correlated with time since last cigarette, i.e. withdrawal time, (patients $r = -0.46$, $p = 0.001$; controls $r = -0.29$, $p = 0.41$), thereby validating blood plasma nicotine levels as an index of short term nicotine consumption. Interestingly, although

mean withdrawal times did not significantly differ between groups, $F(1, 58) = 0.30$, $p = 0.59$, group differences in mean pre-smoking nicotine levels approached statistical significance, $F(1, 55) = 3.55$, $p = 0.065$, and exhibited a large effect size ($d = 0.81$) with patients demonstrating greater mean pre-smoking blood plasma nicotine ($17.19 \text{ ng/mL} \pm 11.39$) than controls ($10.27 \text{ ng/mL} \pm 4.09$). Similarly, patients demonstrated larger post-smoking blood plasma nicotine levels ($33 \text{ ng/mL} \pm 13.50$) than controls ($26.90 \text{ ng/mL} \pm 11.86$), but these differences were not statistically significant, $F(1, 56) = 1.88$, $p = 0.18$, with an effect size in the small to medium range ($d = 0.49$). Nicotine boost, which was calculated as the difference between the pre- and post-smoking blood plasma levels, was comparable between groups, $F(1, 55) = 0.048$, $p = 0.83$. Post-smoking, but not pre-smoking, plasma nicotine level was significantly associated with nicotine boost in both the patient ($r = 0.56$, $p < 0.001$) and control ($r = 0.94$, $p < 0.001$) groups.

Further examination of the relationships among indexes of nicotine consumption and dependence is informative in interpreting the significance of these measures across the two groups. Cotinine was positively correlated with pre-smoking blood plasma nicotine levels in both the patient ($r = 0.33$, $p = 0.03$) and control groups ($r = 0.42$, $p = 0.23$); in the patient group, cotinine was positively correlated with post-smoking nicotine ($r = 0.47$, $p = 0.001$) and nicotine boost ($r = 0.29$, $p = 0.05$) but negatively correlated with both post-smoking nicotine level ($r = -0.31$, $p = 0.39$) and nicotine boost ($r = -0.45$, $p = 0.19$) in the control group. This may suggest that steady blood plasma levels of nicotine, or its breakdown products, attenuates further nicotine intake in controls but not in patients with schizophrenia. Yet, in

neither group was cotinine significantly correlated with either self-report measure of nicotine dependence. Similar to the associations reported between cotinine and other biological indexes of nicotine consumption however, it is interesting to note that cotinine was negatively associated with self-reported nicotine dependence in the control group and that these associations were moderate in magnitude (NDSS: $r = -0.60$, $p = 0.065$; FTND: $r = -0.41$, $p = 0.24$). By comparison, the correlations between cotinine and self-reported nicotine dependence in patients were minor (r values < 0.20) and indicated little association between biological and self-report measures of nicotine dependence in the patient group. In neither group was cotinine significantly associated with time since last cigarette (p values < 0.50), with cigarettes per day, or smoking years. These results suggest a lack of association with immediate nicotine consumption and, unexpectedly, a disjunction between biological indexes and self-reported amount of nicotine use.

Smoking Topography

During an ad-libitum smoking session, participants were asked to smoke one of their own cigarettes through a mouthpiece connected to the CRESS machine from which topography measures were obtained. Participants were instructed to smoke “as you normally would”; all participants smoked only one cigarette. Smoking time was calculated as the difference between the time of the first puff and the time when the subject verbally indicated that they were finished. Topography measures were obtained per puff and then averaged over the ad-lib smoking session for each participant. Topography measures included average puff volume (mL), average puff duration (seconds), average inter-puff-interval (seconds), and average puff velocity

(mL/second). Only valid puffs, defined as a puff of at least 1 mL, were utilized for analyses; inter-puff interval was corrected for the presence of micro-puffs (less than 1mL) and the number of valid puffs per session calculated. The results from the ad-lib smoking session are displayed in Table 2. Group comparisons were conducted to test the hypothesis that patient smokers would demonstrate characteristics of more intense smoking behavior than controls, which may include greater number of puffs per cigarette, greater puff volume, shorter puff duration, shorter inter-puff-interval, greater puff velocity, and shorter overall smoking time.

Table 2. CRESS Smoking Topography

	Patients Mean (SD)	Controls Mean (SD)	P Value	Cohen's d
Number of Puffs	18.04 (13.28)	14.10 (5.68)	0.36	0.39
Avg Volume (mL)	44.17 (16.38)	48.33 (18.21)	0.47	0.24
Avg Duration (sec)	1.19 (0.39)	1.45 (0.36)	0.61	0.67**
Avg Interval (sec)	14.62 (8.61)	18.79 (10.85)	0.19	0.42
Avg Velocity (mL/sec)	54.62 (16.63)	45.69 (13.74)	0.12	0.58**
Smoking Time (sec)	242.24 (79.66)	324.00 (165.41)	0.02	0.63**

** Medium Effect Size

Although differences between groups for number of puffs, average puff volume, duration, interval, and velocity were in the expected direction, none of these differences in smoking topography parameters reached statistical significance. The only exception was for overall smoking time whereby patients demonstrated shorter overall smoking time during the ad libitum smoking session compared to controls. Because a lack of power may have limited the extent to which differences in topography variables could have been found, effect size comparisons were calculated and are presented in Table 2. Of note, for three out of the six parameters examined,

effect sizes were in the medium range, providing some evidence to suggest that the manner in which patients with schizophrenia smoke is different from controls.

Surprisingly, nicotine boost demonstrated very low correlations with all topography measures in the patient group, with all r values below 0.08 in magnitude. In the control group, nicotine boost showed a modest correlation with puff volume ($r = 0.56$) but the association was not statistically significant ($p = 0.089$). Nicotine boost was, however, positively and significantly correlated with average puff duration in the control group ($r = 0.80$, $p < 0.01$) such that greater nicotine boost was associated with longer puff duration.

Correlations among topography parameters were similar between patients and controls. These values are summarized in Table 3 below. In both groups, average puff

Table 3. Correlations Between Topography Measures
(*correlations for patients shown above and controls below the diagonal*)

	Puff Volume	Puff Velocity	Puff Interval	Puff Duration
Puff Volume	----	0.55**	0.26	0.83**
Puff Velocity	0.79**	----	-0.10	0.04
Puff Interval	0.24	0.13	----	0.37**
Puff Duration	0.77**	0.27	0.34	----

** $p < 0.01$

volume was associated with greater puff duration and flow. Greater puff duration was comparably associated with longer inter-puff interval in the two groups, although the correlation only reached statistical significance in the patient group. Shorter time to smoke was significantly associated with shorter inter-puff interval in the patient group, whereas in the control group, time to smoke was negatively associated with puff velocity.

