# SMOKING STATUS, COGNITION AND NEUROBIOLOGY IN SCHIZOPHRENIA

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A THESIS SUBMITTED TO THE FACULTY OF GRADUATE STUDIES

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS

FOR THE DEGREE OF

MASTER OF ARTS

GRADUATE PROGRAM IN PSYCHOLOGY

YORK UNIVERSITY

TORONTO, ONTARIO

AUGUST 2014

## Abstract

Cognitive impairments are considered a core feature of schizophrenia. Nicotine has been suggested to have an effect on cognition in individuals with schizophrenia and in the general population. Since smoking status is seldom controlled for in cognitive research studies understanding the contribution of nicotine dependence is a potentially important issue for data interpretation. Thus, the current study examined whether smoking status has a differential association with cognition and regional cortical thickness in 71 patients and 63 nonpsychiatric control participants. Cognition was measured with the MATRICS Consensus Cognitive Battery (MCCB) and social cognition was measured with the Faux Pas and Reading the Mind in the Eye tasks. The Vocabulary and Matrix Reasoning subtests of the Wechsler Abbreviated Scale of Intelligence (WASI) and Wide Range Achievement Test (WRAT-4) were used to assess general intelligence (IQ) and premorbid functioning, respectively. Cortical thickness was measured with a high-resolution 3-Tesla MR whole body scanner. Results revealed that patients (relative to controls) and smokers (as compared to nonsmokers) showed impairments on all cognitive measures (e.g., attention, processing speed, working memory, social cognition, etc.). Neuroimaging results indicated widespread cortical thinning among patients as compared to controls. However, patient smokers and control nonsmokers had similar cortical thickness patterns in the left parahippocampal gyrus and bilateral medial orbitofrontal gyri. The findings suggest that smoking status should be taken into consideration in cognitive research given that smoking status may confound overall results.

Acknowledgements

First and foremost, I give thanks and praises to the Most High who has guided and strengthened me every step of the way. Indeed, to him be the glory! I would also like to recognize the constant love, encouragement, and support from my immediate and extended family across the globe. From Jamaica, Germany, England, the US, and here in Canada, emails, phone calls and visits have kept my smile the brightest, my laughter the heartiest, my motivation the highest, and my love the deepest. I am forever grateful for your words and reminders that I am where I have always dreamed to be, and I often still cannot believe I am here!

To my friends, thank you for being more like family and sharing moments that seem like lifetimes of joy! To the ladies of my lab and cohort, my new network of friends/ colleagues, thank you for striving with me and being the best at inspiring me to always reach higher. I am so grateful to share this journey with you.

To Walter, my advisor, I remember reading the book you wrote and thinking, “This is it- I have to work with him”! Words cannot express how grateful I am that you granted me this opportunity, an opportunity to realize my dream. I look forward to our continued work together.

Lastly, to the amazing faculty and staff members of the Clinical Psychology program that I have had the opportunity to learn from, speak and laugh with, thank you for making this journey a most beautiful one. You have reminded me to breathe and enjoy every moment I can… cheers to you!

"I've learned that people will forget what you said, people will forget what you did, but people will never forget how you made them feel"- Maya Angelou

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# Introduction

Schizophrenia is a chronic debilitating disorder characterized by an inability to discern reality and has a lifetime prevalence of approximately 4.0 per 1000 (McGrath, Saha, Chant, & Welham, 2008). In 2004, an estimated 234,305 individuals living in Canada with this illness led to an approximate cost of $6.85 billion dollars as a result of the direct impact on the healthcare system, the fact that fewer than 10% were employed, and the associated morbidity and mortality rates (Goeree, Farahati, Burke, Blackhouse, O'Reilly, Pyne & Tarride, 2005; Marwaha & Johnson, 2004). Schizophrenia not only places great demands on the economic system, but it is also a disabling condition for sufferers. In fact, this disorder is the most debilitating mental illness, which in part fuels the considerable amount of research interest it continues to receive.

