

ABSTRACT

Title of Document: SUSCEPTIBILITY TO SMOKING AND
NICOTINE DEPENDENCE IN
SCHIZOPHRENIA

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Evidence suggests that high nicotine dependence observed in schizophrenia is related to its core neuronal deficits such as abnormalities in neural synchronization and sensory gating. Some of these neuronal deficits are shown to mark schizophrenia liability, raising the possibility that the increased nicotine dependence in schizophrenia is related to its etiological factors. This study sought to investigate mechanisms of increased vulnerability to smoking and nicotine dependence in schizophrenia. The individual and interacting effects of familial vulnerability factors, neurophysiological function, and resting cortical oscillatory activity (i.e. resting EEG power) were examined. The study sample was composed of four groups including outpatients with schizophrenia, first-degree relatives of patient index probands, healthy comparison control subjects from the community, and first-degree relatives of control probands. The resulting data demonstrated a pattern of more persistent nicotine use and greater dependence among those with schizophrenia relative to non-psychiatric comparison controls. Persistent smoking was also demonstrated to be

highly heritable across groups with no discernable difference in the extent to which smoking is familial in those affected or unaffected by schizophrenia. With respect to resting oscillatory activity, analyses failed to find diagnostic group differences in EEG power for the alpha, beta, and gamma frequency bands and, unlike other substances of abuse, past and present nicotine use did not have a reliable effect on power in the beta frequency band. Rather, power in the gamma frequency band was significantly associated with smoking status. Furthermore, smoking was uniquely related to neurophysiological processes in probands with schizophrenia, suggesting that smoking status should be assessed in any study of information-processing dysfunction in this population. When all putative susceptibility factors were considered together, diagnosis of schizophrenia and family history of smoking best captured what may be characterized as an underlying (i.e. neurobiological) vulnerability to nicotine dependence, rather than circumscribed indices of electrophysiological functioning. Future studies might be implemented to refine the association between smoking and indices of electrophysiological function and, importantly, relate diagnostic or electrophysiological susceptibility factors to mediating processes and observable behaviors associated with aberrant patterns of nicotine use and dependence in persons with schizophrenia.

SUSCEPTIBILITY TO SMOKING AND NICOTINE DEPENDENCE IN
SCHIZOPHRENIA

By

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Dedication

I am eternally grateful to my father for the life lessons he provided. The values he projected instilled in me an appreciation for learning and hard work, and it is from him that I continue to find inspiration to strive towards realizing my full capability. This paper is dedicated to him.

A teacher by nature and profession, my father taught me how to be resourceful, to lead by example, how to draw from those around me for support and encouragement, and to help others in turn by reinforcing their inherent strengths. He was committed to honoring his obligations, and demonstrated humility and balance in exercising personal responsibility for his family and work. I learned from him to always pursue my interests with industry, fervor, and determination. By his example, I have aspired to set ambitious goals, and intend to persevere in following them through.

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Table of Contents

Dedication	ii
Acknowledgements.....	iii
Table of Contents.....	iv
List of Tables	vi
List of Figures	vii
Chapter 1: Introduction.....	1
Smoking and Nicotine Dependence in Schizophrenia.....	1
Prevalence.....	1
Phenomenology.....	3
Vulnerability to Nicotine Use.....	5
Molecular Links to Nicotine Systems.....	5
Cognitive and Neurophysiological Links to Nicotine	7
The Self-Medication Hypothesis of Smoking and Schizophrenia.....	10
An Alternative Electrophysiological Approach to Studying Nicotine Use in Schizophrenia.....	12
Pathophysiological Perspective on Smoking and Schizophrenia	12
Cortical Oscillatory Activity.....	15
Cortical Oscillatory Activity in Schizophrenia.....	16
The Significance of Beta Band Activity	21
Susceptibility to Alcohol Use	21
Substance Use and Smoking in Schizophrenia.....	28
Genetic Contributions to Nicotine Use.....	31
Building a Working Model of Smoking and Schizophrenia.....	33
Chapter 2: The Current Study.....	36
Rationale	36
Specific Study Aims and Hypotheses.....	37
Additional Considerations	41
Current versus Past Smoking	41
Other Substance Use.....	42
Psychotropic Medication	42
Direct Effects of Smoking	43
Chapter 3: Methodology	45
Procedures.....	46
Participants.....	46
Recruitment.....	47
Study Assessments.....	48
Diagnostic Assessments.....	49
Smoking and Nicotine Dependence Assessments	50
Electrophysiological Assessments	53
Chapter 4: Results	57
Participants.....	57

Specific Aim 1: Smoking and Nicotine Dependence	59
Smoking Prevalence.....	59
Nicotine Dependence	61
Familial Patterns of Nicotine Use	62
Summary of Main Findings: Specific Aim 1	64
Specific Aim 2: Smoking and Bandpower in Resting EEG	65
Specific Aim 2: Post-Hoc Analyses.....	70
Effects of Nicotine Dependence on Bandpower	70
Effects of Medication on Bandpower	72
Summary of Main Findings: Specific Aim 2.....	73
Specific Aim 3: Relationships Among Putative Susceptibility Factors.....	74
P50 Gating	74
Working Model of Susceptibility to Smoking and Nicotine Dependence.....	78
Summary of Main Findings: Specific Aim 3.....	79
Chapter 5: Discussion	81
Smoking and Nicotine Dependence.....	82
Sample Characteristics.....	82
Heritability Analyses	84
Electrophysiological Function and Smoking.....	88
EEG and Smoking Status.....	88
EEG and Schizophrenia	92
Predictors of Smoking.....	99
Summary of Findings: Specific Aim 3	100
Summary of Limitations and Future Directions	102
Limitations of the Research Sample	102
Limitations of the Methodology	104
Conclusion	106
Appendices.....	108
Appendix A.....	108
Neural Oscillations.....	108
CNS Imbalance	110
Disinhibition and Schizophrenia.....	112
Appendix B	114
Nicotine Dependence Assessment	114
Bibliography	116

List of Tables

Table 1. Family Unit Descriptives: Heritability Analyses for Smoking History

Table 2. Mean Log Transformed Bandpower (μV^2) and Diagnosis

Table 3. Mean Log Transformed Bandpower and Smoking Status

Table 4. Bandpower Differences Between Current and Former Smokers

Table 5. Repeated Measures ANOVA Bandpower Comparisons

Table 6. Post-Hoc Bandpower Comparisons

Table 7. Mean P50 Ratio

List of Figures

Figure 1. Demographic Characteristics

Figure 2. Smoking Status

Figure 3. Nicotine Dependence

Figure 4. Group by Smoking Status Interaction for P50 Ratio

Chapter 1: Introduction

Smoking and Nicotine Dependence in Schizophrenia

Prevalence

Elevated rates of tobacco use and nicotine dependence in psychiatric populations are well-established research findings (Hughes, Hatsukami, Mitchell, and Dahlgren, 1986; Foulds, 1999). Moreover, prevalence of smoking among individuals diagnosed with schizophrenia is particularly high, with smoking rates reported between 70 and 90% (Diwan, Castine, Pomerleau, Meador-Woodruff, & Dalack et al., 1998; Glassman, 1993; Glynn & Sussman, 1990; Goff, Henderson, & Amico, 1992; Hughes et al, 1986; Kelly & McCreadie, 1999; de Leon, Dadvand, Canuso, White, Stanilla, & Simpson, 1995; Llerena, la Rubia, Penas-Lledo, Diaz, & de Leon, 2003; Worthington, Fava, Agustin, Alpert, Nierenberg, & Pava, et al., 1996; Ziedonis, Kosten, Glazer, & Frances, 1994), in contrast to the prevalence rate for smoking in the general population, estimated at 22.5% (Lasser, Boyd, Woolhandler, Himmelstein, McCormick, & Bor, 2000; Lethbridge-Cejku, Schiller, & Bernadel, 2004). Smoking among individuals with schizophrenia poses a significant health risk to this population. Evidence suggests a two-fold increase in mortality rates due to smoking related diseases (e.g. lung cancer, circulatory and respiratory diseases, risk of cardiovascular disease) directly associated with lifetime tobacco use in patients with schizophrenia compared to the general population (Brown, Inskip, & Barraclough, 2000; Curkendall, Mo, Glasser, Rose, Stang, & Jones, 2004; Goff, Cather, Evins, Henderson, Freudenreich, Copeland et al., 2005). Driven by the

epidemiological findings of elevated rates of smoking and further motivated by the significance of the consequent health implications, a large literature has developed to characterize and examine the association between nicotine use and schizophrenia.

Examination of factors associated with smoking habits among those with schizophrenia has aimed to distinguish whether smoking in this population is a primary characteristic associated with the illness, or secondary to illness-related factors such as symptoms, chronicity of illness, or medication. Empirical evidence suggests that increased rates of smoking appear to be independent of socio-demographic risk factors such as age, gender, race, or socioeconomic status (Diwan et al., 1998; Hughes et al., 1986; de Leon, Tracy, McCann, McGrory, & Diaz, 2002b). According to self-report, motivational factors behind smoking appear to be similar among smokers in the general population and smokers with mental illnesses including schizophrenia (e.g. relaxation, arousal) and thus do not account for the disparity in smoking prevalence rates (Glynn & Sussman, 1990). Furthermore, high rates of smoking among individuals with schizophrenia are not limited to inpatients or the chronically ill; elevated rates of smoking are found consistently among both inpatients and outpatients with schizophrenia (de Leon et al., 1995). In addition, hospitalized patients with schizophrenia, despite sharing environmental influences with patients affected by other illnesses (e.g. chronic mood disorders), comparatively demonstrate elevated smoking rates (de Leon, Diaz, Rogers, Browne, & Dinsmore, 2002a). Smoking among patients with schizophrenia often appears to precede the onset of illness, prior to hospitalization (Kelly & McCreadie, 1999); smoking initiation has been found to occur prior to antipsychotic drug exposure (Goff et al.,

1992), and in first-episode patients with fewer than 30 day's exposure to antipsychotic medications (McEvoy & Brown, 1999).

Phenomenology

Increased rates of smoking among individuals with schizophrenia are not effectively explained by factors secondary to illness presentation or treatment. In addition to elevated prevalence rates of smoking, evidence suggests that schizophrenia patients are aberrantly heavy smokers, smoking a significant number of cigarettes per day (e.g. 25 or greater; Kelly & McCreadie 1999). Comparisons suggest that individuals with schizophrenia smoke a greater number of cigarettes per day than smokers in other psychiatric populations (de Leon et al., 1995) and smokers in the general population (Herran, de Santiago, Sandoya, Fernandez, Diez-Manrique, & Vazquez-Barquero, 2000). In addition, smokers with schizophrenia appear to exhibit unique smoking patterns, as given by observations of smoking cigarettes with greater nicotine content, smoking more of the cigarette (i.e. down to the filter), and inhaling more deeply than smokers without schizophrenia (Lohr & Flynn, 1992). Such behavioral observations have been further validated by quantitative data demonstrating that smokers with schizophrenia inhale with greater puff volumes, take a greater number of puffs per cigarette, and smoke with shorter inter-puff interval per cigarette than healthy comparison smokers (Tidey, Rohsenow, Kaplan, & Swift, 2005); these measures together support the observations that individuals with schizophrenia exhibit smoking behaviors that are different and more “intense”. In addition to aberrant smoking behavior patterns, smokers with schizophrenia report higher levels of nicotine dependence than smokers in the general population (de Leon

et al., 2002b). Greater levels of nicotine dependence are coupled with a low desire to quit (Kelly & McCreadie, 1999), low spontaneous quit rates (de Leon, 1996), and unsuccessful structured quit attempts, with studies reporting 6 month abstinence rates as low as 12% following smoking cessation programs (Addington, el-Guebaly, Campbell, Hodgins, & Addington, 1998; Zeidonis & George, 1997). This contrasts with successful quit rates of smokers from other populations whereby structured smoking cessation programs have resulted in quit rates upwards of approximately 40% in smokers from the general population and between 18 and 32% in smokers with clinical mood disorders (Brown, Kahler, Niaura, Abrams, Sales, & Ramsey, et al., 2001; de Leon et al., 2002b).

Behavioral phenomenology suggesting abnormal smoking habits leading to greater nicotine intake are complemented by the findings from biological indexes of nicotine use in smokers with schizophrenia. Elevated blood plasma concentrations of nicotine and its metabolite cotinine have been reported irrespective of daily cigarette use, medication status, gender, severity of illness, or nicotine withdrawal time (Olincy, Young, & Freedman, 1997). Elevated levels of cotinine in smokers with schizophrenia in comparison to smokers in the general population is a finding that has been replicated and further investigated in other research groups as well. Williams and colleagues provided evidence for increased nicotine and cotinine levels in smokers with schizophrenia (Williams, Ziedonis, Abanyie, Steinberg, Foulds, and Benowitz, 2005); levels of cotinine were not related to other markers of enzymatic activity, suggesting that nicotine inhalation and absorption, not rates of nicotine breakdown and clearance, are responsible for blood plasma findings. 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 and nicotine or cotinine concentration in blood plasma (Williams et al., 2005). Finally, characteristics of smoking behavior, such as greater puff volume, faster rate of smoking, and longer cigarette smoking duration, appear to be related to higher blood nicotine levels among patients with schizophrenia compared to non-psychiatric smokers in the general population (Bridges, Combs, Humble, Turbek, Rehm, & Haley, 1990). Altogether, these findings suggest that such characteristics of smoking behaviors among those with schizophrenia may be clinically meaningful.

Vulnerability to Nicotine Use

Molecular Links to Nicotine Systems

Phenomenological, biological, and behavioral observations of smoking and nicotine dependence have elicited the development and investigation of multiple hypotheses in explaining the link between smoking and schizophrenia. Smoking and nicotine dependence in this population is not sufficiently explained by demographic factors, medication status, or concomitant use of alcohol or other substances. Rather, neurobiological abnormalities found in schizophrenia have demonstrated compelling linkages to nicotinic and other neurotransmitter systems in the brain.

Evidence in post-mortem brain tissue indicates that schizophrenia is associated with decreased numbers of hippocampal, thalamic, and frontal cortical $\alpha 7$

nicotinic acetylcholine receptors, apart from generalized loss of cell density; decreased receptor expression appears to be unrelated to smoking behavior (Court, Spurden, Lloyd, McKeith, Ballard, & Cairns, et al., 1999; Freedman, Hall, Adler, & Leonard, 1995). Tobacco smoking, known to increase high affinity nicotinic acetylcholine receptor binding sites in healthy smokers in a dose-dependent manner, fails to result in receptor upregulation in smokers with schizophrenia (Breese, Marks, Logel, Adams, & Sullivan, et al., 1997; Breese, Lee, Adams, Sullivan, & Logel, et al., 2000). 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). Abnormalities in neural nicotine receptor functioning might thus be integral to the understanding of smoking patterns and nicotine dependence in schizophrenia.

The downstream effects of nicotine on other neurotransmitter systems may provide further insight into how smokers with schizophrenia may be differentiated from smokers in the general population. Studies of the effects of nicotine on glutamatergic functioning have yielded particularly intriguing findings. The expression of gene groups related to the glutamatergic N-methyl-D-aspartate (NMDA) postsynaptic density is recently shown to be disparately regulated by smoking in individuals with schizophrenia. Among individuals with schizophrenia, aberrantly low expression of genes encoding for postsynaptic NMDA receptors appears to be upregulated and normalized by smoking to levels found in non-psychiatric controls (Mexal, Frank, Berger, Adams, & Ross, et al., 2005). Molecular abnormalities, such as low NMDA postsynaptic density, evident in non-smokers with

schizophrenia, may therefore constitute a pathophysiological abnormality associated with the illness. Findings that gene expression is differentially altered with smoking, uniquely in schizophrenia, suggests that changes in glutamatergic excitatory neurotransmission may contribute to the development of nicotine addiction in this population (Mexal et al., 2005). Thus, the relationship between nicotine and the glutamatergic system in schizophrenia provides additional insight into how smoking has functional relevance in this population at the molecular level.

Cognitive and Neurophysiological Links to Nicotine

In addition to linkages between nicotinic and other neurotransmitter systems, compelling links have been demonstrated between $\alpha 7$ nicotinic cholinergic receptors and observable schizophrenia-related phenomenology including deficits in cognitive and neurophysiological functions. For example, laboratory administration of nicotine transiently improves cognitive deficits, such as in attention and working memory. In nicotine challenge studies, cognitive performance is differentially affected by nicotine administration such that participants with schizophrenia show greater improvement on tasks than non-psychiatric controls (Depatie, O'Driscoll, Holahan, Atkinson, Thavundayil, & Kin, et al., 2002; George, Vessicchio, Termine, Sahady, Head, & Pepper, et al., 2002; Rezvani & Levin, 2001). Such differential effects appear unrelated to baseline differences in smoking (e.g. time since last cigarette). Cognitive deficits in attention, symptoms associated with schizophrenia such as thought disorder, auditory hallucinations, and experiences of sensory overload may all be associated with disrupted neurophysiological function (Leonard, Adler, Benhammou, Berger, Breese, & Drebing, et al., 2001; Lyons, Bar, Kremen, Toomey,

Eisen, & Goldberg, et al., 2002; Williams & Ziedonis, 2004). Neurophysiology generally describes how the brain processes sensory information and how this information is used to guide behavior. The links between neurophysiological functions, as studied in laboratory paradigms, and neural nicotine systems have been well studied. This linkage is exemplified by the study of impaired sensory gating.

It is 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 thus 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 (Adler, Pachtman, Franks, Pecevich, Waldo, & Freedman, 1982; Braff & Geyer, 1990). While a vast array of neurophysiological abnormalities are observed in schizophrenia, the electrophysiological P50 auditory sensory gating response is a widely used laboratory measure for testing the integrity of inhibitory circuits (Braff & Geyer, 1990; see Methodology section for further discussion of the P50 paradigm). Adler, Hoffer, Wisner, & Freedman (1993) localized the neural response to repeated sensory stimulation, represented by the P50 waveform, to originate in and near the hippocampus. Thus, in effect, 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).

Evidence suggests that the P50 sensory gating mechanism is mediated by nicotinic receptors on inhibitory interneurons located in the hippocampus and thalamus. In addition, nicotine receptor expression and sensory gating both

demonstrate relationships with genetic liability for schizophrenia (Waldo, Adler, Leonard, Olincy, Ross, & Harris, et al., 2000). This conclusion has been supported by the co-distribution of sensory gating deficits and schizophrenia in multi-affected families (Waldo, Carey, Myles-Worsley, Cawthra, Adler, & Nagamoto, et al., 1991) and genetic linkage analyses, which have demonstrated that deficits in sensory gating are associated with chromosome 15q13-14, the site of the $\alpha 7$ -nicotinic acetylcholine receptor subunit gene (CHRNA7; Freedman, Coon, Myles-Worsley, Orr-Urtreger, & Olincy, 1997). More specifically, the peak linkage locus for the human P50 deficit is found at CHRNA7 gene marker D15S1360, which is shown to co-segregate with auditory gating deficits in family linkage studies of schizophrenia patients (Freedman et al., 1997). Further genotyping of this marker has revealed significant differences in allelic distributions for smokers and non-smokers with schizophrenia (De Luca, Wong, Muller, Wong, Tyndale, & Kennedy et al., 2004) while no such differences in allelic distributions have been reported in studies of smokers from the general population (Stassen, Bridler, Hagele, Hergersberg, Mehmman, & Schinzel et al., 2000). These findings in particular may implicate a role of the nicotine receptor gene polymorphism in the pathogenesis of nicotine addiction in this patient population.

Like cognitive deficits in memory and attention, nicotine has been shown to improve deficits in auditory sensory gating (P50) among individuals with schizophrenia (Adler et al., 1993). Additionally, smoking in a laboratory setting has been shown to have differential effects on auditory sensory gating between patients with schizophrenia and non-psychiatric controls, with a positive correlation between the P50 ratio and smoking in patients only. Adler, Hoffer, Griffith, Waldo, and

Freedman (1992) demonstrated similar remediation of P50 gating deficits with oral nicotine administration in relatives of individuals with schizophrenia who had diminished gating of the P50 wave.

The link between neurophysiological dysfunction and neural nicotine systems is further illustrated by studies of eye movement deficits in schizophrenia.