Smoking Habits, Nicotine Addiction and Clinical Variables

Clinical assessments based on the Brief Psychiatric Rating Scale (BPRS) were available for a subset of patients ($n = 39$) and were examined to determine if clinical state influences patients' smoking habits. For self-report and laboratory based measures of nicotine addiction, non-significant correlations were observed between BPRS total score and FTND and NDSS total scores, but a modest negative correlation was found between BPRS total score and average cotinine ($r = -0.31$), which approached significance ($p = 0.067$). Although BPRS total score was not significantly associated with any individual topography measure, the BPRS Psychosis Subscale score was moderately correlated with number of puffs per cigarette ($r = 0.37$, $p = 0.02$) and the BPRS Withdrawal Subscale score was moderately negatively correlated with average puff velocity ($r = -0.33$, $p = 0.04$). In addition, total score on the Schedule for the Deficit Syndrome, which measures level of primary and enduring negative symptoms, was significantly correlated with number of puffs per cigarette ($r = 0.69$, $p < 0.001$) and moderately negatively correlated with average puff volume ($r = -0.32$, $p = 0.04$). These results suggest that level of positive and negative symptoms may influence the manner in which patients with schizophrenia smoke, resulting in greater number of puffs per cigarette with lower puff volume and velocity.

Antipsychotic medication information was available for 48 patients with schizophrenia. Among those for whom this data was available, 91.6% were taking primarily atypical antipsychotic medications while only 4.2% were taking typical or 4.2% taking both typical and atypical antipsychotic drugs. Due to the low number of

individuals on typical antipsychotics alone, analyses by medication type were not implemented. However, medication dosages for both typical and atypical antipsychotic drugs were converted to chlorpromazine equivalent doses (CPZ) for additional, although exploratory, analyses; correlations between CPZ dose and smoking related measures were examined to determine if medication dosage in general influenced patients' smoking habits. CPZ dose was negatively associated with NDSS total score ($r = -0.37$, $p = 0.01$) such that greater medication dosage was related to lower self-reported nicotine dependence. The implications of this association are, however, difficult to interpret, as the direction of causation cannot be determined. In addition, although calculation of CPZ equivalents attempts to provide an overall description of medication dosage, the pharmacological effects of antipsychotic medications differ by class. Typical (e.g. haloperidol) and atypical (e.g. clozapine) drugs also appear to have opposite effects on smoking behavior (McEvoy, Freudenreich, McGee, VanderZwaag & Levin et al., 1995). The relationship between clinical variables and nicotine dependence may be better understood instead by examining the association between symptom ratings and smoking behaviors. As reported, the correlation between NDSS and BPRS scores was not significant. Thus, although the association between NDSS and CPZ equivalents is noted, limited interpretability precludes the use of CPZ values in further analyses.

Neurophysiological Markers of Information Processing

Patients with Schizophrenia

Within group analyses were conducted to examine the relationships between neurophysiological functions and smoking related measures in patients and controls separately. Although data were not available to characterize P50 gating performance for the healthy control participants, P50 data were available for the majority of patients with schizophrenia ($n = 46$) for analyses. Within the patient group, 26.1% ($n = 12$) were characterized as having “normal” gating, defined by a S2/S1 ratio of less than or equal to 0.50, and 73.9% demonstrated abnormal P50 gating performance with a mean P50 ratio of 0.75 ± 0.32 . When P50 gating was examined as a continuous measure in the full patient group, performance was not significantly correlated with either self-report measure of nicotine dependence or any biological index of nicotine consumption. P50 gating was also not significantly correlated with any smoking topography measure.

Patients with and without normal P50 gating were compared on self-report and biological indexes of nicotine dependence. There were no group differences on FTND or NDSS total scores ($p = 0.61$ and $p = 0.83$) and no significant differences in mean cotinine ($p = 0.82$) or nicotine boost ($p = 0.27$). Interestingly however, when smoking history and current habits were compared, patients with abnormal P50 gating reported currently smoking significantly more cigarettes per day (22.41 ± 9.91) with greater pack years (45.21 ± 26.62) compared to patients with normal P50 gating (14.50 ± 7.65 cigarettes per day and 28.39 ± 16.04 pack years) with $p = 0.016$ and $p = 0.045$ for each comparison respectively. Despite these differences within the patient

group, correlation analyses revealed no significant association between cigarettes per day or pack years with P50 gating performance when examined among the 46 patients for whom data were available.

Three measures of smooth pursuit eye movement were utilized for analyses. Closed loop pursuit gain (CLGN) provides an index of the extent to which eye velocity matches target velocity during a smooth pursuit eye tracking task. This measurement is obtained when the target is visible and is thus based on information projected directly onto the retina as well as a predictive extraretinal component, which is based on previous retinal velocity information held “on line” in memory. Predictive peak gain (PKG) is calculated from responses when target masking occurs at the beginning of a new initiated pursuit response; this measure is based on extraretinal motion signals from previous target and eye movement information. Similarly, residual predictive pursuit gain (PRGN) is based on extraretinal motion signals and is measured during target masking when the mask interrupts a continuously tracked (visible) target. All three pursuit variables were analyzed for target speeds of 18 and 25 degrees per second.

Interesting relationships between smoking and neurophysiological function emerged when these eye tracking data were examined within the patient group. Calculation of Pearson’s correlations yielded a significant association between both predictive pursuit gain at a target speed of 25 degrees/second (PRGN25) and predictive peak gain at 18 degrees/second (PKG18) and nicotine boost in the patient group with r values of -0.45 ($p = 0.003$) and -0.31 ($p = 0.04$) respectively. These results indicate that greater nicotine boost was associated with lower gain (poorer

performance) during memory guided smooth pursuit eye movement tasks.

Furthermore, PRGN25 was also significantly correlated ($r = 0.31$, $p = 0.03$) with NDSS total score in the patient group. When eye tracking functions were examined with respect to smoking topography, PRGN25 was also correlated with average puff volume ($r = 0.33$, $p = 0.02$) whereby greater puff volume was associated with greater gain (better performance). Similarly, average puff volume was positively correlated with closed loop gain at 25 degrees/second (CLGN25) with a correlation of $r = 0.29$ ($p = 0.045$).