The symptoms those with schizophrenia experience can include delusions and/or hallucinations; they may also lack motivation or drive to accomplish goals; as well as suffer a reduction in their ability to experience and recognize emotional expression (Diagnostic and Statistical Manual of Mental Disorders (*DSM–5*, 2013). There is also evidence to suggest a direct link between poor performance on neurocognitive measures and impaired social functioning (Niendam, Bearden, Johnson, McKinley, Loewy, O'Brien, Nuechterlein, Green, & Cannon, 2006). Indeed, cognitive impairment is a core feature of the disorder found among 70-75% of this population (Heinrichs, 2005; Heinrichs & Zakzanis, 1998) and is predictive of functional outcome (e.g., social, occupational, and living status; Green, Kern, & Heaton, 2004; Heinrichs, Goldberg, Miles & McDermid Vaz, 2008). However, although recognized as a core feature, it is neither included in diagnosis as part of the previous DSM-IV-TR nor the current DSM-5. Currently, more research is needed to enhance clinical utility in distinguishing the specific

cognitive deficits of schizophrenia from those of other psychiatric illnesses (Barch, Bustillo, Gaebel, Gur, Heckers, Malaspina, Owen, Schultz, Tandon, Tsuang, Van Os, & Carpenter, 2013).

When compared with healthy controls, individuals with schizophrenia demonstrate impairments on tests of selective and sustained attention, visuospatial and working memory, deficits in executive function as well as other cognitive impairments (Dickinson & Harvey, 2009; Heinrichs & Zakzanis, 1998). Several research studies have identified the greatest impairments being those of executive function, speed of processing, and attention (Dickinson & Harvey, 2009; Orellana & Slachevsky, 2013). The degree of cognitive impairments may result from progressive changes in the brain of those afflicted with the illness over the course of development leading to structural abnormalities (Andreasen, 2010).

This paper will first review the neuroimaging evidence of structural abnormalities that may be linked to cognitive impairments and symptoms of schizophrenia. Secondly, the role of nicotine in targeting illness-specific cognitive impairments in schizophrenia will be discussed. This review of the literature will provide an understanding of the rationale for the current study.

**Structural Abnormalities**

There are numerous disease-related structural abnormalities in schizophrenia. Findings of enlarged cerebral ventricles have been frequently replicated in imaging studies and are characteristic of the illness, although normal variation in enlargements can be found among healthy populations (reviewed in Jaaro-Peled, Ayhan, Pletnikov, & Sawa, 2010). An increase in ventricular size is associated with decrease cortical volume (Jaaro-Peled et al., 2010). Consequently, there is consistent research evidence to support findings that neuroanatomical abnormalities include a reduction in cortical thickness volume and density in several brain areas, which may be responsible for cognitive deficits seen in patients (Mueser & McGurk, 2004; for

review see Jaaro-Peled et al., 2010 and Honea, Meyer-Lindenberg, Hobbs, Pezawas, Mattay, Egan, Verchinski, Passingham, Weinberger, & Callicott, 2008).

Cortical thickness is representative of densely arranged neurons and glial cells, synaptic spines, and axons (Garey, 2010). Postmortem studies of individuals with schizophrenia show decreased overall brain volume due to reduced size and amount of neurons, dendritic arborization, synaptic spines and interneuronal neuropil in certain brain regions (e.g., frontal and temporal lobes; Garey, 2010; Oertel-Knöchel, Knöchel, Rotarska-Jagiela, Reinke, Prvulovic, Haenschel, Hampel, & Linden, 2013; Orellana & Slachevsky, 2013). The reduction in cortical volume may be due to apoptosis or reduced synaptic connections in local brain regions (Goldman, Pezawas, Doz, Mattay, Fischl, Verchinski, Chen, Weinberger, Meyer-Lindenberg, 2009).

Converging evidence shows that there is reduced cortical thickness within the frontal lobes (particularly the prefrontal cortex), cingulate gyrus, medial temporal lobe structures (hippocampus, amygdala, entorhinal and parahippocampal cortex), superior and middle temporal gyri, and subcortical structures (Ho, Andreasen, Nopoulos, Arndt, Magnotta, & Flaum, 2003; Mjellem & Kringlen, 2001; Mueser & McGurk, 2004; Oertel-Knöchel et al., 2013). Ehrlich and colleagues (2012) found reductions in cortical thickness in both hemispheres among patients, such that the frontal, temporal, inferior parietal, and occipital lobes were areas commonly affected.