Oculomotor dysfunction is closely tied to neuropharmacological mechanisms associated with neuronal nicotinic receptors. Several eye tracking abnormalities (e.g. deficits in peak gain, eye acceleration during initiation of smooth pursuit response, antisaccade eye movement errors) have been shown to be temporarily corrected by laboratory nicotine administration (DePatie, et al., 2002; Sherr, Myers, Avila, Elliot, Blaxton & Thaker, 2002). In addition, the findings of several studies have converged in demonstrating a relationship between nicotine receptor functioning and saccade performance with smoking, nicotine, and nicotine agonists (e.g. ketamine) improving the number of leading saccade eye movements during visual tracking (Avila, Hong, & Thaker, 2002; Avila, Sherr, Hong, Myers, & Thaker, 2003; George, Verrico, Picciotto, & Roth, 2000; Olincy, Ross, Young, Roath, & Freedman, 1998). Taken all together, findings from a variety of research domains converge on the importance of nicotinic receptors in the pathophysiology of schizophrenia, and suggest that nicotine may serve a functional role for individuals with schizophrenia who smoke.

The Self-Medication Hypothesis of Smoking and Schizophrenia

Patterns of nicotine use do not support a self-medication hypothesis whereby pharmacological agents are utilized to alleviate positive or negative symptoms associated with the illness. As indicated, empirical findings lend support for the

alternative hypothesis that the high smoking prevalence rate and the patterns of smoking behavior may represent an effort to remediate neurobiological dysfunctions associated with pathophysiological processes that characterize the disease. That is, nicotine administration via tobacco use may temporarily restore altered nicotinic receptor functioning, leading to improved neurophysiological and cognitive functioning among individuals with schizophrenia. Thus nicotine use and dependence in this population appears to have a unique relationship, among substances of abuse, in linking defects in inhibitory neural pathways to smoking behaviors in individuals with schizophrenia. In sum, the self-medication hypothesis of smoking and schizophrenia postulates that smoking is a means of correcting an inherent neural abnormality, leading to improvements in information processing functions.

Low affinity nicotine receptors ($\alpha 7$) appear to play an integral role in facilitating proper inhibitory functions and nicotine administration tends to correct information processing functions that are otherwise deficient in schizophrenia. Sensory gating and eye tracking dysfunctions represent one manifestation of deficient information processing via cortical-subcortical pathways. The self-medication hypothesis posits that a relationship exists between smoking and schizophrenia through remediation of nicotine receptor function and transient remediation of such information processing deficits. However, neural inhibitory dysfunction may have multiple sources and may stem from an interplay between neurobiological pathways.

The link between schizophrenia and nicotine use may operate through mechanisms other than, or in addition to, the remediation of specific nicotine receptor dysfunctions. Empirical evidence suggests that a functional connection between

nicotine use and schizophrenia is mediated through inhibitory neural circuitry dysfunction. For example, there is considerable evidence that $\alpha 7$ nicotinic acetylcholine receptors and receptors for the inhibitory neurotransmitter GABA coexist and are functionally related (Breese et al., 1997). Furthermore, an array of impairments in functions requiring cognitive control and inhibition of sensory-driven processes have been documented in schizophrenia, even beyond those described above (e.g. deficits in attention shifting, competitive response selection, saccadic eye movement, executive control necessary for working memory), suggesting the presence of a common disinhibitory neural mechanism (Curtis, Calkin, Grove, Feil, & Iacono, 2001; Lewis, Hashimoto, & Volk, 2005). Thus, instead of focusing narrowly on the relationship between specific cognitive or neurophysiological functions and neural nicotinic systems, nicotine dependence in schizophrenia may be examined in relation to integrated neural network activity.

An Alternative Electrophysiological Approach to Studying Nicotine Use in Schizophrenia

Pathophysiological Perspective on Smoking and Schizophrenia

The link between smoking and schizophrenia may be conceptualized from a pathophysiological perspective whereby neurobiological aspects of the illness contribute to nicotine use and dependence. The self-medication hypothesis postulates that a propensity towards nicotine use and an increased risk of dependence among individuals with schizophrenia is associated with the remediating effects of nicotine on basic underlying neurophysiological processes. Contemporary views of

schizophrenia pathology are increasingly focused on the study of dysfunctional neural circuitry rather than the functioning of specific brain areas or neurotransmitter systems. Characteristics of cortical brain functioning, such as the temporal dynamics of neural interactions, form the basis for lower level information processing, sensory integration, regulating consciousness, and for governing higher-order cognitive functions, as well as coordinating purposeful behavior (Begleiter & Porjesz, 2006; von Stein & Sarnthein, 2000). Thus, electrophysiological methodology assessing the integrity of integrated neural networks provides a unique perspective from which to approach the study of mechanisms underlying sensory, perceptual, and cognitive deficits associated with schizophrenia, and may inform processes underlying behavioral phenomena exhibited by those affected with the illness. If elevated rates of smoking and nicotine dependence are a function of schizophrenia pathophysiology (i.e. nicotine receptor and/or inhibitory circuitry dysfunction), then further examination of potential electrophysiological underpinnings may help to elucidate the mechanisms linking the pathophysiology of schizophrenia to smoking. The self-medication hypothesis of smoking and schizophrenia may thus shift from examining the relationship between specific neurophysiological functions and nicotine to the relationship between nicotine and neural system activity.

The study of brain oscillatory activity across the frequency spectrum is a tool that has been used to investigate cortical pathologies underlying other psychiatric conditions. Examining electrophysiological oscillatory activity is a means of assessing the functional integrity of neural circuitry, including inhibitory neural systems. Overlap between disorders with respect to electrophysiological and

behavioral phenomena may be used to expand current neuroscientific and psychological knowledge and theory of brain-behavior relationships. One such area of study that appears promising in linking nicotine use and dependence to schizophrenia is the quantification of beta power in resting EEG. Research from Begleiter and Porjesz (1999) has resulted in the supposition that elevated beta power represents a state of neuronal imbalance between excitatory and inhibitory inputs, which has significant behavioral consequences. Studies of EEG functions in non-schizophrenia populations implicate the unique role of cortical activity in the beta frequency band to vulnerability for alcohol and other substance use. However, delineation of functional linkages between beta power and nicotine use have largely been hampered by confounding comorbidity with other substance use in research samples. Furthermore, the overt behavioral significance of neuronal hyperexcitability or deficient inhibitory circuitry in schizophrenia remains unclear.

This study aims to address these gaps in the literature by clarifying the nature of the linkage between beta power in resting EEG and nicotine, and to characterize the role that this linkage might play in investigating nicotine use in the schizophrenia population. Drawing from a range of empirical findings in the schizophrenia, addictions, and neurophysiological literatures, a relationship between nicotine use and cortical dysregulation in schizophrenia may be hypothesized. Investigation of these relationships builds upon the self-medication hypothesis in linking neural pathophysiology associated with schizophrenia to nicotine use. In the following sections, the methodology of quantifying oscillatory activity ascertained from resting EEG will be described, followed by a brief review of related EEG activity in

schizophrenia. The proposed significance of examining resting EEG in the beta frequency band will be discussed with respect to the findings in the alcohol and substance use literatures. Finally, a working model relating electrophysiology, smoking, and schizophrenia will be discussed in providing a context for the current study.

Cortical Oscillatory Activity

At the neuronal and neuron network levels, rhythmic oscillations and synchronous activity in the electroencephalogram reflect the relative strength and balance of inhibitory and excitatory inputs arising from both intrinsic regulatory mechanisms as well as in response to external stimulation. The frequencies at which neural oscillations (i.e. voltage fluctuations) occur and their spatial and temporal consistency (i.e. coherence, synchrony) are informative with respect to brain mechanisms underlying sensory processing and behavior (Engel, Fries, & Singer, 2001; Salinas & Sejnowski, 2001). As such, fluctuations in cortical excitability, with respect to shifts in oscillatory activity and the level of synchronous activity of distributed neural networks, serve to control incoming sensory information and prime or guide stimulus-evoked responses (Engel et al., 2001).

Oscillatory activity may be characterized with respect to the activity across the frequency spectrum; categorization yields five primary frequency bands, from the slowest to fastest: delta (1.0-3.0 Hz), theta (3.5-7.5 Hz), alpha (8.0-11.5 Hz), beta (12.0-28.0 Hz), and gamma (28.5-50 Hz) (Begleiter & Porjesz, 2006). Analysis of the relationships between specific components of oscillatory activity and human behavior may provide a basis for understanding underlying physiology and etiology of normal

and pathophysiological conditions of the central nervous system (see Appendix A for further discussion of neural oscillations). EEG patterns have been studied extensively using family and twin designs. The majority of EEG parameters studied are stable within individuals and are found to be more similar among biologically related individuals than among non-familial controls (Porjesz, Almasy, Edenberg, Wang, Chorlian, & Foroud, et al., 2002; Tang, Chorlian, Rangaswamy, O'Connor, & Taylor, et al., 2007).

Cortical Oscillatory Activity in Schizophrenia

The study of EEG power, that is the amount of oscillatory activity in a given frequency band (e.g. delta, theta, alpha, beta, gamma), among individuals with schizophrenia may contribute to understanding mechanisms of neural network dysfunction and the mechanisms underlying observable sensory, perceptual, and cognitive deficits (Spencer, Nestor, Perlmutter, Niznikiewicz, & Klump, 2004; van der Stelt, Belger, & Lieberman, 2004). Thus, oscillatory activity in schizophrenia may also be informative in linking sensory processing with illness-related behavior, such as smoking. Although resting EEG is found to be consistent across family members in samples drawn from the general population, vulnerability to schizophrenia appears to be associated with wider ranging inter-individual variability in resting EEG function. EEG differences in monozygotic twins concordant and discordant for schizophrenia suggest both broad genetic and specific pathologically determined abnormalities in cortical functioning (Stassen, Coppola, Gottesman, Torrey, Kuny, & Rickler et al., 1999). Variability in EEG parameters among schizophrenia co-twins is not attributable to measurement artifact or poor reliability; prior studies provide evidence

for similar psychometric properties of resting EEG power (e.g. test-retest reliability) in schizophrenia and healthy populations (Lund, Sponheim, Iacono & Clementz, 1995). Furthermore, frequency characteristics of EEG appear to be consistent in first-episode and chronic schizophrenia patients with no identifiable effects of illness duration or chronic treatment (Sponheim, Clementz, Iacono, & Beiser, 1994).

In the twin study by Stassen and colleagues (1999), schizophrenia probands and unaffected monozygotic co-twins were differentiated by a generalized pattern of increased low frequency theta and decreased alpha activity associated with illness manifestation. Other quantitative comparisons of resting EEG anomalies between schizophrenia and healthy comparison subjects have reported similar findings of less alpha activity, more delta, theta, and beta activity; schizophrenia-related EEG abnormalities in the frequency domain have been described by principle components analysis as demonstrating a high proportion of fast activity, augmented low frequency activity, and diminished alpha band power (Clementz, Sponheim, Iacono & Beiser, 1994; Kahn, Weiner, Coppola, Kudler, & Schultz, 1993; Sponheim et al., 1994).

Examination of clinical and biological correlates of resting state EEG power has aimed to better characterize illness-related anomalies. Variations in resting EEG appear to be unrelated to duration of illness or treatment. Findings from Sponheim and colleagues (2000) replicated the coupling of augmented low frequency (delta and theta) power with diminished alpha power found in patients with schizophrenia as well as in individuals with non-schizophrenia psychosis. Though these EEG characteristics may represent generalized manifestations of cortical pathology, EEG abnormalities in schizophrenia and non-schizophrenia psychosis were differentiated

by associations between abnormal EEG power and negative symptomatology, poorer ocular motor functioning, wider third ventricles, larger frontal horns of the lateral ventricles, and larger cortical sulci in the schizophrenia patients (Sponheim, Clementz, Iacono & Beiser, 2000). Both cortical and subcortical pathologies are suggested by the clinical and biological correlates of augmented lower frequency and diminished alpha band power in schizophrenia.

Metabolic hypofrontality, structural frontal lobe and thalamic anomalies, and cortical disruption thus appear to be a constellation of findings representing a dysfunction of thalamic-cortical projections in schizophrenia. As ascertained from measurements of cortical activity, lower levels of alpha activity may reflect atrophy of the thalamus, while higher theta activity may reflect hippocampal dysfunction (Stassen et al., 1999). Functionally, investigators have postulated that lower alpha and elevated beta activity together correspond to deficits in the modulation of attention and arousal (Kahn et al., 1993). Additional abnormalities in higher frequency gamma oscillatory activity may uniquely underlie other cognitive dysfunctions in schizophrenia, such as perceptual binding and working memory (Bramon, McDonald, Croft, Landau, Filbey, & Gruzelier et al., 2005).

Gamma activity, unlike oscillatory activity in lower delta and theta frequency bands, appears to reflect a fundamental frequency critical for cortico-cortical communication, and is likely responsible for coherent neuronal functioning and, subsequently, integrated normal cognitive functioning (Rodriguez, George, Lachaux, Martinerie, Renault, & Varela, 1999). Investigated in normal subjects, gamma band activity appears to play a role in associative learning, more specifically during

processing of reward stimuli, as given by increasing frontal gamma activity during an operant shaping paradigm (Keil, Muller, Gruber, Wienbruch, & Elbert, 2001).

Investigation of reduced gamma band activity in schizophrenia has gained increasing popularity in characterizing underlying neural network dysfunction and information processing deficits (Light, Hsu, Hsieh, Meyer-Gomes, Sprock, & Swerdlow et al., 2006); the pathophysiological relevance of gamma activity is also supported by findings of lower stimulus- evoked gamma activity in first-degree relatives of schizophrenia probands (Hong, Summerfelt, McMahon, Adami, Francis, & Elliott et al., 2004). Gamma band activity is viewed empirically as a ubiquitous mechanism underlying information processing and, due to the extent of sensory and cognitive integrative dysfunction in schizophrenia, is likely integral in affecting neural processing among affected individuals. In addition, reduced synchronous gamma activity has demonstrated unique associations with clinical symptoms of schizophrenia including thought disorder, visual hallucinations, and disorganization (Spencer et al., 2004).

While the schizophrenia literature has substantiated findings of augmented low frequency power, diminished alpha activity, and reduced gamma band activity, much less research has sought to characterize aberrant oscillatory activity in the beta band. Beta power has been discussed within the context of abnormal alpha power, as regulating arousal and attention, and beta activity has been coupled with gamma band oscillations in representing the coordinated activity of excitatory and inhibitory neural assemblies (Miller, 2007). Higher frequency oscillations within the beta band have been proposed to represent a subharmonic of prior gamma oscillatory activity

(Strelets, Novototsky-Vlasov, & Golikova, 2002) in response to sensory stimuli. Given that inhibitory interneurons appear to be crucial in generating synchronous neural activity in the beta and gamma bands of the EEG (Whittington & Traub, 2003), analysis of cortical activity in both frequency bands together is likely integral to understanding information processing in schizophrenia. Indeed, both beta and gamma band oscillations in healthy individuals have been shown to underlie deficits in sensory gating paradigms (Hong, Summerfelt, McMahon, Thaker, & Buchanan, 2004).

Dysregulation of neural circuit inhibition in schizophrenia is postulated to stem from dysfunctional thalamocortical circuitry, and/or aberrant inhibitory (GABAergic) interneuron or excitatory (glutamatergic) input. All are consistent with evidence for lower neural synchrony and cortical hyperexcitability in schizophrenia (Hoffman & Cavus, 2002). Beta frequency oscillation is linked to cortical inhibitory function in schizophrenia, and has been shown to contribute uniquely to impaired P50 gating. This unique contribution of beta oscillations to aberrant sensory gating may be more robust among individuals with schizophrenia than non-schizophrenia controls, although this finding requires replication (Hong et al., 2004). This study will address the relative lack of focus on oscillatory activity in the beta frequency band and its significance in schizophrenia by examining beta power in resting EEG in a schizophrenia sample.

While the direct contribution of oscillatory activity to information processing deficits in schizophrenia is under study, beta oscillation in the electroencephalogram has been further studied in resting states of other pathological conditions

(Neidermeyer, 1999). As indicated in both the schizophrenia and normal literature, rhythmic activity of neural oscillations within the beta frequency band is considered as an index of cortical excitation or arousal (Begleiter & Porjesz, 1999) and has been associated with multisensory integration and information processing (von Stein & Sarthein, 2000). Outside of the schizophrenia literature, studies of etiologic factors associated with addictions indicate a role for increased absolute beta power in resting EEG (Bauer, 1994; Costa & Bauer, 1997). Resting beta band power, as an index of baseline cortical excitation, may therefore represent a candidate measure for linking basic neural functional activity in schizophrenia to nicotine addiction. Hypotheses regarding the functional significance of resting beta band activity in schizophrenia may be generated by first considering the role of beta activity as it relates to substance use.

The Significance of Beta Band Activity

Susceptibility to Alcohol Use

Analysis of the relationships between specific components of oscillatory activity and human behavior may provide a basis for understanding underlying physiology and etiology of normal and pathological conditions of the central nervous system. Trait and state-like characteristics of cortical activity may be predictive of liability toward the development or maintenance of specified pathologies. In particular, the alcohol use literature may be informative in examining neural network mechanisms associated with physiological as well as behavioral correlates of risk for, and expression of, substance dependence. Early support for elevated beta power associated with alcohol dependence is buttressed by more recent evidence from a

large-scale collaborative study of the genetics of alcoholism. Absolute power spectra derived from resting EEG of alcohol dependent individuals has demonstrated consistent and significant increases in beta band oscillation relative to non-dependent controls, largely over frontal and central brain regions. Though findings tend to be more robust for males than females, beta band amplitudes were reportedly unaffected by characteristics of alcohol use (e.g. quantity or recency of drinking) or age (Rangaswamy, Porjesz, Chorlian, Wang, & Jones, & Bauer, 2002). The lack of significant relationship with alcohol use variables led the investigators to hypothesize that elevated beta band power is associated with the development, rather than a direct consequence of, alcohol misuse.

Further analysis of beta band oscillations from resting EEG has demonstrated similar absolute power elevations in offspring of male alcoholics, relative to family history negative controls, regardless of their current alcohol use disorder diagnosis (Rangaswamy, Porjesz, Chorlian, Wang, Jones, & Kuperman, 2004). Though again, significant elevations in beta power were limited in females with a positive family history while beta power was significantly elevated across the beta frequency band in males, these findings are generally consistent with prior studies reporting higher beta power in the resting EEG of family history positive individuals. Such findings suggest that elevated beta power represents a trait- rather than state-related correlate of alcohol dependence, and suggest that elevated beta power is more likely a precursor to than an effect of alcohol exposure. Furthermore, Rangaswamy et al. (2004) reported greater effect of familial density of alcohol dependence in females

than males, indicating that gender differences within the beta range may be a marker for differential vulnerability in males and females.

Additional characterization of oscillatory activity across the frequency spectrum has underscored the predictive power of increased beta band activity with respect to risk for substance use in general. Power analyses in remitted substance (alcohol or drug) using individuals differentiated between abstinence- and relapse-proneness by higher frequencies in the beta band of resting EEG (Bauer, 2001). Abnormal elevation in beta power did not vary with substance use problem severity, depression, or anxiety, and interactions between outcome and type of substance were non-significant. In addition, while outcome, family history of alcoholism, and childhood history of conduct disorder significantly interacted to predict current beta power elevation, logistic regression revealed that beta power was the only significant predictor of remission status over long term evaluation, such that higher beta power was associated with increased rates of relapse (Bauer, 2001). The findings from this study confirm the association between elevated beta power and risk for alcohol use, and suggest that, among those who have already initiated substance use, elevated beta power may be associated with risk for relapse. Furthermore, the findings from Bauer (2001) extend the findings of previous studies by suggesting that abnormal elevation in beta power might be considered a general vulnerability factor, common to substances of misuse and dependence in addition to alcohol.

Indeed, changes in brain activation are associated with other psychoactive substances and may describe alterations in cortical brain function associated with addiction. Drugs such as benzodiazepines, cocaine, and opioids have demonstrated

drug-induced increases in power spectra, particularly in the alpha and beta bands, in a laboratory setting. Drug-related changes in brain activation also include altered cortical connectivity from alpha and beta generated neuronal networks over time (Fingelkurts, Fingelkurts, Kivisaari, Pekkonen, Ilmoniemi & Kahkonen, 2004; Herning, Glover, Koepl, Phillips, & London, 1994; Jensen, Goel, Kopell, Pohja, Hari, & Ermentrout, 2005). The latter results are thought to indicate a restructuring of neuronal networks with continued drug use, which likely has implications for changes in higher order cognitive functions such as problem solving, set maintenance, set shifting, behavioral control (Fingelkurts, Fingelkurts, Kivisaari, Autti, Borisov, & Puuskari, et al., 2006) with drug use over time.

Complicating the interpretation of the former results is the significant but varied drug use histories of the participants, including past and current use of amphetamine, heroin, barbiturates, hallucinogens, marijuana, cocaine, alcohol, and nicotine. The varied histories of substances used in the past, in addition to recent substance use confound characterization of the specificity and temporal relationship with oscillatory activity. It is noteworthy, however, that similar changes in neural activity were obtained from drugs with both stimulant and depressant properties. This observation underscores the presupposition that neural mechanisms might be non-specific, underlying vulnerability to substance use in general.