Interestingly, the same smoking variables that were related to eye tracking performance variables were also associated with performance on the PPI task. For the patient group, inhibition of the startle response was calculated as the ratio of the peak response at a given inter-stimulus interval to a peak response during a pulse alone condition. For the patient group, pre-pulse inhibition was measured at 9 inter-stimulus-intervals: 30, 45, 60, 75, 90, 120, 180, 420, and 500 milliseconds. Pre-pulse inhibition at an inter-stimulus interval of 60 seconds ($PPI-60 = 0.54 \pm .35$) was associated with nicotine boost ($r = 0.37$, $p = 0.046$) whereby a higher PPI value, corresponding to poorer inhibition, was related to greater nicotine boost. Pre-pulse inhibition at an inter-stimulus interval of 75 seconds ($PPI-75 = 0.71 \pm 0.54$) was significantly correlated with NDSS total score ($r = 0.49$, $p = 0.007$), suggesting that poorer inhibition was related to greater self-reported nicotine dependence. For those measures associated with smoking behavior and nicotine exposure, regression analyses were conducted to determine the proportion of variance in the smoking measure of interest explained by neurophysiological performance. First, two

information processing variables were found to be significantly associated with NDSS total score. A linear regression model was tested to determine the proportion of variance in NDSS total score explained by predictive pursuit gain (PRGN25) and PPI at an inter-stimulus interval of 75ms (PPI-75). These measures were found to be uncorrelated with each other ($r = -0.28$, $p = 0.15$). Despite the significant correlation reported between NDSS and CPZ, the ambiguity surrounding the interpretability of CPZ values limits the utility of including CPZ as a predictor in the regression equation; CPZ equivalent was thus left out of this analysis. As no a priori hypotheses regarding the relative contributions of eye tracking and sensory gating measures were suggested, PRGN25 and PPI-75 were entered into the model together. The model was significant $R = 0.58$, $F(2, 25) = 6.43$, $p = 0.006$ whereby the eye tracking and pre-pulse inhibition variables predicted 34% of the variance in NDSS total score within the patient group. While PPI-75 was a statistically significant predictor in the model, $\beta = 0.58$, $t = 3.43$, $p = 0.002$, predictive pursuit gain (25 degrees/sec) narrowly failed to reach statistical significance as an independent predictor $\beta = 0.33$, $t = 1.97$, $p = 0.06$.

Second, a linear regression model was tested to estimate the amount of variance in nicotine boost explained by associated neurophysiological measures PKGN18, PRGN25, and PPI-60. Eye tracking and PPI measures were entered into the model all at once. The full model was significant, $R = 0.64$, $F(3, 22) = 5.05$, $p = 0.008$, whereby neurophysiological variables accounted for 40.8% of the variance in nicotine boost in the patient group. Due to the significant correlation between PKGN18 and PRGN25 ($r = -0.45$, $p = 0.002$), their individual beta weights could not

be interpreted. PPI-60, however, was uncorrelated with either eye tracking measure and appeared to be a significant independent predictor of nicotine boost, $\beta = 0.49$, $t = 2.95$, $p = 0.007$, in the full regression model.

Finally, two eye tracking measures, PRGN25 and CLGN25, were significantly associated with average puff volume as measured during the ad-libitum smoking session. Other factors that may have influenced topography variables, such as BPRS total score or nicotine withdrawal time were not included in the model, as there was no evidence that such relationships were significant in prior analyses. The eye tracking measures were significantly correlated with each other ($r = 0.58$, $p < 0.001$) and were entered together into a linear regression model to test the significance of their combined effect in predicting smoking behavior. The full model was statistically significant with $R = 0.35$, $F(2, 46) = 3.18$, $p = 0.05$ whereby eye tracking performance predicted 12.2% of the variance in puff volume within the patient group.

Healthy Controls

Prior evidence suggests that the pre-pulse inhibition effect is maximal at an inter-stimulus-interval of 120ms. Control subjects who were tested on the PPI paradigm as a part of this study were assessed utilizing this pre-pulse condition only. PPI was calculated for the 120ms condition as percent inhibition = $(\text{pulse alone response} - \text{pre-pulse 120ms response}) / \text{pulse alone response} \times 100$. Controls demonstrated a mean inhibition of $33.80\% \pm 29.0$. Calculation of Pearson's correlations for PPI-120 performance and nicotine dependence and smoking topography variables yielded no significant associations. Yet, it is interesting to note that the correlations in the control group were moderate in magnitude. The

correlations for PPI-120 within the control group were highest for average cotinine ($r = 0.57, p = 0.085$) and, similar to the results found in the patient group, nicotine boost ($r = -0.47, p = 0.17$) and NDSS total score ($r = -0.42, p = 0.23$), whereby greater inhibition was associated with greater cotinine levels, lower nicotine boost, and lower self-reported nicotine dependence.

Eye movement data were available for eight healthy controls for analyses. ANOVA comparisons were conducted to test the hypothesis that patients with schizophrenia would perform more poorly on smooth pursuit eye tracking measures relative to healthy controls. The results of these comparisons are illustrated in Table 4. Pursuit gain was consistently lower in the patient group; differences were most remarkable for predictive pursuit gain at both 18 and 25 degrees/sec.

Table 4. Smooth Pursuit Eye Movement

	Patients Mean (SD)	Controls Mean (SD)	P Value	Cohen's d
Closed Loop Gain 18	0.732 (0.182)	0.779 (0.124)	0.47	0.31
Predictive Pursuit Gain 18	0.419 (0.112)	0.588 (0.076)	<0.001	1.76 ^{***}
Peak Gain 18	0.472 (0.190)	0.609 (0.157)	0.60	0.79 ^{**}
Closed Loop Gain 25	0.666 (0.169)	0.767 (0.121)	0.11	0.69 ^{**}
Predictive Pursuit Gain 25	0.418 (0.102)	0.549 (0.086)	0.001	1.38 ^{***}
Peak Gain 25	0.466 (0.160)	0.506 (0.161)	0.52	0.25

** Medium Effect Size *** Large Effect Size

Within the control group, closed loop gain at 18 degrees/sec (CLGN18) was significantly negatively correlated with FTND total score ($r = -0.84, p = 0.01$) and with cigarettes per day ($r = -0.87, p = 0.005$). CLGN25 was also moderately negatively correlated with NDSS total score ($r = -0.69, p = 0.058$), but this association narrowly failed to reach statistical significance. Predictive peak gain at 25

degrees/sec (PKG25) was significantly negatively correlated with NDSS total score ($r = -0.79$, $p = 0.02$). In sum, these results indicate that lower levels of nicotine consumption and dependence are associated broadly with better eye tracking performance.