It has also been reported that the most significant reduction in cortical thickness among individuals with schizophrenia is found within the lateral surface of the temporal lobe and frontal lobe (more specifically reduced thickness in bilateral caudal middle frontal gyrus, inferior and superior frontal gyri; Goldman et al., 2009). Interestingly, the most pronounced cognitive deficits

commonly found amongst this clinical population are those affected by frontal and temporal lobe abnormalities (Cobia, Smith, Wang, & Csernansky, 2012; Ragland, Yoon, Minzenberg, & Carter, 2007; Reichenberg, & Harvey, 2007). The possible link between structural abnormalities and both cognitive impairments and symptoms of schizophrenia will be discussed below.

Neuroanatomical abnormalities are reported to have a genetic link and are possible vulnerability markers as unaffected first-degree relatives of individuals with schizophrenia also show brain abnormalities (Chan, McAlonan, & Gong, 2011; Ho et al, 2003; Jaaro-Peled et al., 2010). Among unaffected first-degree relatives, however, abnormalities tend to be less severe than among individuals with the illness. Research studies conducted with unaffected first-degree relatives largely mirror studies of patient population. There are reports of reduced cortical thickness in frontal, temporal and limbic areas to name a few (Oertel-Knöchel et al., 2013). However, relatives tend to show cortical abnormalities at younger ages and these abnormalities tend to disappear by age 20 years (Gogtay Greenstein, Lenane, Clasen, Sharp, Gochman, Butler, Evans, & Rapoport, 2007). Taken together, brain structural abnormalities have been found in individuals with schizophrenia and their first-degree relatives, and these abnormalities may be involved in the pathophysiology of the illness.

**Linking Structure to Function**

Abnormalities found in the frontal lobe have been linked to several deficits. Specifically, diminished cortical white matter density of the frontal lobe is found among individuals with schizophrenia as compared to healthy controls, which may be due to neurodevelopmental abnormalities that led to an arrest in myelination or cortico-cortical connections (Dickinson & Harvey, 2009; Ho et al, 2003; Jaaro-Peled, 2010). Reduced volumes in the dorsolateral prefrontal cortex and medial frontal cortex (including the anterior cingulate cortex) have been observed

(see Lesh, Niendam, Minzenberg, & Carter, 2011 for a review). Volume reductions in the anterior cingulate cortex and dorsolateral prefrontal cortex as well as compromised white matter tracts that allow communication between brain regions may be linked to the cognitive impairments in schizophrenia including episodic and working memory, attention, and processing speed (Dickinson & Harvey, 2009; Lesh, Niendam, Minzenberg, & Carter, 2011).

Individuals with schizophrenia tend to also have impairments in social cognition. For example, in tasks that require empathic reflections or the processing of social information, patients tend to show decreased activation in the left prefrontal cortex and medial orbitofrontal gyrus (Hynes, Baird, & Grafton, 2006; Mueser & McGurk, 2004). The frontal lobe is also important for processing verbal learning, a measure of learning and memory, which is positively correlated with executive function in schizophrenia (Fossati, Amar, Raoux, Ergis, & Allilaire, 1999; Hartberg, Lawyer, Nyman, Jönsson, Haukvik, Saetre, Bjerkan, Andreasen, Hall & Agartz, 2010). In both individuals with schizophrenia and healthy controls, verbal learning is linked to superior and middle fontal gyri such that poor performance is associated with reduced thickness in these areas (Hartberg et al., 2010).

Progressive reductions of white matter connectivity in frontal lobe regions (i.e., orbitofrontal and anterior cingulate cortex) have also been linked to greater severity of negative symptoms in patients and decreased executive functioning (Ho et al., 2003; Orellana & Slachevsky, 2013). Specifically, deficits in abstract reasoning, planning, problem solving, as well as impairments in social cognition are commonly seen in individuals with schizophrenia (Orellana & Slachevsky, 2013). The dorsolateral prefrontal cortex and the anterior cingulate cortex, in particular, are reported to be involved in executive functioning (Minzenberg, Laird, Thelen, Carter, & Glahn, 2009; Snitz, MacDonald, Cohen, Cho, Becker, & Carter, 2005). Weiss

and colleagues (2003) found activation in the inferior frontal cortex as well as anterior cingulate during a functional magnetic resonance imaging (fMRI) study of the Stroop task, another measure of executive functioning. Furthermore, these authors found bilateral activation within the prefrontal cortex of patients, while healthy controls showed activation only in the left hemisphere. This finding suggests that patients may recruit more cortical areas to complete the same cognitive task as healthy controls.