With regard to the specificity and temporal relationship between substance use and beta band activity, in most studies alterations in beta power were not isolated to one substance, nor associated with specific substance use variables such as length or frequency of drug use, severity of dependence, or time since last drug use (Bauer,

1994; Bauer, 2001, Costa & Bauer, 1997). Additional findings reporting on cortical activity in abstinent male heroin users suggest that increased EEG coherence¹ of frequency activity (e.g. theta, low beta, and gamma frequency coherence) may be related to the direct effects of drug use, in contrast to elevated power in the beta band, which may better represent susceptibility to drug use (Franken, Stam, Hendriks, & van den Brink, 2004). These findings are consistent with those reporting the predictive relationship between beta power and relapse-proneness in abstinent individuals (Bauer, 2001), as well as the findings of elevated beta power in unaffected individuals with a positive family history of alcohol dependence (Rangaswamy et al., 2004).

Further support for spectral power as a trait indicator of susceptibility may be provided by genetic findings of a mean reported heritability estimate of 86% for beta power (Porjesz et al., 2002). Notably, the heritability of the beta frequency band of EEG is higher than heritability rates reported for alcohol dependence itself (49-64%; McGue, 1999), recommending such electrophysiological measures as beta power as a more proximal predictor of gene effects than the clinical diagnoses associated with it. Such gene effects likely do not confer risk for use or dependence on any one substance in particular, but may impart vulnerability for other antecedents to substance use or addiction.

Thus, empirical evidence supports a generalized risk for substance use or propensity towards addiction. Family, adoption, and twin studies support the familial aggregation of alcohol dependence and the importance of genetic factors in

¹ EEG coherence refers to the correlation between two signals measured at the same time; high coherence indicates a close functional coupling between neuronal populations in different brain areas (Franken et al., 2004).

developing alcohol use disorders. The aggregation of substance use disorders in addition to alcohol in relatives of alcohol dependent individuals has also been reported, whereby the increased risk for substance dependence in relatives (e.g. marijuana, cocaine, tobacco) is only partly independent of familial alcohol dependence (Bierut, Dinwiddie, Begleiter, Crowe, Hesselbrock, & Nurnberger, et al., 1998; Nurnberger, Wiegand, Bucholz, O'Connor, Meyer, & Reich, et al., 2004). Such data are consistent with specific causative factors in developing types of substance dependence and common addictive risk factors for substance use in general.

Begleiter and Porjesz (1999) theorize that a genetic predisposition to develop substance dependence is signified by a disequilibrium in homeostatic mechanisms controlling the balance between excitation and inhibition in the central nervous system. Individuals with an imbalance in disinhibition/hyperexcitability homeostatic mechanisms may be particularly sensitive to the effects of substances of misuse, including alcohol and other drugs, affecting substance use initiation as well as continued substance use (Begleiter & Porjesz, 1999). Beta power has been identified as an electrophysiological marker for this imbalance, conferring vulnerability for substance use and dependence (see Appendix A for further discussion). Although beta power can be measured over most scalp regions in EEG, beta power measured in frontocentral and centroparietal regions tend to best differentiate individuals with and without alcohol use disorders (Rangaswamy et al., 2002). The source of resting beta oscillatory activity, however, has been localized to the frontal lobe of the brain, a region known to be important to behavioral control (Bauer, 2001). A frontal source for neuropathology underlying alcohol and other substance use disorders has also

been suggested by abnormalities in brain wave amplitudes measured in response to external stimuli (i.e. event related potential deficits). A deficiency in the P300 event related component, a positive fluctuation in brain wave amplitude measured 300 ms following a stimulus event, has demonstrated associations with liability to the development (Rangaswamy, Jones, Porjesz, Chorlian, & Padmanabhapillai, et al., 2007) and risk for relapse of alcohol and drug use (Bauer, 1997).

The low amplitude P300 component has been touted as a putative phenotypic marker of risk for developing alcohol dependence, supported by evidence from family and longitudinal study designs (Begleiter & Porjesz, 1999). Poor P300 response is associated on behavioral tasks with an undifferentiated mode of responding to incoming visual or auditory stimuli, thereby suggesting an electrophysiological problem of cognitive and behavioral disinhibition in alcohol dependent and well as in at-risk individuals (Begleiter & Porjesz, 1999). Poor P300 response is predictive of other disorders, such as attention deficit hyperactivity disorder and antisocial personality disorder. Thus P300 performance deficits, like elevated beta power, represent a mechanism of neural disinhibition associated with both cognitive and behavioral consequences, including significant psychopathology (Moeller Barratt, Dougherty, Schmitz, & Swann, 2001). Given the relationship between poor P300 response, poor information processing, and clinical disorders characterized by disinhibition, it is interesting to note that impairment in the P50 gating response, another electrophysiological measures of neuronal inhibitory processing, has been documented with respect to substance use disorders such as cocaine and alcohol dependence as well (Boutros, Campbell, Petrakis, Krystal, Caporale, & Kosten, 2000;

Marco, Fuentemilla, & Grau, 2005). Furthermore, poor P300 response and P50 gating deficits have both been well documented among those with schizophrenia and their relatives (Bramon, et al., 2005). Thus, multiple neurophysiological, cognitive, and behavioral outcomes may be characterized by an underlying cortical disinhibition/hyperexcitability. This neural network disinhibition may relate etiologically to a number of disorders, including schizophrenia. Yet, the methodology utilized by Begleiter and Porjesz (1999) to characterize this cortical hyperexcitability has not been applied to schizophrenia. In a population characterized by significant rates of substance use and even higher rates of nicotine use, this electrophysiological mechanism may have significant explanatory power (see Appendix A for further discussion of neural network disinhibition and schizophrenia).

Substance Use and Smoking in Schizophrenia

Further study of overlapping neurobiological deficits and behavioral characteristics of disorders is likely to be informative in elucidating the etiology, pathophysiology, and in understanding the phenomenology of various psychiatric conditions. Within the schizophrenia population, consideration of variables contributing to susceptibility for nicotine use and cigarette smoking might include those that overlap with substance use disorders. It is known that schizophrenia is commonly comorbid with substance use disorders, with lifetime prevalence rates estimated between 40 and 50% (Blanchard, Brown, Horan & Sherwood, 2000). As indicated, rates of nicotine use in schizophrenia are estimated in the range of 70 to 90%. In neither case is substance use predicted by overt illness symptomatology; rather premorbid individual difference factors are more likely determinants of

alcohol, drug, or nicotine use than qualities of present illness manifestation (Blanchard et al., 2000). By briefly examining alcohol and substance use within the schizophrenia population, mechanisms of vulnerability to dependence overlapping with nicotine use may be hypothesized.

A relationship between substance use and brain reward circuitry dysfunction in schizophrenia may have some explanatory power with respect to the increased sensitivity to the effects of substances. For example, enhanced positive subjective response to substances has been reported with alcohol, which produces greater euphoria and stimulatory effects among individuals with schizophrenia than non-schizophrenia controls (D'Souza, Gil, Madonick, Perry, Forseliu-Bielen, & Braley, et al., 2006); the degree of subjective response may be a substantial contributor to the risk for substance use initiation, continued use, and the development of dependence. Likewise, individuals with schizophrenia may be more vulnerable to the effects of nicotine such that nicotine may be a stronger reinforcer, compared to smokers without schizophrenia, due to neurobiological substrates associated with the disorder itself (Chambers, Krystal & Self, 2001). According to Begleiter and Porjesz (1999), increased sensitivity to substances of misuse may also be a consequence of an imbalance in cortical excitation and inhibition, thus conferring greater risk for substance dependence.

Neurobiological substrates associated with substance use have been examined with respect to cognitive performance deficits as they may relate to poor behavioral control in schizophrenia. On cognitive or neuropsychological tests, patients with schizophrenia tend to show poorer executive functioning than other populations in

general; poorer executive functioning may translate behaviorally into reward sensitivity as suggested above, impulsive behavior, and/or lack of response to environmental contingencies, all of which may be related to continued substance use. However, the extent to which cognitive performance data support a specific cognitive control problem differentiating schizophrenia patients with or without a substance use disorder is limited (Thoma, Wiebel, & Daum, 2007). It is unclear whether the sensitivity or specificity of cognitive performance measures may obscure important findings. Therefore, other assessments of brain function associated with substance use disorders may provide a more parsimonious link between upstream neurobiological dysfunction and downstream complex behaviors. Gating of sensory information (i.e. P50 response) appears to represent one of those linkages. Yet again, from a broader perspective, examination of cortical processes related to neurophysiological impairment and predisposing to substance use may have more promising implications for understanding the phenomenology of smoking and nicotine dependence in schizophrenia. As cortical oscillatory activity in the beta band has been shown to relate to sensory gating performance, elevated beta power may represent an alternative, but related, mechanism of nicotine use in schizophrenia, complementing the self-medication hypothesis as it pertains to disinhibitory information processing dysfunction.

As presented in this review, vulnerability to nicotine use in schizophrenia may be conceptualized from a pathophysiological perspective whereby broad and specific factors associated with the illness may lead to nicotine use and dependence. Neurobiological dysfunction, such as dysregulation of inhibitory neural circuits, may

predispose individuals affected by the illness to addiction in general. Specific molecular aspects such as aberrant nicotine receptor expression, regulation, or nicotine induced neural activity may confer vulnerability to nicotine use and dependence as well. Broad and specific factors are likely not mutually exclusive, as nicotine and nicotine receptor functions interact with other neurochemical systems (e.g. glutamate, GABA, dopamine) among various neural circuits integral to processing of incoming sensory information and guiding observable behaviors. Vulnerability to nicotine addiction, in both the broad and specific sense, is further illustrated by consideration of genetic contributions, which likely encompass any number of neurobiological or behavioral functional relationships discussed above.

Genetic Contributions to Nicotine Use

As studied in the general population, susceptibility to smoking initiation and nicotine dependence are influenced by a number of individual difference and environmental factors. Genetic evidence from non-schizophrenia populations suggests that factors conferring risk for nicotine use may overlap with those conferring risk for other substance use. Data from family studies and genetic linkage analyses have concluded that both specific and common genetic factors are integral in the development of habitual smoking and alcohol dependence (Bierut et al., 2004). However, the genes or gene products that confer a specific or general vulnerability to substance use and progression to dependence have yet to be deciphered.

With regard to nicotine use, total heritability estimates for initiation and progression to nicotine dependence are approximately 60 to 70% (Kendler, Neale, Sullivan, Corey, Gardner & Prescott, 1999; Sullivan & Kendler, 1999; True, Heath,

Scherrer, Waterman, Goldberg, Lin, et al., 1997). In addition, several aspects of smoking behavior such as initiation, persistent smoking, and level of nicotine dependence each have been found to cluster in families (Bierut, Rice, Goate, Hinrichs, Saccone, & Foroud, et al., 2004). A substantial collection of data from family as well as twin and adoption studies converge in reporting combined genetic (~60%) and environmental (~20% shared, ~20% unshared) influences on smoking initiation, but relatively negligible effects of environment compared to a significant genetic (~70%) contribution to progression to nicotine dependence (Sullivan & Kendler, 1999). That progression to nicotine dependence, as opposed to smoking initiation, is predicted more robustly by genetic factors may reflect the presence of specific genetic mechanisms of addiction related to nicotine use than to substance use in general.

Given that genetic liability for schizophrenia has been clearly demonstrated by the results of family, twin, and adoption studies (McGue & Gottesman, 1989; Tsuang & Faraone, 1994), and that additional evidence supports elevated rates of nicotine mediated neurophysiological dysfunction in unaffected relatives, a plausible hypothesis is that elevated rates of nicotine use would be observable in family members of individuals with schizophrenia as well. Evidence from Lyons and colleagues (2002) do indicate elevated rates of nicotine dependence as well as unsuccessful smoking quit attempts among unaffected co-twins of patients with schizophrenia, providing preliminary support for this hypothesis. However, the extant literature has yet to identify which elements of genetically mediated individual differences in nicotine response are most related to smoking behavior and nicotine

dependence. Speculation as to the mechanism of the genetic effect on nicotine dependence promotes further study with regard to molecular influences on pharmacokinetics and pharmacodynamics governing the activity of bioavailable nicotine, neurotransmitter systems involved in nicotine intake, as well as other individual difference factors conferring risk for nicotine addiction (Bierut et al., 2004; Sullivan & Kendler, 1999; Yoshimasu & Kiyohara, 2003). In considering the range of specific factors contributing to vulnerability to nicotine dependence, this study will aim to first describe the heritability of nicotine dependence associated with genetic predisposition to schizophrenia, thereby laying the groundwork for more molecular investigations in the future.

Building a Working Model of Smoking and Schizophrenia

A baseline imbalance in homeostatic mechanisms regulating excitatory and inhibitory cortical activity may confer susceptibility to addiction. Given the robust literature on neural inhibitory dysfunction associated with vulnerability to substance use disorders, schizophrenia, as well as the frequent comorbidity of substance use with schizophrenia, consideration of Begleiter & Porjesz's (1999) cortical disinhibition/hyperexcitability hypothesis of trait susceptibility to alcohol dependence may have implications for susceptibility to addiction in the schizophrenia population. Elevated resting oscillatory activity in the beta band likely reflects this trait-like condition of cortical dysregulation. Empirical evidence supports elevated beta power in frontal and central brain regions as a significant predictor of substance use and dependence without apparent specificity for drug type or inherent drug effect. In delineating the relationship between beta power and nicotine dependence, concurrent

use of alcohol or other drugs often overshadows an explicit focus on nicotine use or confounds study findings. Yet, nicotine is arguably the most addictive substance and the most commonly used; higher levels of nicotine use are also found in psychiatric populations among whom electrophysiological abnormalities are evident. A clinically meaningful link between nicotine and neurobiological dysfunction is suggested by these findings.

Nicotine use has been shown to have a unique relationship with vulnerability to schizophrenia. As such, nicotine has received attention as a substance of use in its own right, yet there is an apparent lack of both specificity in, and clear integration with the literature on alcohol and other substance use. Examining patterns of electrophysiological activity, which have previously demonstrated linkages with susceptibility to alcohol and other substance use disorders, with respect to nicotine use may ultimately be informative in proposing mechanisms by which vulnerability for nicotine dependence may manifest in those affected by the illness.

The self-medication hypothesis proposes that smoking and nicotine use in schizophrenia represents an effort to remediate basic information processing deficits that characterize the disease and are associated with disease vulnerability.

Information processing dysfunctions intimately tied in the schizophrenia literature to nicotine use and genetic liability include those which rely on frontal cortical function, thalamocortical circuits, and overall inhibitory neural processing. These mechanisms may overlap with those conferring vulnerability to substance use disorders as studied in non-schizophrenia populations.

This study thus aims to incorporate an array of methodologies to investigate mechanisms of increased vulnerability to smoking and nicotine dependence among individuals with schizophrenia. This study will approach this research problem from a perspective encompassing the individual and interactive effects of genetic vulnerability factors, neurophysiological function, and cortical oscillatory activity.

Chapter 2: The Current Study

Rationale

A linkage between smoking and schizophrenia may be conceptualized from a pathophysiological perspective, such that aspects of the neuropathology of the illness confer vulnerability to addiction, particularly to nicotine. At a molecular level and at a behavioral level, nicotine use may serve a clinical or functional purpose for those affected by the illness. The current study aims to further investigate the self-medication hypothesis of smoking in schizophrenia, which purports that smoking behaviors and high rates of nicotine dependence represent an effort to remediate underlying information processing deficits associated with neurophysiological underpinnings of illness vulnerability. Nicotine use has previously been studied in the context of sensory gating and ocular motor dysfunctions, which are thought to represent observable effects downstream of genetic liability to schizophrenia. This study proposes to approach nicotine use and information processing in schizophrenia from a complementary perspective, that of aberrant brain oscillatory activity as assessed with EEG. Cortical oscillatory activity has been shown to underlie such performance deficits.

This study proposes to examine whether the predictive utility of elevated beta power may be extended from predicting alcohol use and dependence to a propensity towards nicotine use, and whether this mechanism also holds explanatory power in linking smoking and elevated nicotine dependence to schizophrenia. The current study proposed to utilize four groups, including patient and comparison control index

probands and their first-degree relatives, in a between groups design to examine multi-level study aims. Data were extracted from semi-structured diagnostic and family history interviews, a self-report questionnaire of nicotine use, and laboratory paradigms to assess sensory gating (P50) and to analyze spectral power in resting EEG. Research hypotheses were formulated according to three broad study aims, first to examine the effect of a family history of schizophrenia on the heritability of nicotine use and dependence, second to examine the relationship between oscillatory activity in the beta band and nicotine use, and third, to examine relationship among variables in predicting nicotine use and dependence. This section will outline each study hypothesis and discuss additional factors that were considered in the study design and statistical analyses that followed data collection.

Specific Study Aims and Hypotheses

Specific Aim 1: Compare rates of smoking and heritability of smoking among individuals with and without a family history of schizophrenia.

- Hypothesis 1a: Prevalence of nicotine use, past or present, will be greater among patients with schizophrenia than healthy comparison controls, and prevalence of smoking will be greater among first-degree relatives of schizophrenia probands than first-degree relatives of probands drawn from the general population.
- Hypothesis 1b: Genetic contributions to nicotine use, as given by heritability estimates, will be greater among those family history positive for schizophrenia compared to healthy comparison subjects and their relatives.

The first hypothesis broadly examines rates of nicotine use and the association between smoking and vulnerability for schizophrenia and aims to replicate previous reports of elevated smoking prevalence in this patient population. Second, data from family members of demographically matched community probands provide a comparison prevalence rate of smoking in the general population with which to examine the prevalence of smoking in those with a family history of schizophrenia. This comparison was proposed for descriptive purposes to document relative rates of smoking in family members, regardless of the smoking status of the index proband. The second hypothesis examines patterns of nicotine use in families, taking into account the smoking status of the schizophrenia or control proband and the degree of genetic relationship among family members (i.e. parent, sibling).

Specific Aim 2: Examine the relationship between nicotine use and beta frequency activity in resting EEG.

- Hypothesis 2a: Beta power will be elevated in those with a smoking history relative to those with no history of nicotine use.
- Hypothesis 2b: Differences in cortical activity in the beta band between smokers and non-smokers will be greater among probands with schizophrenia than comparison controls.
- Hypothesis 2c: A significant relationship between resting EEG spectral power and smoking history will be specific to beta activity as compared to power in the alpha and gamma frequency bands.

The hypotheses associated with the second specific aim are based upon any history of smoking, whereby current and past smokers are considered together (“ever-smoker”),

compared to those without any history of smoking (“never-smoker”). Secondary analyses were proposed to examine differences between current, former, and non-smokers without a priori hypotheses. In examining the relationship between beta power and smoking history, diagnosis was used as a between-groups factor to test the relationship between resting EEG and nicotine use in those with and without schizophrenia. This is specified in hypothesis 2b. A differential effect of smoking between patients and controls might indicate the extent to which electrophysiological functioning has significant utility in explaining smoking in schizophrenia. Given previous findings of the effects of gender in characterizing the relationship between beta power and alcohol dependence, gender was considered an additional factor in examining differences in resting EEG power. Significant histories of past alcohol or drug use were also considered in the study design and in statistical analyses following data collection.

Finally, hypothesis 2c aims to test the specificity of the relationship between nicotine use and electrophysiological activity in the beta band. Comparing relationships between nicotine use and activity across the frequency spectrum may provide insight as to whether smoking is related to a broad increase in cortical arousal, whereby elevations in power across the frequency spectrum would be expected, or whether distinct frequency bands are affected.

Specific Aim 3: Investigate the relationships among variables hypothesized to be associated with nicotine use, and their contributions to current nicotine dependence.

- Hypothesis 3a: Greater beta power in resting EEG will be associated with poorer sensory gating performance and greater levels of nicotine dependence.
- Hypothesis 3b: Variables presumed to underlie vulnerability to nicotine use, including family history of smoking, diagnosis, frequency spectral data, and sensory gating will significantly predict current use and level of nicotine dependence.

The final aim of this study seeks to examine the extent to which variables thought to contribute to nicotine use are related to each other (hypothesis 3a), and to examine their individual and collective contributions (3b) to nicotine use. As the factors included in this working model are presumed to share common variance (e.g. genetic susceptibility to nicotine use may overlap with genetic susceptibility to schizophrenia; beta frequencies have been shown to contribute to sensory gating), the predictive power of all variables are considered together. The extent to which each variable contributes significant variance in predicting current nicotine dependence is of interest.