With respect to eye tracking measures and smoking topography, CLGN25 was significantly associated with average puff volume ($r = 0.86$, $p = 0.007$), puff duration ($r = 0.83$, $p = 0.01$), and puff velocity ($r = 0.77$, $p = 0.03$). In addition, PKGN25 was significantly associated with puff velocity ($r = 0.72$, $p = 0.05$), and PRGN25 with puff duration ($r = 0.73$, $p = 0.04$). These results indicate that, in the control group, more extreme smoking behaviors (i.e. greater puff volume, longer puff duration, and harder draw) are associated with better smooth pursuit eye movements when assessed at a target speed of 25 degrees/sec, which is the more difficult of the two eye tracking conditions. Regression analyses were completed for puff duration and for puff velocity to further examine the significance of these relationships.

First, a linear regression model was tested to determine the proportion of variance in puff duration explained by two associated eye tracking measures, CLGN25 and PRGN25. The full model was significant $R = 0.89$, $F(2, 5) = 9.77$, $p = 0.02$, whereby eye tracking measures together accounted for 79.6% of the variance in puff duration in the control group. CLGN25 and PRGN25 were moderately, although non-significantly, correlated with each other ($r = 0.55$, $p = 0.16$); CLGN25 reached significance as an independent predictor of puff duration, $\beta = 0.62$, $t = 2.58$, $p = 0.05$, although PRGN25 did not, $\beta = 0.38$, $t = 1.59$, $p = 0.17$. A second linear regression model was tested to determine the proportion of variance in puff velocity explained

by associated eye tracking measures. CLGN25 and PKGN25 were significantly correlated ($r = 0.76$, $p = 0.03$) and were entered together in the model. The model was not significant, $R = 0.79$, $F(2, 5) = 4.34$, $p = 0.08$, although the eye tracking measures accounted for 63.4% of the variance in puff velocity, as measured during the ad libitum smoking session. These results overall suggest that, among smokers in the general population, aspects of smoking behavior may have some neurobiological relevance, particularly associated with the mechanisms underlying the generation of smooth pursuit eye movements.

Chapter 6: Discussion

Prior research examining elevated rates of smoking and unique smoking habits among individuals with schizophrenia has aimed to distinguish whether nicotine dependence in this population is a primary characteristic of illness vulnerability, or secondary to other illness related factors. A review of the extant literature suggests that nicotine may serve a specific functional role for individuals with schizophrenia. Findings from a variety of research domains have demonstrated compelling links between $\alpha 7$ nicotinic cholinergic receptors and schizophrenia-related phenomenology including cognitive and neurophysiological deficits (Freedman et al., 1995; Denny-Brown & Fisher, 1976). It has been suggested that heavy smoking preferentially activates $\alpha 7$ receptors (Adler, Olincy, Waldo, Harris & Griffith et al., 1998). Consistent with the data characterizing their heavy use of and dependence on nicotine, it is plausible that individuals with schizophrenia smoke to activate the low affinity $\alpha 7$ nicotinic receptors and affect the neurophysiological processes they mediate. Patients with schizophrenia may thus utilize smoking and nicotine in order to self-medicate, or ameliorate, information processing dysfunctions that have been well characterized and associated with the illness.

Smoking Habits and Nicotine Dependence

The current study proposed to test the self medication hypothesis to explain the relationship between smoking habits and schizophrenia. To extend the findings in the current literature, this study utilized a three-pronged approach to characterize

nicotine use: (1) self-report measures of nicotine use and dependence, (2) biological measures of nicotine consumption, and (3) smoking topography. Patients with schizophrenia and community controls matched on smoking history were compared to address aspects of nicotine addiction as well as to investigate the specificity of the relationship between nicotine use and neurophysiological impairments to smokers with schizophrenia.

Schizophrenia patients and controls were well matched in terms of smoking history, including age of smoking initiation, smoking years, and number of quit attempts, as well as family history of smoking. Groups also reported currently smoking a roughly equal mean number of cigarettes per day. The first hypothesis, that smokers with schizophrenia would exhibit greater levels of nicotine dependence was supported by some self-report and biological measures of nicotine dependence. The Fagerstrom Test for Nicotine Dependence (FTND) is the most widely used measure of nicotine dependence, yet groups did not differ in the level of self-reported nicotine dependence based on the FTND in this study. Steinberg, Williams, Steinberg, Krejci and Ziedonis (2005) noted that in clinical populations, due to environmental restrictions placed on smoking behavior, FTND scores may underestimate actual level of nicotine dependence. Given the limited suitability of the FTND for hospitalized psychiatric patients (20% of the patients in this group), self-reported nicotine dependence may be better accounted for by the Nicotine Dependence Symptoms Scale (NDSS), the Heaviness of Smoking Index (HSI) derived from the FTND, or other biological indexes of nicotine consumption. The HSI is a concise measure consisting of two items derived from the FTND, concerning time to first

cigarette of the day and number of cigarettes smoked per day, while the NDSS assesses nicotine dependence from a broader perspective, taking into account regularity of smoking throughout the day, tolerance, symptoms of nicotine withdrawal, as well as amount smoked per day.

While small sample sizes likely influenced the extent to which group differences from ANOVA comparisons could be found, the effect sizes for the HSI and NDSS were in the medium range, thus providing some evidence to support the primary hypothesis. Furthermore, patients with schizophrenia demonstrated comparatively greater levels of blood plasma nicotine and its metabolite cotinine, with effect sizes in the medium to large range. While blood plasma nicotine levels index more immediate nicotine consumption, within a maximum of one to two hours, cotinine provides a more stable assay of nicotine use, as it has a longer half-life, averaging 16 hours, with an exposure detection range of three to five days (Benowitz, 1983). Blood plasma cotinine was significantly different between groups with an effect size in the large range. Cotinine was 1.4 times greater in patients than controls; this finding is consistent with that of Olincy et al. (1997) who reported 1.6 times greater urinary cotinine in patients relative to healthy smoker controls. Coupled with the finding that patients and controls reported smoking relatively equal numbers of cigarettes per day, the large difference in blood plasma cotinine between groups suggests that patients with schizophrenia extract more nicotine from smoking cigarettes than comparison controls.

Elevated levels of cotinine in smokers with schizophrenia is a finding that has been replicated and further investigated in other research groups as well. Williams,

Ziedonis, Abanyie, Steinberg, and Foulds et al. (2005) provided evidence that increased nicotine and cotinine levels in smokers with schizophrenia is not simply a metabolic effect, whereby rates of nicotine breakdown and clearance, as opposed to nicotine intake, would be accountable for these findings. Williams et al. (2005) reported elevated cotinine levels in patients with schizophrenia with no relationship to other markers of enzymatic activity. Furthermore, the authors reported little overlap between enzymes involved in nicotine and medication metabolism as well as a similar ratio of nicotine metabolites in patients and controls, all together suggesting that antipsychotic medications likely have no substantial effect on nicotine metabolism. The authors thus concluded that elevated nicotine and cotinine in patients with schizophrenia is likely due to increased inhalation and absorption from smoking.