Thus far the discussion has centered on frontal lobe abnormalities and their link to cognitive dysfunction (e.g., impairments in processing social information, deficits in learning and memory, and executive function) among individuals with schizophrenia. Research evidence suggests, however, that structural abnormalities are most pronounced in both frontal and temporal brain regions (Goldman et al., 2009; Oertel-Knöchel et al., 2013). There is also some overlap between these structures and their relationship to symptom severity, verbal learning and processing, and executive functioning (Hartberg et al., 2010).

In particular, gray matter reductions in the left middle temporal gyrus and bilateral inferior temporal gyrus may be involved in semantic memory and language processing in individuals at chronic stages of the disease (Nestor, Onitsuka, Gurrera, Niznikiewicz, Frumin, Shenton, & McCarley, 2007). With respect to symptoms, while frontal regions are involved in negative symptoms, the temporal lobes may be implicated in positive symptoms (Oertel-Knöchel et al., 2013). For example, symptoms such as hallucinations tend to be related to left superior temporal cortex thinning in both patients and unaffected first-degree relatives (Flaum et al., 1995; Oertel-Knöchel et al., 2013). Furthermore, there is a link between the severity of illness, more specifically thought disorders and auditory hallucinations, and reduced volume of the left superior temporal gyrus (see Sun, Maller, Guo, & Fitzgerald, 2009 for review).

Despite the focus on the role of the frontal and temporal lobes in cognitive dysfunction among people with schizophrenia, it is also important to recognize the functional connection of other brain structures in this illness. For instance, limbic structures (e.g., hippocampus, parahippocampal gyrus and amygdala) also play an important role in memory and social cognition (Ehrlich et al., 2012; Mueser & McGurk, 2004). In fact, studies have reported illness-related reduction in volume of structures within fronto-temporolimbic regions (Mjellem & Kringlen, 2001; Glahn, Laird, Ellison-Wright, Thelen, Robinson, Lancaster, Bullmore, & Fox, 2008). In patients, hippocampal volume is correlated with verbal working memory and immediate story recall, particularly within the left hemisphere (Ehrlich et al., 2012).

There is also evidence to suggest that problems with myelination in the prefrontal cortex, fronto-temporal and fronto-parietal tracts may explain disruption in connectivity between structures, which may be related to cognitive impairments and symptomatology of the illness (Orellana & Slachevsky, 2013). Functional neuroimaging studies have emerged that lend support for disruption in neural circuits (Mueser & McGurk, 2004; Orellana & Slachevsky, 2013). This finding supports the view that multiple rather than single brain regions are involved in the widespread cognitive impairments of schizophrenia. Temporal and cerebellar regions are functionally connected to the prefrontal cortex and patients show reduced volume in the fronto-temporo-cerebellar network; further, studies have shown reduced activation in this network while patients complete the Wisconsin Card Sorting Task, a measure of executive function (Riehemann, Volz, Stützer, Smesny, Gaser, & Sauer, 2001; Kašpárek, Mareček, Schwarz, Přikryl, Vaníček, Mikl, & Češková, 2010).

Therefore, although studies generally show reductions in cortical thickness mainly in prefrontal and temporal regions and the possible link to cognitive impairment using fMRI, the

evidence supports the interconnectedness of several brain areas (e.g., limbic structures, auditory cortices, and cerebellar areas) to carry out cognitive functions (Oertel-Knöchel et al., 2013). Goldman and colleagues (2009) suggest that "predominant functional impairment of prefrontal and medial temporal structures in schizophrenia may not be exclusively due to localized structural-functional effects, but also mediated through the extensive interconnections that these regions maintain with the rest of the brain". It is also possible that tasks with high cognitive load will cause the recruitment of more brain regions in individuals with schizophrenia. That is, the more cognitively demanding the task, the more the brain of those with schizophrenia may compensate to overcome abnormal neurodevelopment and possible progressive brain abnormalities of the disease (Ehrlich et al., 2012).