While support for these hypotheses will not provide definitive evidence for a genetically mediated self-medication function for nicotine, support for, or refutation of, this hypothesis will help to lay the groundwork for future, more molecular studies investigating the pathophysiology of nicotine dependence in schizophrenia. In addition, while stimulus-evoked beta oscillations have been linked to sensory gating, this study will examine how resting beta oscillatory activity may be linked to information processing dysfunctions and nicotine use. Thus, in utilizing resting EEG to study nicotine dependence in schizophrenia, this study aims to link together

findings from the addictions, schizophrenia, and electrophysiology literatures in an attempt to further explore the smoking phenomenon prevalent within the schizophrenia population.

Additional Considerations

Current versus Past Smoking

The first two specific aims primarily consider any history of nicotine use, past or current. However, examining those factors which differentiate former and current smokers would be informative in elucidating the mechanisms responsible for susceptibility to addiction, or conversely, the factors associated with the ability to control substance use or to quit. Genetic influence is known to play a role in both smoking initiation as well as smoking persistence. Based on the trait-like nature of oscillatory activity across the frequency spectrum in non-pathological and schizophrenia samples, it may be hypothesized that elevated beta band power also represents vulnerability to substance use, regardless of past or persistent use. However, inter-individual variability in beta power may also represent degree of cortical hyperexcitability, thereby reflecting degree of susceptibility to substance dependence. Thus, it might be hypothesized that those who initiate substance use but are more likely to quit are differentiated by level of cortical activation. Limitations of statistical power must be taken into consideration in comparing former and current smokers in the proposed study.

Other Substance Use

Significant overlap between nicotine use and other substance use disorders are likely, given rates of both within schizophrenia samples and rates of comorbidity in the general population, as reported in prior research. This study attempts to control for the confounding effects of other substance in delineating the relationship between electrophysiological functions and nicotine dependence by limiting the clinical characteristics of the study sample with respect to current substance use. Individuals with some alcohol or drug use are not to be excluded all together, however, so as not to significantly bias the sample. Specific inclusion and exclusion criteria will be explicated in the following methodology section.

Psychotropic Medication

Individuals with schizophrenia must be maintained on their current medications during the assessment period. Psychotropic medications may include not only antipsychotic drugs, but concomitant medications, which may affect electrophysiological data. The pharmacological effects of certain psychiatric drugs on EEG are documented to some extent in the general research literature. Evidence indicates that benzodiazepines increase activity in the beta band, while some evidence indicates that antipsychotic medications slow EEG activity, attenuating beta activity, although some findings indicate minimal to no influence of antipsychotic drugs on resting EEG (Itil, Saletu & Davis, 1972; Joutsiniemi, Gross, & Appelberg, 2001). Assessment of medication history of all research participants may warrant consideration in analyses if effects of such medications on group outcomes are expected.

Direct Effects of Smoking

Cigarette smoking is found to have direct effects on quantitative EEG (Domino & Matsuoka, 2003; Domino, Riskalla, Zhang & Kim, 1992; Newton, Cook, Holschneider, Rosenblatt, Lindhol & Jarvik, 1998). Studies of smokers from the general population have demonstrated changes in specific frequency bands such as decreases in delta and theta power and increases in alpha and beta power (Kadoya, Domino, & Matsuoka, 1994). These effects appear to result from a shift of the overall power spectrum toward higher frequencies. Individual differences have, however, been noted irrespective of nicotine content of cigarettes smoked in laboratory paradigms and placebo effects of sham smoking on EEG activity have been documented (Domino & Matsuoka, 2003). These findings suggest the effects of additional factors in determining EEG activity other than the direct effects of nicotine. Additionally, nicotine induced changes in EEG activity have been reported under particular assessment conditions, namely following a brief period (e.g. 12 hours) of smoking abstinence.

The potential confound that cigarette smoking introduces in this study is considered to the fullest extent possible. First, in this study, participants maintain their normal smoking habits, except for a period of approximately 30 minutes prior to data collection during which laboratory preparations are completed. Thus, EEG power spectral data are not obtained under the influence of nicotine withdrawal or immediately after cigarette smoking. Similar constraints are placed on measurement of P50 gating. Second, this study design provides the opportunity to examine differences in EEG activity between current smokers and former smokers.

Assessment of smoking history thus allows for examination of factors presumed to underlie nicotine use and addiction, rather than physiological changes as a result of immediate nicotine use. As the prolonged effects of nicotine exposure have not been clearly explicated in the literature, this study provides additional opportunities to clarify the nature of the relationship between nicotine use and specific components of cortical neural network activity.

Chapter 3: Methodology

In order to examine the specific aims, data were collected and analyzed in conjunction with a study titled “Familial Schizophrenia and Spectrum Personality Disorders”. Collection of study data was initiated in 2004 after receiving Institutional Review Board approval from the University of Maryland, Baltimore. This study has been ongoing and is being carried out by Dr. Gunvant Thaker, M.D., the Principal Investigator and chief of the Schizophrenia Related Disorders Program (SRD) at the Maryland Psychiatric Research Center (MPRC) in Catonsville, Maryland. Although data collection at the MPRC has been ongoing, it was the express and unique purpose of this protocol to examine the heritability of nicotine dependence in relation to a family history of schizophrenia, and to apply spectral power analysis methodology to nicotine use within the context of susceptibility to smoking in the schizophrenia population. Such analyses had not been utilized in this or other study samples at the MPRC. This study thus aimed to extend previous findings integrating assessments of beta oscillatory activity and sensory information processing by investigating the relationship between auditory P50 gating and beta power in EEG at rest, and furthermore, in describing this relationship with regard to nicotine use and schizophrenia.

Procedures

Participants

Study data were acquired from archived and continuous data collection at the Maryland Psychiatric Research Center. Recruitment of study participants included (1) clinical case probands meeting Diagnostic and Statistic Manual – IV (DSM-IV) criteria for schizophrenia or Research Diagnostic Criteria (RDC) for schizoaffective disorder, (2) community comparison control probands matched with clinical case probands with respect to age, gender, and county of residence who did not meet DSM-IV criteria for schizophrenia or other psychotic disorders, (3) first-degree relatives (e.g. biological parents and siblings) of clinical case probands identified by the case proband, and (4) first-degree relatives of control probands identified by the comparison individual. Guidelines for recruitment of all participants is described by the inclusion/exclusion criteria and recruitment procedures as detailed below.

Criteria for study inclusion dictated that all participants were at least 18 years of age, representing all ethnicities, both males and females. Individuals with serious medical, neuro-opthamological, or neurological illness (e.g. seizure disorder, encephalopathy), mental retardation, current (past 6 months) drug or alcohol abuse or dependence were excluded. Comparison controls drawn from the community were excluded if a family history of psychotic disorder including schizophrenia was reported.

Recruitment

Families with a first-degree relative diagnosed with schizophrenia were recruited via newspaper advertisements in the Baltimore/Washington D.C. metropolitan area. Some clinical case probands were recruited from individuals participating in outpatient programs at the Maryland Psychiatric Research Center. Potentially interested individuals with schizophrenia signed an informed consent form, giving permission to screen their medical records for eligibility, collect demographic information, and contact first-degree family members named by the individual. Upon provision of contact information for first-degree relatives, a letter sent through the mail requested family member participation. Attempts were made to recruit all relatives with contact information provided by the case proband. Recruitment letters were followed by phone calls. Letters and phone scripts were approved by the University of Maryland Baltimore IRB.

Comparison control probands were recruited from the Baltimore/Washington D.C. community. A pool of potential subjects was provided by a search of public records (e.g. Motor Vehicle Administration records) for individuals who matched clinical case probands in age, race, and county of residence. Individuals who met these criteria were contact first by letter and then by phone. For those who agreed to participate, contact information for first-degree relatives of comparison control probands was requested and recruitment of family members of control probands was initiated by letter. Recruitment letters were followed up by phone. Recruitment letters and phone scripts for community controls and family members were approved by the University of Maryland Baltimore IRB.

Clinical case and control proband data were collected and analyzed even if their relatives did not participate. Failure to recruit relatives was due to (1) refusal to participate in the full “Familial Schizophrenia and Spectrum Personality Disorders” study, (2) ineligibility based on inclusion or exclusion criteria (e.g. age), or (3) residing out of area. For these individuals, an alternative method of participation was offered. Family members who did not participate in the full study were contacted by letter and then by phone to request information about past or present smoking behaviors. Recruitment and data collection procedures were approved by the University of Maryland Baltimore IRB.

Study Assessments

After informed consent was completed, schizophrenia probands completed a battery of clinical assessments. Clinical data were extracted from the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) and Research Diagnostic Criteria (RDC), family history interview based on Family History Research Diagnostic Criteria (FH-RDC), and the Nicotine Dependence History including the Fagerstrom Test for Nicotine Dependence (FTND). Only schizophrenia probands who completed the nicotine dependence and EEG assessments were included in data analyses. For the schizophrenia probands, data from electrophysiological testing included P50 gating data and raw data from a five minute resting EEG sample. Unprocessed resting EEG data were subjected to data reduction and analyses for the appropriate outcome measures, which will be described below.

Data were obtained from the following assessments conducted with community control probands and first-degree family members of clinical case and

community control probands: sociodemographic information, medical history, family history interview based on FH-RDC (if not previously completed by a clinical case or community comparison proband), Nicotine Dependence History including the FTND, the SCID Non-Patient Version (SCID-NP), and the Structured Interview for DSM-IV Personality Diagnoses (SIDP). Only community control probands who completed the nicotine dependence and resting EEG assessments were included in analyses for this protocol. The SIDP was used only as a screening measure for personality diagnoses in the community participants; in the case of a positive diagnosis of a personality disorder, study data were not obtained. For family members, analyses were completed without regard for Axis II psychopathology. For community control probands, sociodemographic information, SCID-NP diagnosis (e.g. substance use disorder), nicotine dependence data, and data from electrophysiological testing including P50 gating and a five minute resting EEG sample were obtained. Electrophysiological data were obtained in an unprocessed form with the data from the patient probands without regard for diagnostic status. Thus, data reduction and analyses for the appropriate outcome measures were performed blind to group status.

Diagnostic Assessments

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 routinely assess all study participants for Axis I disorders including mood disorders, psychotic disorders, alcohol and substance use disorders, and anxiety 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). Diagnostic information on each patient was presented by the clinical interviewer in a best estimate diagnosis meeting at the MPRC, chaired by a senior psychiatrist. The SCID was used to verify a diagnosis of schizophrenia for the clinical case proband; diagnoses of alcohol and substance use disorders (not including tobacco dependence), disorders among control and patient probands were documented.

Family History Research Diagnostic Criteria (FH-RDC; Andreasen, Rice, Endicott, Reich & Coryell, 1986): SRD clinicians used the FH-RDC to screen 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). Data were extracted as a dichotomous variable, family history positive or family history negative. For those who are family history positive, the number of affected individuals within the family was ascertained by chart review.

Smoking and Nicotine Dependence Assessments

Nicotine Dependence Data including the Fagerstrom Test for Nicotine Dependence (FTND; Heatherton, Kozlowski, Frecker & Fagerstrom, 1991): Assessment of smoking and nicotine dependence was identical regardless of whether individuals participated in the full study or only completed the nicotine dependence assessment over the phone. This data was acquired for schizophrenia and control probands as well as family members for whom data was available in study databases and family study chart records. All participants were first asked if they have ever been a smoker (yes/no); if the participant responded yes, whether or not the

participant currently smokes was ascertained (yes/no). If the participant smoked in the past but was not currently a smoker, the number of years since the individual quit smoking was calculated. The participant was asked to complete the FTND with respect to their current smoking behaviors, or if not applicable, then with respect to past smoking behaviors. Additional data included age at smoking initiation, age at which habitual smoking began, smoking years, number of quit attempts, and symptoms of nicotine withdrawal experienced during past quit attempts (see Appendix B for the full nicotine dependence assessment).

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).

Measures drawn from this assessment included dichotomous variables, “ever-smoker” (yes/no) and “current-smoker” (yes/no); between-group variables also included classification as “current”, “former”, or “never-smoker”. Rates of smoking were compared between proband groups and rates of ever and current smoking among first-degree family members were described for each group as well. A

continuous variable, FTND total score, was also used in analyses. Additional data (e.g. smoking years) was available for some participants and was obtained for descriptive purposes in characterizing the smoking histories of the study samples. In supplementary analyses, smokers were classified dichotomously as nicotine dependent or not dependent based on a FTND total score equal to or greater than 4. This index has been used in prior investigations (e.g. Gelernter, Panhuysen, Wiess, Brady, & Poling, et al., 2007) to characterize nicotine dependence.

Heritability Analyses: Smoking histories and nicotine dependence data collected from probands and their family members (derived from the FTND) were utilized to calculate heritability estimates for smoking. Pedigree and phenotype data were organized for each family unit utilizing available data from each proband and their participating parents and/or siblings with regard to history of ever smoking and current smoking. The SOLAR (Sequential Oligogenic Linkage Analysis Routines) software package (Almasy & Blangero, 1998) was used to calculate heritability estimates (h^2) for patient and control pedigrees separately. This program allows for smoking data to be analyzed for relatives with varying kinship relations for pedigrees of varying size. A polygenic model was assumed; this analysis yields an estimated percentage of variance explained by genetic and environmental factors based on rates of smoking within families and the degree of genetic relationship between family members. The heritability estimate represents the proportion of variance attributed to additive genetic effects; statistical significance of h^2 was determined by computing the log likelihood between the polygenic model and a sporadic model with a heritability estimate of zero. For each model, age and sex were entered as covariates.

The significance of each heritability estimate and covariates will be reported for each model tested.

Electrophysiological Assessments

Set Up: The procedures for electroencephalogram (EEG) measures consisted of the application of electrodes to the scalp and face, the performance of a number of simple tasks while EEG data was acquired, removal of electrodes, and clean up.

Recordings were obtained from a cap with up to Ag/AgCl active electrodes referenced to linked ears. Vertical and horizontal oculograms were recorded as well. Skin impedance was maintained at less than 10 kOhms. EEG data were collected using a Neuroscan SynAmp amplifier running under Acquire software. EEG data for a battery of tasks were collected in succession, typically within one testing session. Data acquisition uniformly began with resting EEG.

Resting EEG: 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 closed but not to fall asleep for five minutes while data were acquired. Resting recordings were acquired as continuous EEG data; raw data for analyses were obtained in an unprocessed form and then subjected to filtering, artifact rejection, and time/frequency analysis offline. Data processing was completed using the Neuroscan software.

Data reduction and analyses were based on procedures and parameters described by Rangaswamy and colleagues (2002; 2004) and guidelines for EEG analyses described by Pivik and colleagues (Pivik, Broughton, Coppola, Davidson, Fox, & Nuwer, 1993). Data were collected from electrode leads in frontal, central,

parietal, and occipital scalp locations. However, prior studies have found the most consistent significant increases in power across the beta frequency spectrum at the Fz-Cz lead pair, differentiating alcohol dependent individuals from healthy controls. Thus data from two electrodes, Fz and Cz, were utilized for statistical analyses in schizophrenia and healthy control samples in this study. In order to preliminarily assess the consistency of data recordings across the 5 minute sample, markers (marker type 1 and marker type 2) were inserted alternately every 2 seconds through the duration of continuous raw data recording for each participant, yielding in total 144 markers; data reduction and bandpower analyses, described below, were conducted on the basis of type 1 and type 2 EEG data. All statistical analyses of power for each defined frequency band were based on an average of type 1 and type 2 data derived for each individual, thereby providing the full duration of EEG recording for analyses.

Data reduction methods performed with Neuroscan software were as follows. Continuous data was analyzed in 2 second epochs. Baseline correction was performed across the entire sweep utilizing data from all channels. Artifact rejection was based on criteria of $-100\mu\text{V}$ and $100\mu\text{V}$ at the ocular, Cz, and Fz electrode sites. Data were aggregated into bands and averaged across epochs. Bandpass filters were applied to calculate absolute power in the alpha (8-12 Hz), beta (12.0 – 28.0 Hz), and gamma (30 – 50 Hz) frequency bands. Parameters for the bandpower analysis varied slightly between frequency spectra due to edge effects that varied with frequency. For power in the alpha band, each 2 second epoch was trimmed at the beginning and end by 200ms, yielding epochs that were 1600ms in length. For power in the beta and

gamma frequency bands, epochs were trimmed at either end by 100ms, yielding 1800ms epochs that were averaged together in the bandpower analysis. Data were visually inspected for errors in recording or processing and for significant noise which excluded bandpower data from 7 subjects. Bandpower across the frequency spectrum was converted from Neuroscan to data files in Excel; mean bandpower for electrode sites Cz and Fz were calculated across time for each epoch. Mean bandpower was log transformed to normalize the sample distributions (Pivik et al., 1993) and subjected to statistical analysis in accordance with the second specific aim of the study.

The second study aim was to examine the relationship of EEG activity in the beta band to nicotine use history, and to compare whether this relationship varies with respect to a diagnosis of schizophrenia. Repeated Measures Analysis of Variance was used to examine this specific aim for power in the alpha, beta, and gamma frequency bands. Gender and past substance use were considered as variables in preliminary analyses in addition to diagnostic group and smoking status in main analyses. Main effects and interactions for between-group variables were examined.

P50 Auditory Evoked Potentials: Participants are instructed to keep their eyes open and listen to paired click stimuli through headphones. Auditory stimuli were generated by a programmable sound module (Neuroscan) and delivered at a sound intensity of 75dB. Auditory clicks were delivered in pairs with a 500ms inter-click interval, at a rate of 1 pair every 10 seconds for a total of 150 pairs. 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 gathered 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. In the P50 gating paradigm, a decremented evoked response to the second auditory stimulus is expected, as inhibitory mechanisms activated by the first auditory stimulus attenuate the secondary reaction (Adler et al., 1982). A failure to suppress the second response indicates that the inhibitory mechanism is impaired (Adler et al., 1999). Disrupted gating was defined as a S2/S1 ratio that exceeds 0.50 (Freedman, Adler, Myles-Worsely, Nagamoto & Miller et al., 1996). Data were extracted as S1 and S2 amplitudes and the S2/S1 ratio. For exploratory purposes, continuous P50 data were also classified dichotomously as being “impaired” or “unimpaired.”

Sensory gating performance was compared between patients with schizophrenia and controls and interactions with smoking status were considered as well. The relationships between P50 gating performance and level of nicotine dependence, and P50 gating performance and resting EEG power across the frequency spectrum were examined. In accordance with the third specific aim, the contribution of electrophysiological data (P50 ratio and bandpower) to history of ever and current smoking was investigated using logistic regression analyses.

Chapter 4: Results

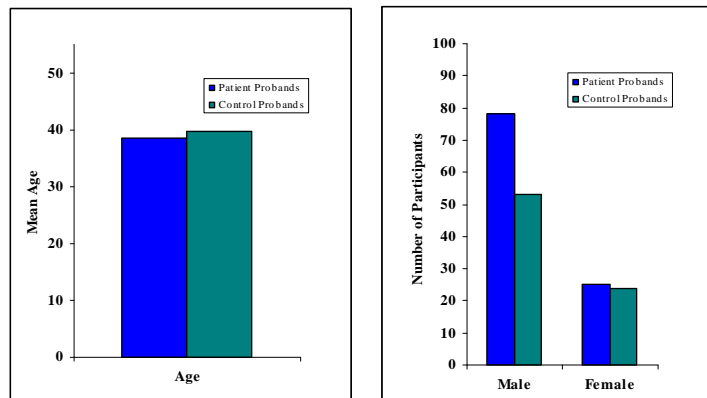
This study utilized four groups to examine three multi-level study aims. In this section, participants from each group will first be described with respect to demographic characteristics as well as past and present alcohol and drug use. The three specific aims and the hypotheses contained within each will then be described, and statistical analyses and results will be reported.

Participants

Participants included (1) 141 probands affected by schizophrenia or schizoaffective disorder recruited from outpatient programs at the Maryland Psychiatric Research Center, (2) 158 first-degree relatives of affected probands, (3) 109 healthy comparison control probands recruited from the Baltimore/Washington D.C. area, and (4) 44 first-degree relatives of comparison control probands. Based on availability of data provided by index probands, recruitment efforts targeted 78 patient families (55.32% of patient probands) and 35 control families (32.11% of control probands). Of those probands who identified first-degree relatives, there was no statistically significant difference in actual recruitment rates between patient and control groups ($\chi^2 = 0.75$, $p = 0.39$). For each proband who had a family member recruited, between 1 and 6 first-degree relatives participated. For patients with schizophrenia, successful recruitment resulted in a family group composed of equal numbers of siblings and parents, whereas first-degree relatives of comparison controls included 59% siblings and 41% parents.