It is interesting to note, in the present study, that cotinine was negatively related to the biological measures of nicotine intake and both self-report measures of nicotine dependence in the control group, while a positive relationship was found between cotinine and nicotine intake variables among the patients. This may be interpreted as indicating some differential threshold effect, whereby lower levels of consumed nicotine are subjectively satisfying and thereafter limit the amount of nicotine intake in normal smokers. Conversely, patients with schizophrenia not only extract more nicotine from cigarettes, but steady-state levels of cotinine in the bloodstream may not significantly moderate (i.e. attenuate) further smoking behavior. This interpretation would be consistent with the hypothesis that patients with schizophrenia and controls aim to achieve different outcomes from their smoking behavior (Russell, 1980): healthy smokers to achieve rapid rises in blood plasma

levels of nicotine, which is related to the subjective feeling of immediate reward, and patients to achieve and to maintain a high level of nicotine in the bloodstream to affect pathophysiological processes associated with the illness.

The mechanism by which patients with schizophrenia were predicted to achieve greater levels of nicotine intake was by the manner in which cigarettes were smoked. Thus, the second hypothesis tested in this study was that patients with schizophrenia would demonstrate more extreme smoking topography (greater number of puffs, larger puff volume, longer puff duration, shorter inter-puff interval, larger puff velocity, shorter overall smoking time) and greater nicotine boost during an ad libitum smoking session in the laboratory. Unexpectedly, group mean comparisons did not yield support for this hypothesis. Laboratory constraints may have, however, limited the extent to which these measures adequately captured the significance of smoking behaviors. For instance, some individuals may not extract a significant amount of nicotine from one cigarette alone, as was measured in this laboratory paradigm, but instead from smoking more than one cigarette or several in succession. In addition, the novelty of using the CRESS equipment and smoking through a mouthpiece may have altered smoking behavior during the one cigarette from which topography measures were obtained. In a study by Tidey, Rohsenow, Kaplan, and Swift (2005) topography measures were obtained by averaging the above parameters across a 90 minute ad libitum smoking session, during which participants were allowed to smoke as much as they preferred. Compared to controls, patients with schizophrenia demonstrated greater number of total puffs per 90 minute session, as well as greater number of puffs per cigarette, shorter inter-puff interval per cigarette,

and greater total puff volume. Although post session blood nicotine levels were not measured, in a separate study of non-psychiatric smokers, shorter inter-puff interval, higher total puff volume, and longer cigarette duration were most closely associated with blood nicotine level, with shorter inter-puff interval described as the strongest predictor of nicotine level compared to the other parameters (Bridges, Combs, Humble, Turbek & Rehm et al., 1990). Results from Tidey et al. (2005) unfortunately, also found inter-puff interval to have the lowest test-retest reliability of all smoking topography variables.

The values for individual topography parameters are difficult to compare between this and the Tidey et al. (2005) study due to dramatic differences in testing paradigms and patient characteristics. For inclusion in the Tidey et al. study, participants were required to smoke at least 20 cigarettes per day and to score 6 or higher on the FTND. In contrast, participants in this study reported lower levels of cigarette consumption and only moderate levels of nicotine dependence. It may be the case that smoking topography is less reliable among those with lower levels of nicotine use, but there are no data to currently support this. For additional consideration, while 50% of the patients in the Tidey et al. sample were taking atypical antipsychotics, which was associated with fewer cigarettes per day, lower FTND scores, and had medium to large effects on topography parameters, 91.6% of patients in the current study were taking atypical antipsychotic drugs. Prior evidence has suggested that the pharmacological effects of clozapine, an atypical antipsychotic drug, reduce tobacco use in patients with schizophrenia (McEvoy et al., 1995b). Fifteen patients in this sample were receiving clozapine as opposed to other

antipsychotic medications. Consistent with the findings of Tidey and colleagues, patients receiving clozapine in this study reported lower levels of nicotine dependence and reported smoking fewer cigarettes per day than those on other antipsychotic medications. As medication type was limited with respect to the effects on other outcome measures, formal consideration of medication type was not included in statistical analyses. Yet, medication type can be considered as a potential confound, and may have further affected the results presented here. That the correlations between topography measures showed similar relationships in patients and controls, however, provides some confidence that aspects of the smoking topography paradigm did not itself introduce measurement error and account for the lack of significant differences across groups.

Despite the limitations of the smoking topography paradigm in this study, the results of the effect size comparisons provide evidence that patients with schizophrenia exhibit some differences in smoking behaviors relative to controls. Additional mechanisms by which patients are hypothesized to extract more nicotine from cigarette smoking is the depth of inhalation or the amount of smoke held in the lungs, and/or occlusion of the cigarette filter by the lips or fingers (Olincy et al., 1997), which were not assessed in this study. If patients and controls were to extract different amounts of nicotine by such behaviors, we would have expected patients to show greater nicotine boost from the ad libitum session, regardless of the topography measures. Nicotine boost was, however, equivalent between patients and controls. While five minutes has been previously demonstrated as adequate time for nicotine levels to peak in the bloodstream (Armitage, Dollery, George, Houseman & Lewis et

al., 1975), it is possible that different rates of immediate nicotine metabolism between patients and controls or other limitations of the ad libitum paradigm (e.g. novelty of the situation, use of a mouthpiece) may have contributed to these negative results. Based on the findings from Tidey et al. (2005) and the limited results presented here, further examination of smoking topography variables in contributing to nicotine inhalation and absorption in patients with schizophrenia is warranted.

Additional research may also investigate how facets of the illness may affect smoking topography in different ways. In the results presented here, positive and negative symptoms were shown to be related in patients to greater number of puffs per cigarette but also to lower puff volume and velocity. As lower puff volume and velocity in relation to greater symptom levels was an unexpected effect, replication and further examination of the relationship between symptoms and smoking behaviors is warranted. These results also demonstrate how individual smoking topography variables might interact to predict outcomes; rather than considering each topography parameter with respect to nicotine dependence alone, greater consideration might be given to interpreting individual measures in relation to each other. In sum, effect size comparisons between patients and controls yielded some support for the hypothesis that patients with schizophrenia exhibit greater levels of nicotine dependence than smokers in the general population. Differences in blood plasma cotinine provided the most convincing evidence to suggest that patients with schizophrenia extract more nicotine from cigarette smoking than controls. The hypothesis that greater nicotine intake is achieved through individual topography parameters received only limited support from these data. Constraints imposed by the

ad libitum smoking paradigm may have affected the extent to which significant smoking behaviors and outcomes were accurately assessed. Finally, antipsychotic medications, with respect to dosage and medication type, may have further influenced dependence and topography outcomes, although difficulties in interpreting medication effects precluded formal consideration in accounting for the results of this study.