**Smoking and Schizophrenia**

There has been considerable interest in targeting cognitive deficits in schizophrenia given that these deficits are strong predictors of functional outcome (Green, Kern, & Heaton, 2004; Heinrichs, Goldberg, Miles & McDermid Vaz, 2008). The effects of nicotine have gained significant attention following reports linking nicotine to increased activity in an otherwise hypoactive prefrontal area, which may activate the dopaminergic reward system and affect motivation and other negative symptoms of the disorder (Glassman, 1993; Šagud, Mihaljević-Peleš, Mück-Šeler, Pivac, Vuksan-Ćusa, Brataljenović, & Jakovljević, 2009). Furthermore, nicotine consumption among patients has also been credited for possibly reducing drug side effects and enhancing cognitive performance in patients (Glassman, 1993; Šagud et al., 2009; Winterer, 2010).

Smoking prevalence within the schizophrenia population is approximately 2-3 times that of the general population (Goldberg & Van exan, 2008; Mitchell & Dahlgren, 1986; Üçok, Polat,

Bozkurt, & Meteris, 2004) with rates as high as approximately 90% (de Leon & Diaz, 2005; Strand & Nybäck, 2005; Ücok et al., 2004), and is also the highest among clinical populations (Kalman, Morissette, & George, 2005). While cigarette consumption may have some so-called 'benefits' for individuals with schizophrenia, such benefits come at a tremendous cost given the increased health risks of lung cancer, cardiovascular disease, and associated mortality risks (Baliunas, Patra, Rehm, Popova, & Taylor, 2007; Wildgust, & Beary, 2010). In fact, smoking-related acute care resulted in a total cost of 2.5 billion dollars in Canada in 1 year alone (Baliunas et al., 2007).

Nonetheless, research evidence suggests that when compared to nonpsychiatric controls, individuals with schizophrenia smoke cigarettes that contain higher levels of nicotine, and also extract more nicotine from each cigarette smoked causing higher nicotine blood levels (Olincy, Young, & Freedman, 1997; Strand & Nyback, 2005). However, studies have found diminished concentration of nicotinic receptors in postmortem brains of individuals with schizophrenia than in nonpsychiatric controls (Breese, Lee, Adams, Sullivan, Logel, Gillen, Marks, Collins & Leonard, 2000; Marutle, Zhang, Court, Piggot, Johnson, Perry, Perry & Nordberg, 2001). Additionally, nicotinic receptors are not upregulated in smokers with schizophrenia following consumption of nicotine unlike in controls, (Breese et al., 2000). Using an animal model analog, Breese et al. (2000) also found evidence to support an upregulation of nicotinic receptors in rats even with chronic psychotropic treatment. Thus, there appears to be some differences between patients and controls not only in smoking behaviour, but also potential differential neurobiological mechanisms of action of nicotine dependent on psychiatric status.

Nicotine's supposed benefits for patients have led to the self-medication hypothesis. That is, individuals with schizophrenia smoke to improve the negative symptoms of the disorder (such

as apathy), alleviate side effects associated with psychotropic medications, and also improve cognitive deficits (for reviews see Kumari, 2005; Winterer, 2010; Freedman, 2014). However, the self-medication hypothesis is not without its criticisms as evidence emerged of the potential role of the tobacco industry in research funding, biasing publications, as well as lending support to deter the prohibition of smoking in psychiatric settings (Prochaska, Hall, & Bero, 2008).

Notwithstanding, nicotine has been suggested to enhance such cognitive functions as memory and attention in nonsmokers and nicotine-deprived and non-deprived smokers (see Heishman, Kleykamp, & Singleton, 2010 for meta-analysis and Jasinska, Zorick, Brody, & Stein, 2014 for a review). It follows, therefore, that given the smoking prevalence in the schizophrenia population, studies continue to emerge examining the possible role of nicotine on cognition. Research interest in nicotine and the self-medication hypothesis in schizophrenia may possibly be due to the importance of cognitive functioning for day-to-day functioning and need for targeted treatment.