Patient and control probands were compared on demographic characteristics including sex, age, and race/ethnicity. The distributions for proband demographic characteristics are represented in Figure 1. In both groups, participants were predominantly Caucasian (54 patients and 53 controls) and Black/African American (45 patients and 21 controls). There were no statistically significant differences with respect to the proportion of males and females in each proband group ($\chi^2 = 0.49$, $p = 0.48$), with respect to the rates of participant-identified race or ethnicity ($\chi^2 = 4.66$, $p = 0.46$), nor with respect to mean age ($F_{(1,249)} = 0.006$, $p = 0.94$).

Figure 1. Demographic Characteristics



Community participants were excluded from the study if a family history of schizophrenia-spectrum disorder was present. Within the patient proband group, 14.4% reported having at least one first-degree family member with schizophrenia ($n = 7$) or schizophrenia spectrum personality disorder (schizotypal or schizoid personality disorder; $n = 8$). Patient and control participants were screened for lifetime and current substance abuse or dependence. Among probands and family members screened ($N = 360$), 11.8% reported a history of lifetime alcohol abuse and 9.5% reported a history of lifetime alcohol dependence. Among all participants screened, 17.4% reported a history of lifetime drug abuse (e.g. sedative, cannabis,

stimulant, opioid, cocaine, hallucinogen, poly-substance, or other drug use) and 14.8% reported a history of lifetime drug dependence. In the patient proband group alone, 38.5% reported any lifetime alcohol/drug abuse or dependence with 2.7% reporting current diagnostically significant substance use. In the control group, 24.4% reported any lifetime alcohol/drug abuse or dependence with 1.2% reporting current substance use.

Specific Aim 1: Smoking and Nicotine Dependence

Specific aim 1 sought to compare rates of smoking and the heritability of smoking among individuals with and without a family history of schizophrenia in order to characterize rates of nicotine use in the study sample, and examine the association between smoking and vulnerability for the illness. Based on prior research demonstrating elevated rates of smoking and nicotine dependence among individuals with schizophrenia, hypothesis 1a proposed that the prevalence of nicotine use, past or present, would be greater among patient probands than healthy comparison controls. This hypothesis also proposed that the prevalence of smoking would be greater among first-degree relatives of affected probands than first-degree relatives of probands drawn from the general population.

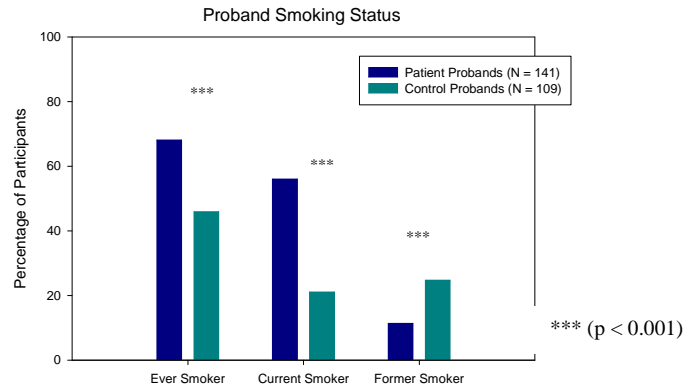
Smoking Prevalence

Nicotine dependence data was available for 141 probands with schizophrenia/schizoaffective disorder and 109 comparison controls. Rates of smoking were compared utilizing Pearson Chi-Square analyses; these results are presented in Figure 2. Rates of ever smoking (past or present) were significantly

different between patients and controls ($\chi^2 = 12.49$, $p < 0.001$) with 68.1% of patients and 45.9% of controls reporting ever smoking. Among the patient group, 11.4% were former smokers, compared to 24.8% of controls; among those with any smoking history, a greater proportion of control probands (50%) than patient probands (15.3%) were former smokers ($\chi^2 = 14.73$, $p < 0.001$). The difference between proband groups for the rate of current smoking was also statistically significant ($\chi^2 = 31.05$, $p < 0.001$) with 56.0% of patients and 21.0% of controls reporting current smoking. To further characterize differences in smoking history across diagnostic groups, years of smoking was compared; patient and control probands reported a mean number of smoking years of 20.4 (SD = 12.3) and 15.6 (SD = 12.8) respectively. An independent samples t-test indicated that this difference was not statistically significant ($p = 0.06$).

Ever smoking and current smoking were also examined using Chi-Square analyses in the subgroup of patient probands with a family history of schizophrenia-spectrum disorder. Among patient probands who were family history positive ($n = 15$), 12 reported a history of ever smoking and 3 reported no smoking history ($\chi^2 = 2.73$, $p = 0.09$). Ten patient probands reported current smoking and 5 were classified as former or never smokers; Chi-Square values for current smoking relative to family history approached statistical significance ($\chi^2 = 3.63$, $p = 0.057$).

Figure 2. Smoking Status

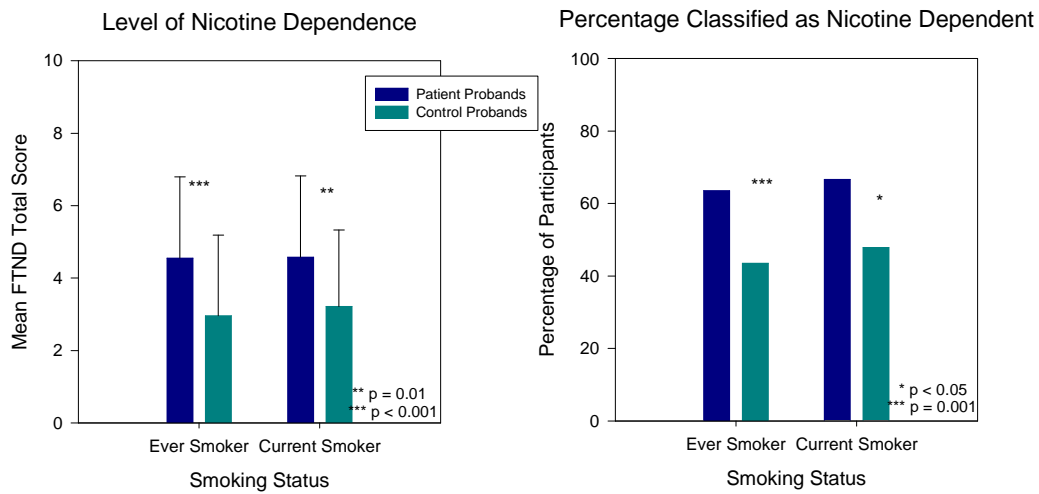


Nicotine Dependence

Mean levels of self-reported nicotine dependence were compared between patient and control proband groups utilizing ANOVA for total score on the Fagerstrom Test for Nicotine Dependence (FTND). Among patients (N = 94) and controls (N = 46) who reported a history of ever smoking, patient probands reported a mean total score of 4.55 (SD = 2.24), which was significantly greater than the mean total score of 2.96 (SD = 2.23) for the control probands ($F_{(1, 140)} = 15.632, p < 0.001$). On the basis of a total FTND score of 4 or greater, participants were also categorized dichotomously as nicotine dependent or not dependent and rates of nicotine dependence were compared between groups using a Chi-Square analysis. Results are presented in Figure 3. Among ever smokers, patients were more likely to be categorized as nicotine dependent (63.57%) than controls (43.48%; $\chi^2 = 11.94, p = 0.001$). Among patients (N = 79) and controls (N = 23) who reported current smoking, patient probands reported a mean total FTND score of 4.58 (SD = 2.24), which was significantly greater than the mean total score of 3.22 (SD = 2.11) for the control probands ($F_{(1, 101)} = 6.79, p = 0.01$). The magnitude of the group differences in mean

FTND scores between patient and control probands was also quantified by calculating Cohen's d. Effect sizes for level of nicotine dependence were in the medium range for ever smokers ($d = 0.71$) and current smokers ($d = 0.63$).

Figure 3. Nicotine Dependence



Compared dichotomously, rates of nicotine dependence were greater ($\chi^2 = 4.74$, $p = 0.029$) among current smokers with schizophrenia/schizoaffective disorder (66.67%) than among comparison current smokers from the general population (47.83%).

These results are also summarized in Figure 3.

Familial Patterns of Nicotine Use

A second goal within specific aim 1 was to examine patterns of nicotine use in families with or without a history of schizophrenia/schizoaffective disorder. The smoking habits among participating first-degree relatives were preliminarily characterized, followed by a more rigorous analysis of nicotine use patterns, for which heritability estimates for smoking were calculated separately for those families affected and unaffected by schizophrenia/schizoaffective disorder. Among all participating first-degree relatives (parents and siblings) of patient probands, 64 out of

158 (40.51%) reported a history of ever smoking and 21 out of 158 (13.29%) reported currently smoking. Among all participating first-degree relatives of controls probands, 17 out of 44 (38.64%) reported a history of ever smoking and 8 out of 44 (18.18%) reported currently smoking. These differences were not statistically significant ($\chi^2 = 2.81$, $p = 0.25$ and $\chi^2 = 2.70$, $p = 0.26$ for rates of ever and current smoking, respectively).

The heritability analysis for nicotine dependence was conducted to test hypothesis 1b, that genetic contributions to nicotine use would be greater among those family history positive for schizophrenia, compared to healthy comparison subjects and their relatives. The heritability analysis differs from the preliminary characterization of nicotine use patterns by taking into account the smoking status of the schizophrenia or control proband and the degree of genetic relationship among participating family members (i.e. parent or sibling status). A polygenic model was assumed in estimating the heritability (h^2) for ever smoking and current smoking. For each analysis, age and sex were entered into the model as covariates.

Table 1 presents information on family unit size for patient and control groups utilized in the heritability analyses. Importantly, 112 sibling-sibling pairs and 110 parent-offspring pairs were included in the heritability analyses for the patient group while 23 sibling-sibling pairs and 25 parent-offspring pairs within the control group were available for analyses.

In the patient group, the heritability estimate for history of ever smoking was $h^2 = 0.9236$ (SE = 0.20), which was significant at $p = 0.00001$. Both age ($p = 0.02$) and sex ($p = 0.008$) were significant as covariates. For current smoking in the patient

group, $h^2 = 0.9674$ (SE = 0.31) which was statistically significant at $p = 0.0008$. Both age ($p = 0.049$) and sex ($p = 0.00001$) were significant as covariates.

Table 1. Family Unit Descriptives: Heritability Analyses for Smoking History

<i>Family Unit Size</i>	<i>Number of Patient Family Units</i>	<i>Number of Control Family Units</i>
<i>Family Unit n = 2</i>	48	29
<i>Family Unit n = 3</i>	21	5
<i>Family Unit n = 4</i>	8	1
<i>Family Unit n = 5</i>	5	0
<i>Family Unit n = 6</i>	1	0
<i>Family Unit n = 7</i>	1	0

In the control group, the heritability estimate for history of ever smoking was $h^2 = 0.9306$ (SE = 3.86) which was significant at $p = 0.024$. Both age and sex were significant as covariates ($p = 0.0004$ and $p = 0.039$ respectively). For current smoking in the control group, $h^2 = 0.515$ (SE = 0.63) which was not statistically significant ($p = 0.23$). Covariates were entered but not included in the final model, as age ($p = 0.44$) and sex ($p = 0.87$) were not statistically significant.

Summary of Main Findings: Specific Aim 1

The prevalence of ever and current smoking was significantly elevated among patients with schizophrenia/schizoaffective disorder relative to demographically and geographically matched healthy comparison controls drawn from the general population. Among index probands who reported a positive smoking history, mean number of smoking years was not significantly different between groups but patients self-reported a greater level of nicotine dependence and were less likely to have quit smoking after initiating than controls. Heritability estimates for history of smoking

were highly significant and appear comparable among those with and without a family history of schizophrenia.

Specific Aim 2: Smoking and Bandpower in Resting EEG

Specific aim 2 sought to examine the hypothesis that abnormalities in the power of resting EEG, particularly in the beta frequency band, would be associated with nicotine use, as given by prior reports of the association of elevated beta bandpower with alcohol and other substance use disorders. Preliminary analyses sought to characterize the sample of patient (N = 104) and control (N = 78) probands whose EEG and smoking history data were both available for analyses. This subset of participants excluded 1 patient and 1 control, both with current alcohol dependence, and excluded 7 participants with faulty EEG recordings (i.e. data unscorable due to irremovable artifact or errors in recording). No significant differences between patients and controls were found for any demographic characteristics in this subgroup, including mean age ($F_{(1, 178)} = 0.46, p = 0.50$), the proportion of males and females ($\chi^2 = 1.06, p = 0.30$), and the proportions of individuals identifying with racial or ethnic groups ($\chi^2 = 6.109, p = 0.19$). Preliminary analyses also sought to characterize and compare groups on the basis of smoking history. Patient probands within this subset of participants were more likely than control probands to report ever smoking (69.9% versus 46.75%; $\chi^2 = 9.84, p = 0.002$) and current smoking (58.25% versus 23.38%; $\chi^2 = 21.83, p < 0.001$). Patient probands also reported greater mean nicotine dependence on the FTND ($F_{(1,76)} = 9.64, p = 0.003$). When compared dichotomously on the basis of a FTND total score greater than or equal to

4, a greater number of patients (75.0%) than controls (44.4%) were characterized as nicotine dependent ($\chi^2 = 5.936$, $p = 0.015$).

Prior to hypothesis testing for resting EEG bandpower, mean power values were log transformed and the reliability of EEG power was examined for alpha, beta, and gamma frequency band activity for patient and comparison control probands separately. Intraclass correlation coefficients (ICCs) were calculated for type 1 and type 2 EEG data to test the consistency of data recordings over time (5 minutes). In the patient group, EEG data in the alpha, beta, and gamma bands were highly consistent with values of 0.968, 0.979, and 0.991 respectively at electrode site Cz and values of 0.960, 0.963, and 0.988 for alpha, beta, and gamma frequency bands at electrode site Fz. Similarly, data from the control proband group showed high ICCs with values of 0.970, 0.990, and 0.984 for alpha, beta, and gamma bandpower respectively at electrode site Cz and values of 0.963, 0.988, and 0.986 for alpha, beta, and gamma frequency bands at electrode site Fz.

In the total sample ($N = 180$), preliminary analyses revealed no significant main effect for sex or race/ethnicity, and no significant correlations with age for mean alpha and mean beta bandpowers (all p values greater than 0.10), or gamma bandpower (all p values greater than 0.05). Demographic variables were therefore not included as covariates in subsequent analyses. Mean log transformed bandpower was also preliminarily examined by gender. ANOVA revealed no statistically significant differences in power between males and females at either electrode site with p values well above 0.05 (0.37 and greater). Considering the lack of evidence for gender

differences in bandpower in this study sample, subsequent between-groups analyses were also performed without entering gender as a covariate.

In accordance with specific aim 2, three hypotheses were proposed to examine the relationship between smoking and resting EEG. First, it was hypothesized that beta power in resting EEG would be elevated in those with a smoking history relative to those with no history of nicotine use. Second, it was hypothesized that differences in beta bandpower would also be affected by diagnostic status whereby probands with schizophrenia would demonstrate elevated power relative to control probands. Third, it was hypothesized that a significant relationship between resting EEG power and smoking history would be specific to beta activity as compared to power in the alpha and gamma frequencies.

The group means for averaged log transformed bandpower values for electrode sites Cz and Fz are presented in Table 2.

Table 2. Mean Log Transformed Bandpower (μV^2) and Diagnosis

<i>Frequency Band</i>	<i>Electrode Site</i>	<i>Patient Probands (N = 103) M (SD)</i>	<i>Control Probands (N = 77) M (SD)</i>
<i>Alpha (8-12 Hz)</i>	<i>Cz</i>	1.51 (0.46)	1.49 (0.64)
	<i>Fz</i>	1.49 (0.44)	1.43 (0.59)
<i>Beta (12-28 Hz)</i>	<i>Cz</i>	1.55 (0.38)	1.54 (0.49)
	<i>Fz</i>	1.55 (0.35)	1.51 (0.46)
<i>Gamma (30-50 Hz)</i>	<i>Cz</i>	0.97 (0.32)	0.94 (0.39)
	<i>Fz</i>	0.95 (0.34)	0.94 (0.36)

Hypotheses associated with specific aim 2 were addressed with repeated measures ANOVA using electrode site (Cz and Fz) as within-subjects factors, and between-subjects factors including group (patient and control) and smoking status (never, former, current smoker). Mean log transformed power data by diagnostic and smoking group are presented here in Table 3. Within-subjects results demonstrated a significant effect for electrode site for alpha bandpower only ($F_{(1, 174)} = 4.66, p = 0.03$), but there were no significant interactions between electrode site and group ($F_{(1, 174)} = 0.23, p = 0.64$) or smoking status ($F_{(2, 174)} = 0.95, p = 0.39$).

Table 3. Mean Log Transformed Bandpower and Smoking Status

<i>Frequency Band</i>	<i>Electrode Site</i>	<i>Schizophrenia Probands (N =103)</i>			<i>Control Probands (N =77)</i>		
		<i>Never Smoker (N = 31) M (SD)</i>	<i>Former Smoker (N = 12) M (SD)</i>	<i>Current Smoker (N = 60) M (SD)</i>	<i>Never Smoker (N = 41) M (SD)</i>	<i>Former Smoker (N = 18) M (SD)</i>	<i>Current Smoker (N = 18) M (SD)</i>
<i>Alpha (8-12 Hz)</i>	<i>Cz</i>	1.44 (0.41)	1.63 (0.24)	1.52 (0.51)	1.50 (0.51)	1.64 (0.36)	1.33 (1.00)
	<i>Fz</i>	1.35 (0.53)	1.60 (0.26)	1.54 (0.40)	1.43 (0.49)	1.59 (0.31)	1.27 (0.93)
<i>Beta (12-28 Hz)</i>	<i>Cz</i>	1.54 (0.33)	1.69 (0.17)	1.53 (0.43)	1.56 (0.39)	1.63 (0.23)	1.37 (0.80)
	<i>Fz</i>	1.51 (0.36)	1.73 (0.18)	1.55 (0.36)	1.54 (0.37)	1.02 (0.24)	1.35 (0.73)
<i>Gamma (30-50 Hz)</i>	<i>Cz</i>	0.97 (0.31)	1.10 (0.29)	0.95 (0.33)	0.96 (0.24)	1.02 (0.24)	0.81 (0.68)
	<i>Fz</i>	0.95 (0.33)	1.13 (0.29)	0.92 (0.35)	0.97 (0.25)	1.02 (0.62)	0.79 (0.62)

Repeated measures ANOVA revealed no significant main effect for smoking status for log transformed power in the alpha ($F_{(2, 174)} = 1.66, p = 0.19$) or beta ($F_{(2, 174)} = 2.62, p = 0.07$) frequency bands. There was a significant main effect for smoking status in the gamma frequency band ($F_{(2, 174)} = 3.34, p = 0.03$). Post-hoc comparisons (Least Significant Difference) for power in the gamma frequency band revealed that

this main effect of smoking status was due to a significant difference in bandpower between former and current smokers ($p = 0.03$) such that current smokers demonstrated lower mean bandpower in the gamma band than former smokers².

Given that this pattern of lower power among current smokers, relative to former smokers, was observed in the alpha and beta frequency bands as well, effect sizes were calculated to assess the magnitude of the differences between current and former smokers across the frequency spectrum; effect sizes were in the small range for differences in the alpha frequency band and in the medium range for differences in the beta and gamma frequency bands. These results are summarized in Table 4.

Table 4. Bandpower Differences Between Current and Former Smokers

	<i>Schizophrenia Probands (N = 103)</i>		<i>Control Probands (N = 77)</i>
<i>Frequency Band</i>	<i>Electrode Site</i>	<i>Cohen's d</i>	<i>Cohen's d</i>
<i>Alpha (8-12 Hz)</i>	<i>Cz</i>	0.28	0.41
	<i>Fz</i>	0.18	0.46
<i>Beta (12-28 Hz)</i>	<i>Cz</i>	0.49	0.44
	<i>Fz</i>	0.63	0.61
<i>Gamma (30-50 Hz)</i>	<i>Cz</i>	0.48	0.41
	<i>Fz</i>	0.65	0.37

Hypotheses 2a and 2c were not supported in that beta bandpower did not significantly vary relative to smoking status. Rather evidence for an association between gamma bandpower and smoking status was demonstrated. Repeated measures ANOVA revealed no significant main effect of group on log transformed power in the alpha ($F_{(1, 174)} = 0.34, p = 0.56$), beta ($F_{(1, 174)} = 1.43, p = 0.23$), or gamma ($F_{(1, 174)} = 1.59, p$

² As there was no within-subjects effect for electrode site for beta and gamma frequency bands, values for Cz and Fz were averaged for each and univariate ANOVAs were conducted using collapsed log transformed bandpower. Patterns of results were unchanged for between-subjects effects of diagnostic group and smoking status for both frequency bands, and post-hoc differences between former and current smokers in the gamma band were maintained.