Neurophysiological Functioning

The self medication hypothesis asserts that patients with schizophrenia use smoking to deliver therapeutic doses of nicotine to restore altered nicotine receptor functioning, leading to improved cognitive functions. To test the specificity of the link between patterns of nicotine use and neurophysiological markers of dysfunctional information processing to schizophrenia, three paradigms previously shown to be affected by laboratory administration of nicotine were utilized: smooth pursuit eye movements, P50 gating, and pre-pulse inhibition of the acoustic startle response. Although this study originally intended to test the hypothesis that patients with schizophrenia will, first and foremost, demonstrate impaired neurophysiological performance compared to controls, only smooth pursuit eye movement data were comparably collected in the two groups to allow for such comparisons to be made. Consistent with prior reports of eye tracking dysfunction, measures of closed loop gain, residual predictive pursuit gain, and peak predictive pursuit gain, obtained during a ramp-mask-ramp procedure, were lower in the patient group compared to controls. Analysis of variance yielded significant group differences for residual

predictive pursuit gain measures, and effect size comparisons for other eye tracking measures yielded medium effects for closed loop and peak predictive pursuit gain.

Residual predictive, and peak predictive pursuit gain are based on extraretinal motion signals, while closed loop gain combines a predictive extraretinal component with the processing of motion information projected directly onto the retina. The data presented here provide further support for a hypothesized deficit in the extraretinal component of smooth pursuit eye movement, which has also been reported in prior studies (Thaker et al., 1996; Thaker et al., 1999; Thaker, Avila, Hong, Medoff & Ross et al., 2003). Extraretinal motion signals arise from information integrated by the frontal eye fields, stemming from posterior parietal and medial superior temporal neuroanatomical correlates (Avila et al., 2002). Identification of a specific neurophysiological abnormality, such as extraretinal motion processing, is informative in characterizing underlying dysfunctions in neural circuitry associated with the pathophysiology or genetic risk for schizophrenia. Indeed, studies in non-psychotic first-degree relatives of patients with schizophrenia have found evidence for a similar deficit specific to predictive pursuit gain, thereby suggesting a genetic association (Thaker et al., 1998).

Smoking and Neurophysiological Markers of Information Processing

The self medication hypothesis predicts that if functional deficits resulting from abnormalities in nicotine receptors are remediated by self administration of nicotine, then poorer neurophysiological performance would most likely be associated with greater nicotine consumption, greater nicotine dependence, and more extreme smoking behaviors. As information processing functions have been found to

be poorer among patients with schizophrenia than among healthy controls, these associations were predicted to be more robust in the patient, as compared to the control group in this study.

The results of the present study contribute to the self medication hypothesis in demonstrating that poorer neurophysiological function in patients with schizophrenia is coupled with greater self-administration of nicotine. Greater immediate nicotine intake and self-reported nicotine dependence were associated with poorer predictive pursuit measures and poorer sensorimotor gating. Neurophysiological variables together accounted for significant variance in nicotine intake and dependence, thereby extending previous findings of nicotine induced improvements in smooth pursuit eye movement and pre-pulse inhibition functions measured in laboratory paradigms. Whereas prior studies have found normalization of eye movement functions associated with pursuit initiation and closed loop gain, which indicate nicotinic effects on retinal motion information processing, the present study demonstrated an association of nicotine intake with eye movement functions related to the processing of extraretinal motion among patients with schizophrenia. In addition, prior studies have examined the effects of controlled laboratory administered doses of nicotine, and may better reflect the immediate impact of nicotine on cognitive functions. In this study, performance and nicotine intake measures were obtained at different points in time. The associations reported may thus be more generalizable, reflecting the relationship between individual differences in smoking behaviors or smoking patterns and neurophysiological dysfunction.

It is surprising that no relationships were found between smoking and P50 gating, which has been the most studied neurophysiological measure with respect to the involvement of nicotinic receptor functioning. Temporary normalization of P50 gating deficits is thought to involve nicotinic receptors in the hippocampus; reduced numbers of two kinds of nicotine receptors, low affinity $\alpha 7$ and high affinity $\alpha 4/\beta 2$, have been found in post mortem brain tissue of schizophrenic patients (Freedman et al., 1995) and genetic linkage studies have found specific associations between P50 sensory gating and the $\alpha 7$ nicotinic receptor in families affected by schizophrenia (Freedman et al., 1997).

Patients in this study demonstrated markedly impaired sensory gating, and the proportion of patients showing abnormal P50 gating in this sample (73.9%) was relatively equal to the proportion of patients with schizophrenia showing gating deficits reported in the literature (> 75%; Leonard, Breese, Adams, Benhammou & Gault et al., 2000). Thus it does not appear as though task performance likely influenced the negative results reported here. Despite the lack of significant correlations found between P50 gating performance and indexes of nicotine dependence in this study, it is interesting to note that when the patient group was split between those with and without abnormal gating performance, those with abnormal P50 gating reported smoking a significantly greater number of cigarettes per day. This finding provides some, albeit weak, support for a link between nicotine intake and sensory gating aspects of neurophysiological dysfunction in this study.

The relationships demonstrated between neurophysiological functions and measures of nicotine consumption in the healthy control smokers may be informative

in further interpreting the results found within the patient group. In the control group, associations between neurophysiological functions and self-reported nicotine dependence and nicotine intake were negative, such that their poorer performance was associated with greater levels of self-reported nicotine dependence and consumption. These associations were, unexpectedly, large and significant. Contrary to expectations, these results suggest that relationships between markers of information processing and nicotine dependence may not be specific to patients with schizophrenia.