= 0.21) frequency bands. Group by smoking status interactions were not significant for log transformed power in the alpha ($F_{(2, 174)} = 1.33, p = 0.26$), beta ($F_{(2, 174)} = 1.07, p = 0.35$), or gamma ($F_{(2, 174)} = 0.02, p = 0.54$) frequency bands. These results therefore do not support hypothesis 2b. These and other results from post-hoc analyses (described below) examining relationships between smoking status, diagnosis, and resting EEG are summarized in Table 5.

Table 5. Repeated Measures ANOVA Bandpower Comparisons

	<i>Primary Analysis</i>			<i>Secondary Analysis</i>		
	<i>Group F(1,174)</i>	<i>Smoking Status F(2,174)</i>	<i>Group x Smoking Status F(2,174)</i>	<i>Group F(1,74)</i>	<i>Nicotine Dependency Status F(1, 74)</i>	<i>Group x Nicotine Dependence F(1,74)</i>
<i>Alpha (8-12 Hz)</i>	F = 0.34 p = 0.56	F = 1.66 p = 0.19	F = 1.33 p = 0.26	F = 2.24 p = 0.14	F = 1.25 p = 0.26	F = 1.11 P = 0.29
<i>Beta (12-28 Hz)</i>	F = 1.43 p = 0.23	F = 2.6 p = 0.07	F = 1.07 p = 0.35	F = 2.27 p = 0.13	F = 2.08 p = 0.15	F = 1.63 P = 0.20
<i>Gamma (30-50 Hz)</i>	F = 1.59 p = 0.21	F = 3.34 p = 0.03	F = 0.02 p = 0.54	F = 2.84 p = 0.09	F = 5.07 p = 0.02	F = 0.12 p = 0.52

Specific Aim 2: Post-Hoc Analyses

Effects of Nicotine Dependence on Bandpower

Considering that the group classified as “never smokers” is likely to be heterogeneous in that factors contributing to their current non-smoking status are unknown (i.e. due to a lack of exposure to smoking in psychosocial environment, occasional cigarette use without the development of a regular pattern of smoking, etc), repeated measures ANOVA was conducted to examine the relationship between resting EEG power, schizophrenia, and nicotine dependence in the subgroup of

current smokers. Current smokers represent a group who have had exposure to cigarette use and currently demonstrate a regular smoking pattern. These individuals reported currently smoking at least 1 cigarette per day and included 60 patient and 18 control probands. Current smokers were classified dichotomously on nicotine dependence, based on a FTND Total Score of greater than or equal to 4; of all current smokers in the sample, 25 were classified as non-dependent and 53 current smokers were classified as dependent.

Between-subjects factors included both patient or control status and nicotine dependence status. Repeated measures ANOVA again revealed no statistically significant main effects for group across the frequency spectrum, and no statistically significant main effects for nicotine dependency for power in the alpha ($p = 0.26$) or beta ($p = 0.15$) frequency bands. Classification by nicotine dependency yielded a significant main effect for gamma bandpower ($F_{(1, 74)} = 5.07, p = 0.02$). Group by nicotine dependency status interactions were non-significant across frequency bands (all p values 0.20 or above).

Given the significant effect of smoking status on power in the gamma frequency band and the same significant effect of nicotine dependency among current smokers, zero order correlations were calculated to examine the strength of the relationship between variations in power and level of nicotine dependence. Despite the statistical significance of differences in gamma power when current smokers were dichotomized according to a cut-off score on the FTND, correlation analyses including log transformed power in the alpha, beta, and gamma frequency bands and Total FTND score were not significant across the frequency spectrum.

Effects of Medication on Bandpower

As certain psychotropic drugs are known to affect EEG in predictable patterns, and individuals with schizophrenia are likely to be treated with such medications, post-hoc analyses were conducted, excluding individuals based on a review of medication records. In the patient sample, 12.8% of individuals were currently prescribed clozapine; clozapine has been shown to shift bandpower towards slower frequencies. Thus, to determine whether differences in power were significantly influenced by antipsychotic medication status, repeated measures ANOVA was conducted excluding 23 patients prescribed clozapine, using electrode site as the within-subjects factor and group (patient or control) and smoking status (never, former, current) as between-subjects factors.

Table 6. Post-Hoc Bandpower Comparisons

	<i>Clozapine Excluded</i>			<i>Benzodiazepines Excluded</i>		
	<i>Group F(1,151)</i>	<i>Smoking Status F(2,151)</i>	<i>Group x Smoking Status F(2,151)</i>	<i>Group F(1,162)</i>	<i>Smoking Status F(1, 162)</i>	<i>Group x Smoking Status F(1,162)</i>
<i>Alpha (8-12 Hz)</i>	F = 0.02 p = 0.89	F = 1.47 p = 0.23	F = 0.94 p = 0.39	F = 0.04 p = 0.83	F = 1.49 p = 0.23	F = 0.92 P = 0.40
<i>Beta (12-28 Hz)</i>	F = 0.34 p = 0.56	F = 2.82 p = 0.06	F = 0.80 p = 0.45	F = 0.72 p = 0.39	F = 2.47 p = 0.08	F = 0.92 P = 0.40
<i>Gamma (30-50 Hz)</i>	F = 0.95 p = 0.33	F = 3.59 p = 0.03	F = 0.62 p = 0.54	F = 1.16 p = 0.28	F = 3.14 p = 0.04	F = 0.69 p = 0.49

Within-subjects results revealed no significant effects of electrode site in any frequency band (main effect for electrode site was no longer significant for alpha bandpower, $F_{(1, 151)} = 2.92$, $p = 0.09$). Results for between-subjects comparisons are summarized in Table 6. Main effects for smoking status were not significant for

power in the alpha or beta frequency bands but the main effect of smoking status on power in the gamma frequency band remained significant ($p = 0.03$). Main effects for group were not significant across the frequency spectrum. Similarly, group by smoking status interactions were not significant for any bandpower spectrum. Thus the original pattern of results reported was not significantly affected by inclusion or exclusion of individuals prescribed the antipsychotic drug clozapine.

Anxiolytic medications belonging to the benzodiazepine class of drugs are also commonly prescribed among individuals with mental illness and have been shown to affect resting EEG by increasing beta band activity. In this sample, 6.7% were currently prescribed a benzodiazepine (e.g. alprazolam, clozapepam, lorazepam); the general linear model was retested with repeated measures ANOVA, excluding 11 patients and 1 control proband, to ensure that the primary findings were not significantly affected by the effects of this class of medication. Within-subjects results indicated a significant effect of electrode site for alpha bandpower only ($F_{(1, 162)} = 4.45, p = 0.03$). Main effects for smoking status were not significant for power in the alpha or beta frequency bands. Similar to the results reported from the full group, the main effect of smoking status was significant for power in the gamma frequency band ($F_{(1, 162)} = 3.14, p = 0.04$). The main effect of diagnostic group was not statistically significant across the frequency spectrum and there was no significant interaction between group and smoking status.

Summary of Main Findings: Specific Aim 2

Data reduction of a five minute resting EEG sample yielded means for log transformed absolute power in the alpha, beta, and gamma frequency bands. Former

smokers demonstrated relatively increased power across the frequency band range from alpha to gamma. Repeated Measures ANOVA revealed a main effect for smoking status in the gamma frequency range with significant differences in mean log transformed bandpower between current and former smokers. Statistical analyses did not yield support for the proposed hypotheses as no specific abnormalities in the beta frequency band were found with respect to smoking status or diagnostic group.

Relative increases in bandpower among former smokers may suggest long-term effects of nicotine on resting EEG. Alternatively, lower bandpower in current smokers may be reflective of an underlying state of low activity which is subsequently elevated by nicotine, or may, to some extent, reflect a state of nicotine withdrawal. Causality could not be determined by these data. Notably, in secondary analyses, a significant effect of nicotine dependency based on total FTND score was observed for gamma power in a subgroup of current smokers whereby those who were classified as being dependent exhibited lower power than non-dependent smokers. Correlational analyses, in contrast, did not yield significant associations between level of nicotine dependence (i.e. continuous FTND total score) and power across the alpha through gamma frequency bands.

Specific Aim 3: Relationships Among Putative Susceptibility Factors

P50 Gating

The final specific aim sought to investigate the relationships among variables hypothesized to be associated with nicotine use. Hypothesis 3a predicted a relationship between sensory gating performance on the P50 gating paradigm and beta power, and between sensory gating performance and level of nicotine

dependence. It was predicted that poorer sensory gating, indicating deficient neural inhibition, would be associated with elevated beta power, as an indicator of an imbalance between cortical inhibition and excitation. Based on prior hypotheses that nicotine use represents an effort to improve cognitive functioning, including sensory information processing, it was predicted that poorer sensory gating would be associated with greater nicotine dependence. Univariate ANOVA was conducted to test differences in P50 gating performance by diagnostic and smoking status, first on the basis of ever versus never smoker, and then on the basis of current smoking status. Means for P50 ratio (S2/S1) are reported for patients and controls in Table 7. The mean differences in P50 component amplitudes are shown as well as an alternate representation of P50 gating performance and descriptive purposes.

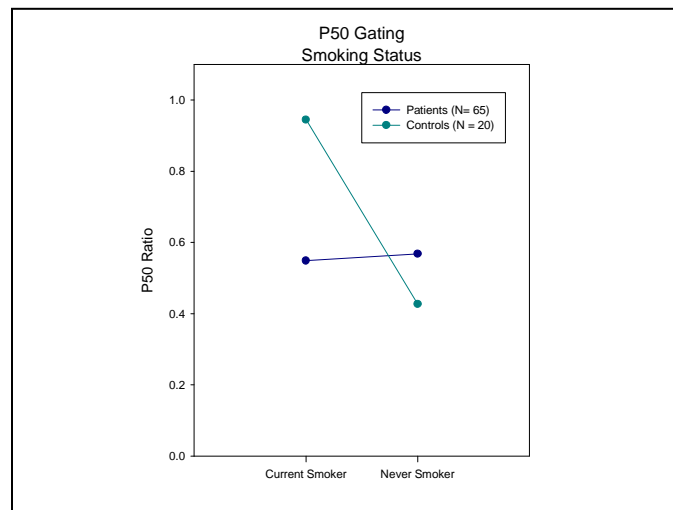
Table 7. Mean P50 Ratio

<i>Group</i>	<i>P50 Ratio M (SD)</i>	<i>Amplitude Difference M (SD)</i>	<i>Smoking Status</i>	<i>P50 Ratio M (SD)</i>	<i>Amplitude Difference M (SD)</i>
<i>Patients (72)</i>	0.56 (0.27)	1.81 (1.94)	<i>Ever</i>	0.56	1.80
			<i>Smoker (47)</i>	(0.27)	(1.95)
			<i>Current</i>	0.55	1.65
			<i>Smoker (39)</i>	(0.28)	(1.89)
			<i>Never</i>	0.57	1.83
<i>Controls (23)</i>	0.51 (0.26)	2.21 (1.53)	<i>Smoker (25)</i>	(0.28)	(1.96)
			<i>Ever</i>	0.75	1.26
			<i>Smoker (6)</i>	(0.26)	(1.55)
			<i>Current</i>	0.94	0.45
			<i>Smoker (3)</i>	(0.08)	(0.08)
<i>Never</i>	0.43	2.55			
<i>Smoker (17)</i>	(0.21)	(1.42)			

Univariate ANOVA testing the effects of diagnostic and smoking status on P50 ratio revealed no significant main effect of diagnostic group ($F_{(1,89)} = 0.55$, $p = 0.46$) and a significant main effect of smoking status ($F_{(2,89)} = 3.88$, $p = 0.02$). There was also a significant disordinal interaction between diagnostic group and smoking

status ($F_{(2,89)} = 4.65, p = 0.01$) whereby nicotine use appeared to affect P50 gating in patients (i.e. normalizing deficient gating) but not in controls. Univariate ANOVA was repeated examining the effects of diagnostic group and smoking status, with the exclusion of former smokers, comparing current and never smokers only. Again, the main effect of diagnostic group on P50 was not significant ($F_{(1,81)} = 2.05, p = 0.15$) but there was a significant main effect of current smoking ($F_{(1, 81)} = 7.87, p = 0.006$) and a significant disordinal group by smoking status interaction ($F_{(1,81)} = 9.11, p = 0.003$). This interaction is depicted in Figure 4.

Figure 4. Group by Smoking Status Interaction for P50 Ratio



In the full group of current smokers, P50 ratio was not significantly correlated with FTND Total Score ($p = 0.29$) and t-tests revealed that FTND Total Score did not significantly differ between current smokers with impaired (4.67 ± 2.22) and unimpaired (4.71 ± 2.10) P50 gating ($p = 0.94$). Given the significant interactions between diagnostic group and smoking status, the effect size for P50 was calculated for never smokers in order to directly compare P50 gating performance between

patients and controls without the confound of current or past nicotine use. This analysis yielded an effect in the medium range (Cohen's $d = 0.56$) supporting prior evidence for impaired P50 gating in patients with schizophrenia relative to healthy comparison controls. Subsequent analyses were conducted to further examine the relationships between current nicotine use and electrophysiological activity.

In both patient and control smokers, correlations between power in the alpha, beta, and gamma frequency bands and P50 ratio were not statistically significant (all p values greater than 0.10). However, distinct relationships between power and P50 components were demonstrated among current smokers. Among patient probands ($N = 65$), power in the gamma frequency band was significantly correlated with S1 amplitude at Cz ($r = 0.35$, $p = 0.004$) and Fz ($r = 0.33$, $p = 0.007$) electrode sites, and with S2 amplitude at Cz ($r = 0.25$, $p = 0.04$) and Fz ($r = 0.25$, $p = 0.04$) electrode sites. When current smokers in the patient group were considered independently, the relationship between S1 and gamma power remained significant at both Cz ($r = 0.57$, $p < 0.001$) and Fz ($r = 0.51$, $p = 0.001$) electrode sites but these effects were diminished when patient never smokers were considered alone ($r = 0.29$, $p = 0.07$ and $r = 0.26$, $p = 0.10$ for Cz and Fz sites respectively).

The pattern of relationships between bandpower and P50 components with gamma bandpower and P50 components differed in the control group ($N = 20$). The strength of association between gamma bandpower and P50 components was lower in the control group, with r values ranging between 0.19 and 0.25 (p values of 0.27 and above). However, there was a significant correlation between S1 amplitude and power in the alpha frequency band at Cz ($r = 0.51$, $p = 0.02$) and Fz ($r = 0.46$, $p =$

0.04) electrode sites. The number of control smokers was too small for these analyses to yield meaningful comparisons between smokers and never smokers. Overall, greater amplitude responses in the P50 gating paradigm were associated with greater power across the frequency spectrum, yet these relationships were statistically significant at the higher and lower ends of the frequency bands examined in patient and controls respectively. Within the patient group, significant relationships between gamma power and P50 components were limited to current smokers. Thus, although these findings are significant, hypothesis 3a was not supported in that P50 gating was not significantly associated with beta bandpower in patients or controls.

Working Model of Susceptibility to Smoking and Nicotine Dependence

The final hypothesis tested was that variables previously presumed to underlie vulnerability to nicotine use including diagnosis, family history of smoking, and electrophysiological functioning would predict smoking behavior. Hypothesis 3b was tested using binary logistic regression first to predict history of ever smoking, followed by current smoking. In the first model, predictor variables including diagnostic group, family history of ever smoking (which includes both current and former smokers), log transformed power in the beta and gamma frequency bands, and P50 ratio were entered simultaneously to test the overall predictive value of the model; beta coefficients were examined to determine the significance of each variable in predicting ever smoking. For the resting EEG data, log transformed power for electrode sites Cz and Fz were averaged together to create one variable per frequency band. This first model was significant ($R^2 = 0.16$, $\chi^2 = 11.59$, $p = 0.04$) and accurately classified 71.6% of probands overall (accurate classification rate of 63.6% for ever

smoking). Beta coefficients for diagnosis ($\beta = 1.65$, $p = 0.016$) and family history of ever smoking ($\beta = 1.20$, $p = 0.03$) were the only significant predictors. The regression analysis was repeated utilizing relative current smoking as a predictor variable, rather than family history of ever smoking; the overall model was significant ($R^2 = 0.197$, $\chi^2 = 14.72$, $p = 0.01$) and accurately classified 69.7% of ever smokers. Diagnostic group ($p = 0.009$) and family history of current smoking ($p = 0.01$) were both significant predictors in the model.

The same regression models were tested again to predict current smoking among probands. The overall model was not significant ($R^2 = 0.128$, $\chi^2 = 9.16$, $p = 0.10$) when family history of ever smoking was used as a predictor ($p = 0.37$) although the beta coefficient was significant for diagnostic group ($p = 0.016$). Again, electrophysiological data did not have significant predictive power in the logistic regression model. The model improved and was significant in predicting current smoking status among probands when family history of current smoking was entered as a predictor instead of family history of ever smoking. The logistic regression model including diagnostic group, relative current smoking, log transformed power in the beta and gamma frequency bands, and P50 ratio correctly classified 70.1% of cases overall ($R^2 = 0.192$, $\chi^2 = 14.24$, $p = 0.01$). Diagnostic group ($\beta = 2.37$, $p = 0.01$) and family history of current smoking ($\beta = 1.90$, $p = 0.02$) were both significant predictors while electrophysiological data remained non-significant.

Summary of Main Findings: Specific Aim 3

Electrophysiological activity measured during an evoked P50 gating paradigm was differentially effected by smoking in patient and control probands. Although

patient non-smokers demonstrated impaired gating relative to control non-smokers, unexpectedly, overall diagnostic group differences in P50 performance appeared to be minimized due to current nicotine use; a significant disordinal interaction between diagnostic group and smoking status rendered main effects uninterpretable in these analyses. Smoking status had an effect on resting EEG as well, such that resting activity appeared elevated in former smokers across alpha, beta, and gamma frequency ranges. The original study hypotheses were not supported, as beta power was not significantly aberrant with respect to diagnostic group or smoking status. While differences in beta power between current and former smokers approached statistical significance, group differences were significant in the gamma range. Greater amplitude responses in the P50 gating components were associated with greater power across the frequency spectrum, yet these relationships were statistically significant at the higher and lower ends of the frequency bands when examined in patient and controls respectively. Finally, a series of regression analyses suggested that having a schizophrenia-spectrum disorder and a family history of smoking are highly significant factors in predicting regular nicotine use. Diagnostic status and the familial (genetic and/or environmental) effects of smoking appeared more salient than electrophysiological variables.

Chapter 5: Discussion

This study aimed to characterize factors which putatively contribute to nicotine use and the development of dependence among individuals with schizophrenia. The literature to date indicates that increased rates of smoking, elevated levels of dependence on nicotine, aberrant smoking patterns, and low rates of quitting among smokers with schizophrenia are not effectively explained by sociodemographic factors or factors secondary to treatment. Rather, the relationship between smoking and schizophrenia may be more primary. This study sought to investigate mechanisms of increased vulnerability to smoking and nicotine dependence through three specific aims examining the individual and interacting effects of familial vulnerability factors, neurophysiological function, and cortical oscillatory activity. Based on the empirical literatures on schizophrenia and on substance use and addictions, hypotheses were formulated to examine smoking patterns relative to a diagnosis of schizophrenia, the effect of a family history of schizophrenia on the heritability of nicotine use, the relationship between oscillatory activity in the beta frequency band of resting EEG and nicotine use, and the relationship among putative susceptibility factors in collectively predicting smoking and nicotine dependence.

The study sample was composed of four groups including outpatients with schizophrenia or schizoaffective disorder, first-degree relatives of patient index probands, healthy comparison control subjects from the community, and first-degree relatives of control probands. Comparison controls were recruited from the community to match patient probands in terms of sociodemographic characteristics;

in preliminary statistical analyses, there were no significant differences between proband groups with respect to age, sex, or race/ethnicity. Lifetime prevalence of comorbid drug or alcohol abuse and dependence in the patient proband group (38.5%) was elevated relative to the control proband group (24.4%). The rate of substance abuse within patients was consistent with the rate of co-occurring substance use with schizophrenia reported in the literature (40 to 50%; Blanchard et al., 2000). The rate of family history of schizophrenia-spectrum disorder (14.4%) in the sample of patient probands is consistent with empirical findings from family studies indicating rates of psychotic disorder, schizophrenia-spectrum personality disorder, and schizophrenia between 9% and 15% among first-degree relatives of schizophrenia probands (Glatt, 2008). The patient sample in this study appeared adequately representative of the larger schizophrenia population.

Smoking and Nicotine Dependence

Sample Characteristics

The first specific aim of the study was to characterize past and present smoking behaviors and level of nicotine dependence in the sample to examine the relationship between smoking history and vulnerability for schizophrenia. This relationship was examined in two ways, first by comparing rates of smoking and level of dependence between proband groups, and second by calculating heritability estimates for smoking. As expected, history of smoking significantly varied between groups, whereby patient probands were more likely to have ever smoked (68.1%) and were more likely to be current smokers (56%) than community controls (45.9% and 21% respectively). Given prevalence rates of smoking in the general population of 22

to 23%, the rate of current smoking in the healthy controls was on par with population rates, and patient proband reports of current smoking were significantly elevated in comparison.

When proband groups were compared with respect to never, former, and current smoking, individuals drawn from the general population appeared more likely than patients to initiate smoking without becoming addicted, or were more likely to have been able to quit. This observation is given by the percentages of former smokers in each proband group; in addition, a significantly greater proportion of ever smokers were former smokers in the sample of healthy controls than in the patient proband group. Consistent with these findings and in support of the hypothesis that smokers with schizophrenia are more likely to develop dependence on nicotine, patient smokers reported greater levels of nicotine dependence on the Fagerstrom Test for Nicotine Dependence (FTND total score) than comparison control smokers when both a history of smoking and current smoking were considered. Also compared dichotomously based on FTND total item endorsement, patient smokers were more likely to be classified as nicotine dependent than control smokers when ever smokers (current and former) and only current smokers were considered. The mean number of smoking years reported by patient smokers was relatively greater than smoking years reported by the comparison controls, although the statistical significance of this difference depended on the inclusion of those individuals who reported current substance use; regardless, this difference yielded an effect size in the small range. Thus, despite reporting a similar number of years of smoking, smokers with schizophrenia in this sample were more likely than smokers from the general

population to have a history of persistent smoking, more likely to become nicotine dependent, and report greater levels of nicotine dependence than other smokers.

Given that propensity towards nicotine dependence is hypothesized to be associated with biological substrates of schizophrenia (e.g. overlapping genetic vulnerabilities), elevated rates of smoking were expected among first-degree relatives of schizophrenia probands in comparison to first-degree relatives of healthy controls. Preliminary investigation of rates of smoking among participating family members did not lend support to this hypothesis. The rate of current smoking among first-degree relatives was actually relatively greater among participating parents and siblings of controls (18%) and closer to general population rates than the rate of current smoking reported among participating parents and siblings of patient probands (13%).

Heritability Analyses

A more rigorous analysis of the familial liability towards nicotine use entailed calculation of heritability estimates based on a polygenic model, taking into account both age and sex as covariates, for each group. Review of the literature to date on the heritability of smoking did not yield reports of heritability estimates specific to populations with schizophrenia. This study is therefore unique in providing this report. Heritability estimates were high for patients and controls with similar values between groups for history of ever smoking (approximately 0.90). Interestingly, the heritability estimate for current smoking in the patient group remained high and was significant while the same calculation yielded a much lower value when current smoking was considered in the control group. The heritability estimate for current

smoking in the control group was not statistically significant. Although the heritability estimate for current smoking in the control group is within a valid range, the lack of statistical significance and within group difference in values between ever and current smokers suggests that current smoking was likely a less accurate reflection of the heritability of smoking in this sample. The between-group difference may have been a result of the likelihood that, in the sample of healthy controls, smokers were more likely to have smoked in the past and few reported currently smoking. In contrast, rates of past and present smoking were high in the patient group, thus appearing to provide equally valid assessments of propensity towards nicotine use.

The heritability estimate for current smoking may, in general, be a better estimate of the genetic contribution to nicotine dependence. The group classified as ever smokers is a more heterogeneous group, composed of both current and former smokers and may include individuals who were exposed to nicotine (i.e. initiated use) but failed, for myriad possible reasons, to develop a longstanding pattern of use indicative of nicotine addiction. Prior studies report total heritability estimates for initiation and progression to nicotine dependence to be between 60 and 70% (Kendler et al., 1999; Sullivan & Kendler, 1999; True et al., 1997) with some estimates of heritability for persistent smoking as high as 84% (Li, 2006). The findings of significant heritability for smoking history in this study, and for current smoking in particular, are consistent with published reports suggesting a large familial component to persistent nicotine use. While environmental and genetic factors interact in an additive fashion to confer liability to smoking initiation, empirical data

suggest that genetic factors play a larger role in conferring vulnerability towards continuing nicotine use and the progression towards dependence (Maes, Sullivan, Bulik, Neale, & Prescott, et al., 2004; Sullivan & Kendler, 1999).

Ideally, this study would have also utilized the total score on the FTND to calculate heritability for nicotine dependence directly, rather than on relying dichotomous variables relating to smoking history and on a differentiation between ever and current smokers to approximate dependence. The number of first-degree relatives of control probands who participated and completed the FTND was too small to provide an accurate evaluation or point of comparison for the schizophrenia group. However, limitations due to the psychometric properties of the FTND may constrain the utility of this measure, particularly in interpreting heritability estimates for nicotine dependence. Retrospective versus current reporting biases in former and current smokers may impact the reliability of FTND nicotine dependence data. Prior research utilizing DSM criteria for diagnosing nicotine dependence and/or a cut-off score of 4 or greater on the FTND have provided heritability estimates in the range of 0.40 to 0.70 (Gelernter et al., 2007; Saccone, Hinrichs, Saccone, Chase, & Konvicka, et al., 2007; Uhl, Liu, Drgon, Johnson, & Walther, 2007). Specific genes have been investigated and found to be significantly associated with nicotine dependency including those related to nicotine receptors themselves such as CHRNA5 (Saccone et al., 2007) and CHRNA4 (Li, Beuten, Ma, Payne, & Lou et al., 2005), nicotine metabolizing enzymes, dopamine receptors, and GABA receptors including GABAB2 (Beuten, Ma, Payne, Dupont, & Crews, et al., 2005) and GABRA4 (Saccone et al., 2007). Thus, evidence from data gathered on smoking

history and measures of nicotine dependency converge in suggesting a significant genetic contribution to persistent smoking and the development of nicotine addiction. The findings from this study, particularly in the schizophrenia proband group, add to this existing literature.

In sum, the hypotheses for the first specific aim were partially supported. Based on rates of former and current smoking in the patient and control groups in this study, the data presented here demonstrate a pattern of more persistent nicotine use and greater dependence among those with schizophrenia relative to non-psychiatric comparison controls drawn from the general population. Persistent smoking was also demonstrated to be highly heritable. Analyses failed to yield results consistent with the hypothesis that smoking would be more familial in those affected by schizophrenia. Given that probands were recruited to match on demographics and geographical location, and that groups were statistically similar when group composition was compared, sociodemographic factors are not likely accountable for the differences between groups observed here. Additionally, participants in both groups reported histories of drug or alcohol use and individuals with current substance use (past 6 months) were excluded from the study sample. Rates of persistent smoking in both groups and the elevated prevalence of current nicotine use and dependence in the patient group did not appear to be explained by co-occurring substance use. However, this study sought to utilize electrophysiological measures that appear to relate to a vulnerability towards alcohol and other substance use to test a more basic index of brain-behavior relationships in relation to nicotine use and schizophrenia.

Electrophysiological Function and Smoking

Quantifying brain oscillatory activity is a tool that has been used to investigate cortical pathologies underlying a variety of psychiatric conditions. In the addictions literature, elevated power in the beta band of resting EEG has demonstrated significant predictive utility with respect to behavioral outcomes; though initial reports focused on predicting alcohol use, findings have been extended to include prediction of illicit drug use as well. Although the precise significance of excitatory and inhibitory dysregulation, as discussed by Begleiter, Porjesz and colleagues, is not known, cortical hyperarousal may confer vulnerability to substance use or the development of physiological dependence, or may result in poor modulatory control over substance use behaviors resulting in persistent use and addiction. In a separate literature, altered cortical activity observed in schizophrenia has been linked to aberrant information processing at the neurophysiological (i.e. sensory gating) and neuropsychological (arousal/attentional processes) levels. Altered cortical activity may also have implications for behavioral abnormalities, such as those related to addictions. The second specific aim of this study sought to characterize the relationship between EEG power and addiction to nicotine among schizophrenia and healthy comparison control probands.

EEG and Smoking Status

The hypotheses associated with the second specific aim were mostly unsupported. Repeated measures ANOVA failed to find diagnostic group differences in power for the alpha, beta, and gamma frequency bands and, contrary to expectation, beta bandpower did not vary significantly relative to smoking status.

However, analyses did reveal interesting associations between power in the gamma frequency band and smoking status whereby former smokers demonstrated greater mean bandpower in the gamma band than current smokers. This pattern was generally observable in the alpha and beta ranges as well, with effect sizes in the small to medium range, but a comparison of means yielded statistically significant results in the higher frequency range of resting EEG only. The main findings were unaffected by differences in medications such as clozapine or benzodiazepines.

Although an association between beta power and nicotine dependence was plausible to hypothesize given established findings relating elevated beta power to alcohol and other substance use, mechanisms conferring vulnerability to nicotine dependence may be different. In distinguishing factors relating to nicotine dependence, prior studies of susceptibility to substance use have been confounded due to the common co-occurrence of nicotine and other substance abuse or dependence. Conclusions about the relationship between nicotine and beta frequency activity at rest have thus not been established. As suggested by the data in this study, there may be a unique association between nicotine use and electrophysiological activity at high frequency bands; this unique association may be limited to gamma frequency activity, or may potentially include beta as well.

Given that current and former smokers were distinguished by significantly different gamma power and that differences in beta power approached, but failed to reach, statistical significance ($p = 0.07$), the data from this study might be interpreted as indicating alterations higher frequency range activity more broadly, rather than distinguishing between effects in specific bands. The lack of significant association

between beta power and nicotine use may be attributable to the methodologies employed, i.e. the wide range in which beta activity was defined in this study compared to the frequency ranges defining beta in other studies. Additional analyses examining a narrower range of beta activity, limited to the upper end of the frequency spectrum, might help to clarify the role of beta in conjunction with gamma activity as conferring susceptibility to nicotine use.

The acute effect of nicotine on EEG activity is characterized by a shift towards higher frequency band activity and has been reported to effect the beta band (Domino, 2003; Kadoya, Domino, & Matsuoka, 1994). The pattern of EEG activity relative to smoking status in this study may be considered for interpretation more broadly. Since subjects were not under the direct influence of nicotine at the time of testing, lower power in high frequency ranges (i.e. beta and/or gamma) might be expected among current smokers, constituting a withdrawal effect. A dose-dependent increase in EEG activity and concurrent improvement in cognitive processing has been documented with acute nicotine administration, as well as decrements in cognitive functioning and decreased activity with short-term or overnight nicotine abstinence (Kadoya et al., 1994). Electrophysiological withdrawal effects have been reported to occur between 6 and 15 hours after nicotine use (Domino, 2003) or within as early as 4 hours after smoking (Heishman, 1999). Participants in this study were instructed to refrain from smoking only 30 minutes prior to testing. Nonetheless, abstinence effects should not be ruled out.

When participants were classified dichotomously for nicotine dependence, dependent smokers demonstrated lower gamma power than non-dependent smokers.

Correlational relationships between FTND Total score and power were not, however, significant. Although power may not vary as a function of dependence severity, dependent smokers may consume more nicotine than non-dependent smokers; given evidence for a relationship between plasma concentrations of nicotine and cortical activity, altered EEG activity among current smokers may be attributed to short-term nicotine consumption (or lack thereof). If not a withdrawal effect, decreased activity among current smokers may be interpreted as a baseline low level of activity, reflective of some neuroelectric deficit, that is subsequently boosted by nicotine with smoking. This remains hypothetical.

Alternatively, relatively elevated power among former smokers might reflect a long-term effect of past nicotine use. The prolonged effects of nicotine exposure on EEG have not been clearly defined in the literature, yet there is some evidence to suggest persistent brain changes in former smokers; Neuhaus and colleagues (2006) documented dysfunctional activation of frontal lobe networks in long-term nicotine abstiners (Neuhaus, Bajbouj, Kienast, Kalus, & von Haebler, et al., 2006). The pattern of activity in never, former, and current smokers in this study may suggest that past and present nicotine use results in prolonged cortical arousal and that current smokers may have been undergoing acute withdrawal at the time of testing, resulting in marked decreases in cortical activation. Findings reported by Domino (2003), that nicotine enhances brain function through both reversal of withdrawal and an additional stimulatory effect on EEG, supports this interpretation alongside findings reported by Neuhaus and colleagues (2006), that nicotine may have a prolonged effect on brain function evident even after long-term abstinence. Since the nature of

the present study is not longitudinal and time of last cigarette was not assessed, conclusions about alterations in power among former or current smokers, as being attributable to an underlying pathophysiological process conferring vulnerability to dependence, a stable effect of long-term use, or an acute effect of nicotine withdrawal remain speculative.

EEG and Schizophrenia

There is ample evidence reported in the literature that schizophrenia is associated with aberrant EEG activity. The lack of diagnostic differences observed here was unexpected. The majority of research on quantitative EEG power spectra has reported augmented lower frequency range activity (delta and theta) and lower alpha band power when at rest (Clementz et al., 1994; Sponheim et al., 2000). There is some evidence supportive of increased beta frequency power as well (Gross, Joutsiniemi, Rimon, & Appelberg, 2006; Whitford, Farrow, Rennie, Grieve, & Gomes et al., 2007). Irregular patterns in electrophysiological functioning do not appear to be epiphenomena associated generally with psychopathology. Aberrant spontaneous lower range frequency activity found in schizophrenia is thought to be associated with poor modulation of arousal and attention, and may be associated with the presence of neuroanatomical abnormalities and negative symptoms (Sponheim et al., 2000). Gross and colleagues (2006) reported a specific association between elevated beta frequency activity, as measured at a fronto-central site at rest, and ratings of psychomotor poverty in schizophrenia.

Whitford and colleagues (2007) presented longitudinal data demonstrating an association between reductions in fronto-parietal grey matter volumes in first-episode

schizophrenia patients and increases in fronto-parietal EEG power in slow wave and beta frequency bands over time. Interestingly, the authors note that grey matter damage, as may be found in patients with traumatic brain injury, has been associated with increases in slow wave power and decreases in beta power, thus suggesting that a unique association exists between grey matter volume and electrophysiological functioning in schizophrenia (Whitford et al., 2007). Elevations in EEG power in higher frequency bands at rest might indicate abnormal neural synchrony, which is thought to be related to information processing abnormalities manifested as cognitive disorganization and reality distortion (Whitford et al., 2007). Of note, the beta frequency band in the Whitford et al. study (12.5 to 34.5 Hz) extended into the frequency range defined as gamma in this study (30 to 50 Hz); although this overlap is fairly minimal, caution in interpreting EEG data with respect to functional distinctions between frequency bands appears warranted. Prior interpretations of aberrant resting bandpower have, however, been based on such functional distinctions.

In a recent investigation of baseline spontaneous and stimulus-evoked cortical activity however, schizophrenia patients did not demonstrate aberrant resting oscillatory activity in any frequency band examined, but did evidence significant reductions in frontal gamma oscillations, relative to non-psychiatric controls, in response to direct stimulation (Ferrarelli, Massimini, Peterson, Riedner, & Lazar, et al., 2008). Other investigations of higher range frequency activity in EEG have found substantial evidence for decreased entrainment of EEG oscillations in the beta and gamma frequencies in schizophrenia patients and reduced power and synchronization

of induced or stimulus-evoked beta and gamma band activity (Kwon, O'Donnel, Wallenstein, Green, & Hirayasu, et al., 1999; Light et al., 2006; Spencer, Nestor, Perlmutter, Niznikiewicz, & Klump, et al., 2004). Thus, while the extant literature is inconclusive with respect to aberrant activity at higher frequencies while at rest, there is more sufficient evidence to suggest that schizophrenia is associated with deficient evoked activity in higher frequencies in response to stimulation.

In addition to irregular patterns in spontaneous cortical activity, aberrant stimulus-evoked higher range frequency activity appears to be associated with altered processing of sensory stimuli, particularly in the auditory domain, and is thought to relate to impairments of local GABAergic inhibitory interneurons (Kwon et al., 1999). Impairment in the ability to generate gamma oscillations is hypothesized to indicate dysfunction in thalamocortical circuits which underlie inhibitory processing deficits, such as those found with sensory gating paradigms. However, Hong and colleagues (2008) reported significant contributions of beta band activity to impairments of sensory gating with the presentation of auditory stimuli. Additional alterations in synchronous gamma oscillatory activity, indicating poor neural integration in thalamic and cortical neuronal circuits, may relate to alterations in perceptual binding (i.e. encoding of sensory information) integral to accurate cognitive processing. As mentioned by Whitford and colleagues (2007), higher frequency range abnormalities, such as those in the gamma band, may also have implications for positive and disorganized symptoms of schizophrenia (Kwon et al., 1999; Whitford et al., 2007).

Given the substantial evidence for early sensory and higher order cognitive processing impairments found in schizophrenia, as well as evidence for aberrant oscillatory activity, the lack of diagnostic differences in resting EEG was unexpected. However, these results are consistent with the findings of Ferrarelli et al. (2008) with respect to the lack of diagnostic differences in EEG activity at rest and the dissociation reported between oscillatory activity measured at rest and aberrant evoked oscillatory activity in response to sensory stimuli. The unique association between beta activity and P50 gating performance in schizophrenia reported by Hong et al., 2008 were also within the context of stimulus-evoked activity and not cortical activity at rest. Data reduction procedures in this study were, however, limited to examining resting EEG activity from 8 to 50 Hz, segregated into broad frequency ranges representative of alpha, beta, and gamma activities. Lower frequency power in the delta and theta bands was not examined, and a more refined analysis of power data within each frequency band may have yielded more informative results with respect to diagnostic differences.

For example, beta may be further segregated into beta 1, beta 2, and beta 3; given that the implications of low beta, coupled with power in the alpha band may have different correlates in schizophrenia than high beta, coupled with power in the gamma band, subsequent analyses may consider refining the data reduction techniques. Additionally, the gamma frequency band is broad and functional correlates, such as those found in this study, may be further examined with respect to more narrowly defined frequency ranges. For example, reduced auditory stimulus-evoked gamma power reported by Kwon and colleagues was specific to stimulation at

40 Hz, whereas non-significant differences in power were found between schizophrenia patients and controls with frequency stimulation at 20 and 30 Hz. As mentioned prior, elevated resting EEG power reported by Whitford and colleagues (2007) was found in a broad frequency band defined by the authors as beta, which corresponded to high beta and low gamma frequencies as defined in this study. Thus, the findings of power abnormalities across the frequency spectrum in schizophrenia may be subject to significant methodological variance. Given the relationship between reduced evoked gamma activity and cognitive processing deficits, and the interaction between nicotinic and GABAergic neurotransmission in modulating inhibitory neuronal processes, the implications of the association found between reduced gamma power at rest and smoking status is open for interpretation.

The functional implications of cortical activity at rest were further investigated in this study by examining the relationship between frequency band power and P50 gating. Although schizophrenia is commonly associated with poor P50 suppression, the lack of significant main effect of diagnostic group for P50 gating in this study appears attributable to smoking status. When never smokers were considered alone, patients with schizophrenia in this study demonstrated poor P50 suppression relative to comparison controls. The magnitude of the difference between patient and control non-smokers yielded an effect size in the medium range, supporting prior findings of deficient gating in schizophrenia. There was a significant disordinal interaction between diagnostic group and smoking history whereby current smokers demonstrated similar P50 ratios to non-smokers in the patient group while current smokers demonstrated greater P50 ratios than non-smokers in the control

group. A closer examination of the effect of smoking on sensory gating between groups demonstrated significant differences in P50 performance between current and former smokers, and between current and never smokers in the control group, with similar P50 ratios among never and former smokers. These significant contrasts were not observed in the patient group.

In addition to the differential effect of current smoking on P50 gating performance across groups, it is noteworthy that even among patient probands who were former or never smokers, patient P50 ratios were lower than might be expected as given by prior reports in the literature. Similarly, among controls who currently smoke or who have ever smoked, the P50 ratio might be considered aberrantly high. Recent meta-analytic findings reported by Patterson and colleagues (2008) documented significant variability in the range of results reported across different research groups, with mean P50 ratios of 0.799 ± 0.243 for patients with schizophrenia and 0.388 ± 0.153 for non-psychiatric controls. Other reviews of P50 gating also note methodological variance and significant heterogeneity of results reported in the literature; de Wilde and colleagues (2007) indicate that assessment of smoking status is inconsistent across studies and is thus one such variable that likely contributes to variability in findings (de Wilde, Bour, Dingemans, Koelman, & Linszen, 2007).