Interestingly, both patients and controls demonstrated moderate negative associations between Nicotine Dependence Symptoms Scale total score, nicotine boost, and pre-pulse inhibition. Whereas patients demonstrated similar associations between eye tracking performance and nicotine intake, eye tracking measures appeared to be more strongly associated in controls with self-reported nicotine dependence than other biological indexes. This may be interpreted as reflecting a dissociation between patients and controls in how actual nicotine consumption influences neurophysiological functions. However, within-control group analyses yielded strong predictive effects for smoking topography variables in relation to all smooth pursuit eye movement measures assessed, whereby more severe smoking behaviors were associated with better eye tracking performance. In this study, greater puff duration and, to a lesser extent, greater puff volume were positively associated with nicotine boost within the control group. Thus, indirectly, these results may indicate that greater nicotine consumption via smoking behaviors is associated with better eye tracking function in non-psychiatric controls, despite the fact that better eye

tracking performance was also related to lower nicotine dependence by self report. Thus, there tends to be a disjunction between self-reported and some biological indexes of nicotine consumption in their associations with neurophysiological performance in the control group.

In contrast to the negative associations found between nicotine and pre-pulse inhibition in the control group, it is intriguing to again note the moderate positive correlation ($r = 0.57$) between blood plasma levels of cotinine and PPI performance. This finding is consistent with the observation that cotinine was inversely related to other self-report and biological indexes of nicotine dependence including nicotine boost among the controls. The observation made in this study that healthy smokers appear to moderate the amount of nicotine intake based on pre-existing systemic levels of nicotine or cotinine, its metabolite, may reflect the ability of non-psychiatric smokers to regulate aspects of nicotine receptor function. Perhaps it is due to such self regulatory behavior that non-psychiatric smokers, compared to patients with schizophrenia, report lower levels of nicotine addiction.

As indicated by the strong association found between smoking topography and neurophysiological variables, healthy smokers may also be better able to use smoking behaviors and nicotine intake to enhance some neurophysiological functions. This appears to be the case particularly with eye tracking performance, whereby lower severity of self-reported nicotine dependence but more extreme smoking topography measures, possibly indicating greater immediate nicotine intake, were related to better closed loop, peak predictive pursuit, and residual pursuit gain. With respect to PPI, nicotine intake and self-reported severity of nicotine dependence were

both inversely related to performance, but this was also coupled with a moderate positive correlation of better pre-pulse inhibition performance with greater blood plasma cotinine, suggesting a moderating effect of prior nicotine intake and steady levels of nicotine, or cotinine, in the system. Although both PPI and smooth pursuit eye movement performance were inversely correlated with nicotine intake and severity of self-reported nicotine dependence in patients with schizophrenia, these associations were smaller in magnitude, suggesting a looser coupling of nicotine use and neurophysiological markers of information processing.

Differences in nicotinic receptor number may provide some insight into the type of mechanism underlying differences in smoking behaviors in patients and controls. Patients with schizophrenia show a 40% reduction in levels of low affinity $\alpha 7$ nicotinic receptors in the CA3 region of the hippocampus, a site which animal models have demonstrated to be involved in auditory gating mechanisms (Leonard, Gault, Adams, Breese & Rollins et al., 1998). This nicotinic receptor abnormality is thought to link smoking and auditory gating dysfunction in schizophrenia. Low affinity receptors are not the only potential link between smoking and schizophrenia, however. A dose-dependent increase in high affinity nicotine receptor number has been reported in the thalamus and hippocampus of normal smokers compared to normal non-smokers or smokers who had quit, such that greater long term smoking history (pack years) and greater recent smoking behavior (packs per day) have been shown to be associated with up-regulation of nicotine receptors in post-mortem brain tissue (Breese et al., 1997). This regulatory mechanism is thought of as a response to nicotine receptor desensitization with repeated stimulation and is presumed to

underlie nicotine tolerance and addiction (Breese et al., 1997). Yet individuals with schizophrenia show a decrease in high affinity receptors in the hippocampus, cortex, striatum, and thalamus (Breese et al., 1997) and, moreover, smokers with schizophrenia exhibit lower levels of high affinity receptor up-regulation than controls, regardless of smoking level. It is unclear why this up-regulation does not occur as it does in non-psychiatric smokers, whether it is the rate of receptor desensitization or rate of up-regulation that is dysfunctional, for example. Nonetheless, the adaptive dose-dependent response to nicotine consumption appears to be absent or impaired in patients with schizophrenia. Both basal levels of nicotine receptors and mechanisms of up-regulation could contribute to individual differences in sensitivity to reward, persistence of smoking behavior, and severity of nicotine addiction (Collins, 1990).

Although sensory gating deficits have been most strongly associated with $\alpha 7$ nicotine receptor functioning, George and colleagues recently demonstrated that smoking induced enhancement of PPI function is blocked by a nicotinic receptor antagonist mecamylamine, which binds to $\alpha 4/\beta 2$, $\alpha 3/\beta 4$, $\alpha 3/\beta 2$, as well as $\alpha 7$ nicotinic receptors (George, Termine, Sacco, Allen & Reutenauer et al., 2006). Thus, smoking may alter abnormal neurophysiological function in schizophrenia through mechanisms other than the $\alpha 7$ nicotinic receptor. Other evidence has suggested a role of these additional nicotine receptors in mediating the beneficial effects of cigarette smoking on cognitive dysfunctions, such as in spatial working memory and sustained attention associated with schizophrenia (Sacco, Termine, Seyal, Dudas & Vessicchio et al., 2005). In sum, a generalized abnormality in nicotinic receptor functioning (i.e.

reduced receptor number, abnormal regulation) may lead to greater nicotine consumption and higher reported levels of nicotine dependence in patients with schizophrenia. The nicotinic receptor abnormality may not, however, be limited to the $\alpha 7$ nicotinic receptor, as originally proposed, and the dysfunctional processes that cigarette smoking is presumed to remediate may not be limited to sensory gating or eye tracking functions. Furthermore, because healthy smokers undergo changes in nicotine receptors which mediate cognitive and neurophysiological processes, associations between smoking and such functions may not be specific to patients with schizophrenia.

Considering the findings presented here in the context of prior animal models and human molecular biology research, neurobiological mechanisms of nicotinic receptor function and regulation appear to deserve additional research attention in testing the self medication hypothesis of smoking and schizophrenia. Further clarification of which neurophysiological processes are affected by specific aspects of smoking behaviors, nicotine receptors, and nicotinic regulatory mechanisms (or vice versa), and how these processes interact is warranted. Furthermore, the relatively smaller proportion of variance in smoking measures explained by neurophysiological performance in the patient group signifies that, while cognitive or neurophysiological dysfunction may contribute to smoking behaviors, there are additional factors that contribute to the smoking phenomenon observed among patients with schizophrenia.