Given that diagnostic groups were stratified and compared using smoking status as a between groups variable in this study, the deviations from expected P50 values observed here may not be abnormal. Rather, these data underscore the importance of considering smoking history in comparisons of sensory gating as noted

by de Wilde and colleagues. Considering the pattern of P50 data among patient and control non-smokers, the dataset presented here may be considered an adequate representation of P50 performance in the schizophrenia and general non-psychiatric populations. The significance of considering smoking status as a between groups variable in future studies is highlighted by these data.

In addition to the effects of nicotine on sensory gating, patient and control proband groups were further distinguished by the relationships observed between electrophysiological measures. Brain responses to auditory stimulation utilizing the P50 paradigm were analyzed by examining correlates of S1 and S2 amplitudes separately. S1 amplitude may be considered representative of general activity, whereas S2 is expected to be decremented due to the neural inhibitory mechanism. Overall, greater amplitude responses were associated with greater power across the frequency spectrum. In patients, power in the gamma frequency was significantly correlated with response amplitudes to both auditory stimuli whereas in the control group, amplitudes of responses to auditory stimulation were significantly correlated with lower frequency activity in the alpha frequency band. Thus in the control group, general indicators of arousal, S1 and alpha power, were expectedly related. In the patient group, relationships between higher resting frequency activity and evoked responses were limited to smokers, as the correlations between amplitudes and power were significantly reduced when never smokers were considered alone. These results again underscore the importance of assessing smoking status when studying electrophysiological activity in patients with schizophrenia.

Relationships between electrophysiological indices were not as expected and the results did not support the hypothesized relationship between beta power and P50 gating as presented in the third specific aim. Additional analyses may further examine the relationship between power in fast resting EEG and other indices of neural processing by segregating spectral power into more distinct frequency bands within the beta and gamma ranges. It appears that smoking is uniquely related to electrophysiological activity in probands with schizophrenia and that smoking status should be assessed in any study of information-processing dysfunction in this population.

Predictors of Smoking

In addition to characterizing relationships among electrophysiological variables in relation to diagnostic and smoking status, the third specific aim sought to examine the collective predictive value of all relevant putative susceptibility factors for nicotine use. Logistic regression was utilized to test the significance of diagnostic group, family history of smoking, and cortical electrophysiological activity, including stimulus-evoked P50 gating and higher frequency oscillatory activity (12 to 30 Hz) measured at rest, to predict smoking status. Among all regression models tested, diagnostic group and family history of smoking were the only significant predictors of smoking status, considering both ever and current smoking. Family history of current smoking appeared to be a more consistent predictor of proband smoking than family history of ever smoking. Given that the group of ever smokers is more heterogeneous and is more likely to include past smokers who were not addicted or

able to quit, whereas the group of current smokers represents those for whom smoking has been more persistent, this result seems logical.

Notably, the logistic regression model including diagnostic group, family history of current smoking, and electrophysiological data correctly classified 70.1% of cases when current smoking was predicted and 69.7% of cases when ever smoking was predicted. The lack of predictive value of electrophysiological data in these models is difficult to interpret due to methodological constraints and the potential confounding effects of the interactions between nicotine use, diagnostic group, and electrophysiology. However, these data clearly underscore the important roles that family history of smoking and a diagnosis of schizophrenia play as susceptibility factors to nicotine use and dependence.

Summary of Findings: Specific Aim 3

In summary, schizophrenia appears to be uniquely related to smoking behavior and nicotine dependence. Susceptibility to smoking in general is strongly impacted by familial patterns of smoking. Prior research and the present findings together implicate both environmental and genetic factors in influencing smoking initiation and persistent patterns of nicotine use are likely influenced more heavily by genetic factors. A diagnosis of schizophrenia and a familial predisposition to smoking are, together, significant predictors of persistent patterns of nicotine use. In the present study, when data were subjected to statistical analysis, diagnosis and family history best captured what may be characterized as an underlying (i.e. neurobiological) vulnerability to nicotine dependence, rather than circumscribed indices of electrophysiological functioning.

The nature of the relationship between nicotine use and various aspects of electrophysiological functioning in this study is difficult to define due to evidence that nicotine differentially influences cortical activity in persons with schizophrenia relative to non-psychiatric controls. In this study, non-smokers with schizophrenia demonstrated relatively deficient P50 gating, as might be expected based on the extant literature. Among patients who currently smoke, P50 gating performance was within a range typically found in the non-schizophrenia population, while controls who currently smoke demonstrated aberrant gating performance. Across groups, gamma power at rest was significantly different between former and current smokers, but unique relationships between stimulus evoked activity and resting electrophysiological activity were found when patients and controls were considered separately and when further examined with respect to smoking status. In patients with schizophrenia, gamma power was significantly correlated with amplitude of responses to auditory stimuli in the P50 paradigm among current smokers but not in never-smokers. While high frequency activity at rest was significantly associated with responses to sensory stimulation in smokers with schizophrenia, low frequency activity (i.e. alpha bandpower) was associated with level of response to auditory stimulation in the sample of non-psychiatric controls. Due to the few number of control smokers with P50 data available, differential associations in smokers and non-smokers could not be distinguished within this group.

Although this study sought to characterize the relationship between resting EEG activity in the beta frequency band and nicotine use, strong associations were not found. Due to the apparent functional significance of elevated beta power in

predicting alcohol dependence and, perhaps vulnerability to substance use more generally, the lack of association with nicotine use in this sample was unexpected. Given prior evidence that abnormal stimulus evoked activity in both the beta and gamma frequency bands have been reported to be associated with indices of neurophysiological functioning among individuals with schizophrenia (e.g. Hong et al., 2008), a more refined investigation of resting EEG activity (e.g. higher frequency activity within the beta range) may be considered for future studies. With regard to future research in general, given the unique relationship between electrophysiological activity and smoking in persons with schizophrenia, future studies are wise to consider smoking status as a variable of significance which should be accounted for methodologically and statistically.

Summary of Limitations and Future Directions

Limitations of the Research Sample

The study data were consistent with prior findings that rates of smoking and nicotine dependence are aberrantly high in persons with schizophrenia compared to non-psychiatric controls from the general population. The study data presented here suggest that in addition to demonstrating greater levels of nicotine dependence, persons with schizophrenia who present with a history of smoking are less likely than smokers from the general population to have successfully quit. Despite these informative findings, the low number of current smokers in the control proband group and the low number of former smokers in the schizophrenia proband group posed limitations on additional analyses to differentiate those who have been exposed to but were more/less likely to develop a persistent pattern of smoking, or were better/less

able to quit. With a larger sample including more former smokers, factors differentiating former from never smokers and from current smokers might yield interesting results. Patterns of smoking over time (e.g. number of quit attempts, duration of smoking before quitting, level of past nicotine dependence) might be compared in future studies of former and current smokers.

A larger study sample would also allow for better characterization of familial factors affecting smoking in patients with schizophrenia relative to non-psychiatric controls. A greater number of first-degree relatives in the control group, for example, may have allowed for a better characterization of the heritability of current smoking. Nevertheless, the data collected did allow for the calculation of heritability estimates for smoking history for schizophrenia and control group participants. Estimates were high and statistically significant, consistent with prior reports of significant genetic contributions to persistent smoking. Although direct comparisons were not made, there appeared to be no appreciable difference in the heritability estimates between patients and controls when history of ever smoking was considered. Thus, the familial factors that contribute to smoking in families with a history of schizophrenia and in those without are likely to be similar.

It should be noted that the heritability estimates reported here demonstrate familial relationships between smokers. These estimates signify the additive effects of genetic and environmental factors and should not be interpreted as indicating genetic contributions alone. Given this inherent limitation, recruitment of a greater number of probands and family members with reported levels of nicotine dependence on the Fagerstrom Test for Nicotine Dependence may have allowed for a better

characterization of the familial effect on nicotine use patterns. However, limitations of the FTND should be noted here as a caveat for future analyses. The reliability of the FTND has been demonstrated in prior studies as being adequate (0.61); in this study sample, the reliability was lower, $\alpha = 0.503$ for current smokers and $\alpha = 0.507$ for ever smokers. Other measures of nicotine dependence may demonstrate greater reliability. With respect to future analyses, potential reporting biases for past versus current smoking may impact the validity and reliability of the FTND. Retrospective assessment of nicotine dependence may be biased due to inaccurate recall or, due to a tendency to recall and report smoking patterns consistent with a period of heaviest use. Current smokers' patterns of use may not, however, reflect a period of heaviest use. Assessment of nicotine dependence among ever smokers, including both current and former smokers, may thus require specification of reporting parameters which may artificially elevate estimates of nicotine dependence, in order to improve the reliability of the measure.

Limitations of the Methodology

Aside from sampling limitations, methodological limitations with respect to differentiating between alpha, beta, and gamma power should be noted. Based on the research question at hand, resting EEG was analyzed in three frequency bands as defined by the general research literature. A re-examination of the data might include investigation of lower frequency activity in the delta and theta bands. In the absence of external stimulation, low frequency EEG activity is dominant relative to high frequency activity. Augmented low frequency activity has commonly been reported in the schizophrenia literature and is considered well-established. Thus, inclusion of

lower frequency bands in the analyses would have provided a useful control in statistical comparisons of higher frequency activity between patients and healthy comparison subjects, as well as provided a point of comparison with data collected in other electrophysiological studies. Similarly, the monopolar electrode sites chosen for analyses were based on the literature suggesting that frontal and central leads yield the most consistent results with respect to beta power and alcohol dependence vulnerability. In expanding the frequency range in which to investigate susceptibility to nicotine use, additional electrode sites may also need to be considered.

The main effect of smoking status for beta power in the current sample approached statistical significance with a p value of 0.07. Given this statistical trend and that the hypotheses described within the second specific aim were unsupported in favor of an association with gamma power, future examination of this data might utilize a more refined analyses of frequency activity within the beta band.

Electrophysiological studies of beta power in relation to susceptibility to alcohol dependence (e.g. Rangaswamy et al., 2002) have divided the beta band into three frequency ranges, beta 1 (12.5 to 16 Hz), beta 2 (16.5 to 20 Hz), and beta 3 (20.5 to 28 Hz). Although Rangaswamy and colleagues (2002) reported elevated mean log beta power across the beta frequency band in relation to alcohol dependence, such distinctions might prove useful in studying nicotine dependence and would add to the existing literature characterizing high and low frequency activity in persons with schizophrenia.

Conclusion

The lack of diagnostic differences in resting EEG power demonstrated in this study does not lend support to the hypothesis that this measure of cortical activity indexes processes contributing to susceptibility for nicotine use, thereby explaining aberrant rates of smoking in patients with schizophrenia. These data do, however, demonstrate that nicotine use significantly impacts cortical activity and suggest that both prolonged and acute effects may be observed. As this study was a preliminary investigation of the relationship between power in resting EEG and nicotine use with respect to a diagnosis of schizophrenia, statistical analyses were limited to comparisons of group differences and examination of cross-sectional relationships among variables. The larger research question upon which this study was based is one that is more causal in nature. That is, does aberrant cortical activity among individuals with schizophrenia have implications with regard to persistent nicotine use via nicotine's impact on neurobiological substrates associated with information-processing impairment?

Based on research in behavioral genetics and cognitive neuroscience, aberrantly high rates of persistent smoking and levels of nicotine dependence among persons with schizophrenia, as demonstrated here, might be explained in part by the unique remediating effects of nicotine on neurophysiological and neurocognitive impairments. These study data support the assertion that nicotine affects individuals with schizophrenia and non-psychiatric smokers differently and may suggest that nicotine has a prolonged effect and short-term effect on cortical activity, with acute administration or nicotine withdrawal, irrespective of diagnostic status. Study data

presented here also support evidence for the additive genetic and environmental impact that a family history of smoking contributes in predicting nicotine use in addition to diagnosis.

Due to the interacting effects of nicotine and electrophysiological function described in this study, together with the limitations of the study sample, the independent contributions of electrophysiological abnormalities and diagnosis to smoking, prolonged use, and the development of nicotine dependence could not be distinguished. Given the unique relationships reported and discussed herein, future studies might be implemented to (1) better distinguish between indices of electrophysiological function, utilizing both resting and stimulus-evoked paradigms, (2) relate putative susceptibility factors, whether diagnostic or electrophysiological in nature, to mediating processes and observable behaviors, and finally (3) better account for the confounding effects of acute nicotine use and smoking history in order to continue investigating factors underlying susceptibility to current nicotine use and dependence in schizophrenia.

Appendices

Appendix A

Neural Oscillations

Neural oscillations are natural electrical fluctuations that occur spontaneously in the brain. Oscillatory activity is generated by ensembles of neurons through neurochemical processes, producing rhythmic activity at varying frequencies (Begleiter & Porjesz, 2006). Each frequency (measured in Hertz, or Hz) reflects a different order of brain activity (Niedermeyer, 1999). Measurement of brain oscillations may be performed during resting states, without external stimuli triggers, or during states of activation whereby changes in oscillatory activity are locked to the timing of stimulus presentation and measured accordingly. Choice of methodology is dependent upon the research question.

In general, the study of brain oscillations may elucidate the functional organization of neuroelectric activity (Begleiter & Porjesz, 2006), and thereby characterize important correlates of human information processing and cognition. Oscillatory activity can be assessed in terms of power, or the amount of activity in a given frequency band. Elevations in power within a frequency band may be indicative of a dominant state of electrical activity, which might bias the neural system towards a specific mode of sensory processing or mode of responding. Oscillatory activity can also be assessed with respect to coherence and neural synchrony, which refer to the covariation in amplitudes and timing of oscillations recorded from different sites. These qualities of oscillatory activity refer to the functional coupling of neuronal

ensembles across distributed neural populations and thus also affect information processing and influence modes of responding (Uhlhaas & Singer, 2006). Power and covariation of oscillatory activity, although both underlying coordinated brain function, may be studied independently and have demonstrated distinct behavioral correlates (Franken et al., 2004). This study will focus on the power of oscillations across the frequency spectrum. Of particular interest is the power in the beta band of resting EEG.

In addition to describing modes of neural functioning, measures of oscillatory activity have been used in the field of behavior genetics. Variations in oscillatory activity are likely more proximal indicators of gene effects than complex neural processes, to which neural oscillations contribute. Human brain oscillations are highly heritable, with estimates ranging from 80 to 90% (van Beijsterveldt et al., 1996). Characterization of oscillatory power in resting EEG, reflecting a natural state of electrical activity, may yield fruitful results in identifying genes which contribute to more complex outcomes, such as cognitive performance and psychiatric symptomatology (Begleiter & Porjesz, 2006). A better understanding of gene variants associated with specific brain oscillations may yield important information about neural processes underlying clinical disorders.

CNS Imbalance

Begleiter and Porjesz (1999) propose that an inherited predisposition to developing alcoholism is represented by a general state of central nervous system (CNS) disinhibition or hyperexcitability. This innate CNS imbalance likely influences the occurrence of other disinhibitory conditions and is thus hypothesized to contribute to a number of externalizing disorders including drug abuse. The electrical output as a result of this condition of cortical hyperexcitability can be measured using EEG techniques. One such technique is to assess brain oscillations, or natural electrical fluctuations, as they occur spontaneously in the brain. The presence of augmented beta and gamma oscillations (12 – 28 Hz and 29-50 Hz respectively) is thought to signify an activated state of neural activity, and is thus hypothesized to underlie the condition of CNS imbalance discussed by Begleiter and Porjesz. In brief, this imbalance is generated by the interplay between gamma amino butyric acid (GABA) and glutamate, the major inhibitory and excitatory neurotransmitters of the central nervous system. Neural excitatory activity, mediated largely by glutamate, is intimately connected with the activity of GABAergic interneurons, which serve to modulate and balance the feedforward excitatory signals between pyramidal cells through inhibitory feedback.

A common feature of beta oscillations, in particular, is the involvement of networks of inhibitory interneurons. This is supported by a significant genetic linkage for the beta frequency in resting EEG reported as being located within a cluster of GABA_A receptor genes on chromosome 4 (Porjesz et al., 2002). The networks of inhibitory interneurons act as “pacemakers” of electrical activity. Thus, oscillatory

activity in the beta band appears to be a useful indicator of coordinated electrical activity and a measure of CNS balance. It is the elevation in beta power in resting EEG, indicating relative disinhibition, which has demonstrated an association with susceptibility to substance use and dependence.

Disinhibition and Schizophrenia

Regulation of excitation and inhibition in the central nervous system is crucial for complex cognitive processes. Clinical features of schizophrenia include disturbances in cognitive processes such as impairments in attention, memory, and executive functions. These disturbances may be related to neural disinhibition. At a basic level, these cognitive processes rely on the coordinated activity of pyramidal neurons in the dorsolateral prefrontal cortex (DLPFC). In turn, coordinated activity requires the modulatory function of GABAergic inhibitory interneurons. Impairments in GABA-mediated inhibition in the DLPFC may provide a mechanism for the disturbances in working memory in individuals with schizophrenia. Consistent with this hypothesis are gene expression deficits and neuronal abnormalities in the DLPFC affecting GABAergic activity in schizophrenia samples (see Lewis et al., 2005 for full review).

In addition to cognitive dysfunction marked by poor inhibitory control in the prefrontal cortex, individuals with schizophrenia show significant neurophysiological dysfunction associated with inhibitory interneuron activity. Evidence suggests that inhibitory circuits in the hippocampus and thalamus, influenced by GABAergic interneurons, are particularly active in regulating sensory-driven neural processes such as sensory gating. Deficient P50 gating in schizophrenia is likely influenced by aberrant GABAergic interneuron activity in the hippocampus. Indeed, the expression of GABAergic receptors has been found to be reduced in post mortem hippocampal brain tissues of individuals with schizophrenia (Freedman et al., 2000). A reduction in the number of inhibitory interneurons has also been reported (Waldo et al., 2000).

Given the purpose of the proposed study, it is interesting to note the coexistence of $\alpha 7$ nicotinic acetylcholine receptors and GABAergic receptors in the hippocampus, and the reduced expression of both receptor types associated with schizophrenia. Given the association between beta band oscillatory activity and P50 response (Hong et al., 2002; Hong et al., 2004) and the linkage between GABA genes and the beta band (Porjesz et al., 2002), it is possible that GABA receptor dysfunction and nicotinic acetylcholine receptor modulation of neural networks might together account for sensory gating deficits documented in schizophrenia. These findings are compelling in light of the high prevalence of smoking and high levels of nicotine dependence demonstrated in the schizophrenia population, and the relationship demonstrated between beta power and substance use. This study proposes to address the potential linkages between beta power, sensory information processing dysfunction, nicotine use, and schizophrenia.

Appendix B

Nicotine Dependence Assessment

____ Have you ever been a smoker? Y = Yes; N = No

If No, participant is a Non-Smoker, STOP. If yes, then proceed

____ Are you currently a smoker? Y = Yes; N = No

If No, how long ago did you quit? _____ (Specify days, weeks, months, or years)

Fagerstrom Test for Nicotine Dependence (FTND)

*Directions: Please fill in the response with the appropriate number, then total the scores. If participant used to be a smoker but is not currently, please answer the following for when participant **was** a smoker.*

____ 1. How soon after you wake up do you smoke your first cigarette?
 3 = within 5 minutes 2 = 6-30 minutes 1 = 31-60 minutes 0 = after 60 minutes

____ 2. Do you find it difficult to refrain from smoking in places where it is forbidden (church, library, cinema, etc)?
 1 = Yes 2 = No

____ 3. Which cigarette would you hate most to give up?
 1 = First one in morning 0 = All others

____ 4. How many cigarettes/day do you smoke?
 0 = 10 or less 1 = 11-20 2 = 21-30 3 = 31 or more

____ 5. Do you smoke more frequently during the first hours after waking than during the rest of the day?
 1 = Yes 0 = No

____ 6. Do you smoke if you are so ill that you are in bed most of the day?
 1 = Yes 0 = No

____ **Total Score**
 0-2 = very low 3-4 = low 5 = medium 6-7 = high 8-10 = very high

- ___ 7. At what age did you begin to smoke?
- ___ 8. At what age did you become a regular smoker?
- ___ 9. How many years have you smoked cigarettes?
- ___ 10. Have you ever tried quitting? (Y = Yes; N = No)
- ___ 11. How many times have you quit for 24 hours or more? (State number in days)
- ___ 12. What was the longest period you quit smoking? (Specify days, weeks, months, or years)
13. If you have quit for 24 hours or longer, did you experience any of the following symptoms? (Check all that apply)
- A) craving for tobacco ___ Yes ___ No F) impatience ___ Yes ___ No
- B) irritable, angry, ___ Yes ___ No G) disrupted sleep ___ Yes ___ No
frustrated
- C) anxiety ___ Yes ___ No H) increased eating ___ Yes ___ No
- D) trouble concentrating ___ Yes ___ No I) feeling drowsy ___ Yes ___ No
- E) restlessness ___ Yes ___ No

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