Limitations and Future Directions

The greatest limitation of this study was the small sample size of the comparison control group. Due to a lack of power, ANOVA and correlational comparisons may have underestimated the extent to which patient and control smokers differed on various dimensions of nicotine dependence, and the degree to which associations between measures could be demonstrated and compared between groups. To compensate for this methodological shortcoming, effect size estimates were used when possible to demonstrate differences between groups and the magnitude of within group correlations were carefully considered in making inferences and drawing conclusions about the data. However, significant caution must be taken in regard to these inferences and conclusions, since the study findings were largely integrated on the basis of non-significant results.

A second methodological flaw in this study is that patient and control data were not collected simultaneously. Although the patient data alone was collected across the span of one to two years, that control data were collected at a separate time all together introduces the possibility of significant confounds and potential unknown sources of error. Changes in laboratory equipment, data reduction strategies, or other more subtle changes in procedures or lab personnel may have had significant and unpredictable effects on the data collected. Furthermore, although procedures were designed to minimize either withdrawal or acute nicotine effects on neurophysiological assessment, data on time of last cigarette were not obtained so as to systematically control for the effects of nicotine consumption on P50, eye tracking, and pre-pulse inhibition performance. Timing effects of administration of nicotine

and nicotine withdrawal are crucial to understanding neurophysiological dysfunction in patients with schizophrenia. Acute nicotine administration can have a significant effect on ameliorating deficits in sensory gating and some eye tracking functions. Nicotine administration may also differentially affect some neurophysiological functions in non-psychiatric controls (e.g. P50 gating, smooth pursuit initiation) whereby nicotine has no effect or even the opposite effect in comparison to the effects of nicotine in patients (Adler et al., 1993; Sherr et al., 2002). The inability to systematically control for time of last cigarette poses a significant challenge to the interpretation of the measures of neurophysiological function between groups, and the relationships within groups among nicotine dependence indexes and neurophysiological markers of information processing.

In addition to methodological limitations, it is important to note that patients with schizophrenia tended to report lower levels of nicotine dependence in this sample as compared to other patient samples. Prior research has frequently characterized smoking behaviors and indexes of nicotine consumption among individuals with high levels of nicotine dependence, as measured by a Fagerstrom Test for Nicotine Dependence total score of greater than or equal to 6, or a minimum number of cigarettes per day. More moderate levels of nicotine dependence and smoking patterns in the current patient sample may have affected the ability to characterize smoking topography in relation to nicotine dependence. In addition, the differences observed in the magnitude of the associations between smoking and neurophysiological functions between patients and controls may be moderated by level of nicotine dependence. It may be the case, for example, that the strength of

associations between indexes of nicotine dependence and neurophysiological functions are greater in a sample of more highly addicted individuals.

A significant drawback to the overall approach used in the current study is that the analyses were largely correlational. While associations between the data were suggestive of relationships relevant to the self medication hypothesis of smoking and schizophrenia, causal pathways could not be tested, whereby other illness-related factors, such as symptom and medication levels, or methodological considerations, such as the timing of nicotine use as mentioned above, could be better accounted for. Further within-group analyses may be warranted before relationships among measures of nicotine dependence and neurophysiological functioning between patients with schizophrenia and controls are compared.

With respect to future directions, data collection is currently ongoing for both healthy controls and patients with schizophrenia. Design considerations for future studies, however, should attempt to remedy some of the methodological weaknesses of the current study. First, the potentially confounding effects of additional individual difference variables such as cigarette type, nicotine yield, and time since last cigarette with respect to neurophysiological testing should be systematically measured and accounted for in data analyses. Second, alterations to the smoking topography paradigm may be implemented such as a longer ad libitum smoking session, which would allow for repeated measurement of topography parameters. Repeated measurement would not only provide the opportunity to gather reliability data, but would also allow for situational variables, such as novelty of the smoking paradigm, to be accounted for, as well as for variables, shown in previous studies to be more

strongly associated with actual nicotine intake, to be obtained. Third, collecting more than one post-smoking blood sample from which to obtain multiple measures of blood plasma nicotine may be considered for future studies. This may better account for individual differences in the rate of metabolism between subjects and may therefore provide a more accurate assessment of nicotine boost as a result of self administered nicotine.

Finally, future studies might consider expanding the inclusion criteria for subject recruitment. This study excluded individuals with significant substance use history, which may have resulted in the recruitment of a biased less heterogeneous sample, and a less severely addicted group. Expansion of the sample to include those with a history of significant substance use may also allow for additional comparisons to be made such that the specificity of the relationships between neurophysiological functions and measures of addiction to nicotine could be tested. Considering addiction to other substances might significantly impact current theories which attempt to account for the relationship between smoking and schizophrenia, such as the self medication hypothesis.

Additional explanations for the remarkably high prevalence of smoking and nicotine addiction in schizophrenia should be considered for future research. Behavioral genetics studies of smoking and schizophrenia may lead to the development of new theories or help to refine already existing hypotheses such as those addressed by the current study. Both genetic and environmental factors have considerable influence on rates of smoking initiation. Yet, a greater genetic component has been demonstrated in explaining the transition from smoking

initiation to nicotine dependence; heritability estimates for initiation and progression to nicotine dependence are approximately 60 to 70% (True, Heath, Scherrer, Waterman & Goldberg et al., 1997; Sullivan & Kendler, 1999). Whether genetic effects on nicotine dependence are higher among patients with schizophrenia than among non-psychiatric smokers in the general population is currently unknown. Genetics studies may provide further insight into how nicotinic receptor number and mechanisms of receptor regulation may influence nicotine addiction and smoking behaviors. Genetics research may also shed more light on which nicotine receptors are more or less responsible for nicotine addiction, on the common mechanisms underlying nicotine and neurophysiological functions, and the neurobiological mechanisms underlying the observed relationship between smoking and schizophrenia.

Concluding Remarks

As smoking is a lethal but preventable cause of disease and premature death, the extremely high rate of smoking among individuals with schizophrenia poses a significant health risk to the population and compounds the burden of this devastating mental illness. Understanding the link between smoking and schizophrenia may not only have implications for understanding neuropathological processes associated with the vulnerability to and manifestation of the illness, but characterizing behavioral and biological links between nicotine dependence and schizophrenia may aid in the design of new treatment strategies. If patients with schizophrenia utilize nicotine to remediate symptoms, cognitive, or neurophysiological aspects of the illness, then nicotine replacement therapies could be used rather than cigarettes to fulfill this

function. Characterizing individual differences in smoking and nicotine dependence among patients with schizophrenia will aid in designing appropriate replacement therapies such that dosages and schedules of administration would most closely match the needs of the patients who use them. While this study provided some support for the self medication hypothesis of schizophrenia, further research on the influence of neurophysiological variables and neurobiological regulatory mechanisms on smoking and nicotine dependence in schizophrenia is warranted.

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