The evidence suggests that nicotine consumption may improve cognitive deficits since individuals with schizophrenia who smoke outperform nonsmoking patients on measures of sensory gating (Dalack, Healy, & Meador-Woodruff, 1998; George, Termine, Sacco, Allen, Reutenauer, Vessicchio, & Duncan, 2006; Hong, Wonodi, Lewis, & Thaker, 2007; Kumari, Soni, & Sharma, 2001; Swerdlow, Light, Cadenhead, Sprock, Hsieh, & Braff, 2006), selective and sustained attention (George et al., 2002; Sacco et al., 2005), and working memory (reviewed in Freedman, 2014). Furthermore, patients who have no previous history of smoking have reported to be at a greater disadvantage than former or current smokers with schizophrenia on neurocognitive tests of sustained attention, processing speed, and response inhibition (Wing, Bacher, Sacco & George, 2011).

Thus far, findings support the notion that nicotine consumption temporarily improves performance on such cognitive tasks as working memory and selective attention. Neuroimaging studies also found that patients who smoke show greater activation in brain areas important for optimal performance of these tasks than patients who do not smoke (e.g., thalamus, anterior cingulate, and frontal cortex; Jacobsen, D'Souza, Mencl, Pugh, Skudlarski, & Krystal, 2004; McClernon, 2009). Furthermore, Tregellas and colleagues (2007) found that patients who smoke have greater gray matter volume in certain disease-related brain areas compared to non-smoking patients. Specifically, gray matter volumes among patients who smoked were greater in the dorsolateral prefrontal cortex, superior temporal gyrus, orbitofrontal cortex, medial frontal gyrus, and insula in comparison to nonsmoking patients (Tregellas et al., 2007; McClernon, 2009). Reduced gray matter in these particular areas among patients have been linked to deficits in working memory (dorsolateral prefrontal cortex), integration of sensory information with internal states (insula), the presence of positive symptoms such as hallucinations and thought disorder (superior temporal gyrus) and social cognition (medial frontal gyrus and orbitofrontal cortex; Tregellas et al., 2007). Although patient smokers had more gray matter in disease-related areas their volumes were not comparable to that of controls (Tregellas et al., 2007).

There is mixed evidence, however, that patient smokers (particularly chronic smokers) show disruptions in functional-connectivity networks (Jasinska et al., 2014). Furthermore, current research findings not only suggest that acute nicotine has limited clinical benefit for patients as compared to controls (Hahn, Harvey, Concheiro-Guisan, Huestis, Holcomb, & Gold 2013), but also that chronic nicotine exposure may be responsible for cognitive impairments (Counotte, Goriounova, Li, Loos, Van Der Schors, Schetters, Schoffelmeer, Smit, Mansvelder, Pattij, & Spijker, 2011). Smokers with no psychiatric history have also been found to have

poorer performance on cognitive measures (e.g., working memory and sustained attention), reduced activity and gray matter volume in certain brain areas when compared to nonsmoking controls (Ernst, Heishman, Spurgeon & London, 2001; Rusted, Caulfield, King & Good, 2000; Lawrence, Ross & Stein, 2002; Jasinska et al., 2014).

There are also findings of cortical thinning amongst nonpsychiatric control smokers in several brain regions including the lateral prefrontal cortices, orbitofrontal cortex, and anterior cingulate, regions involved in working memory, sustained attention, decision-making, motivation, and arousal (Brody, Mandelkern, Jarvik, Lee, Smith, Huang, Bota, Bartzokis & London, 2004; Gallinat, Meisenzahl, Jacobsen, Kalus, Bierbrauer, Kiensat, Witthaus, Leopold, Seifert, Schubert & Staedtgen, 2006). There is further evidence to suggest that cigarette smoking has no effect on cognitive performance in nonsmoking controls (Wing et al., 2011).

**Current Study**

Evidently, additional research is needed to elucidate the relationship between smoking, cognition, and brain structure. To date, the relationship between psychopathology and smoking on cognitive performance and neural substrates remains unclear. Since smoking status is seldom controlled for in cognitive research outside of studies examining the effects of nicotine, understanding the contribution of nicotine dependence is a potentially important issue for data interpretation. Additionally, an examination of the illness-specific cognitive processes, rather than general cognition, is beneficial given the consensus that these processes are potentially modifiable by treatment and are strong predictors of functional outcome (Green, Kern, & Heaton, 2004; Heinrichs, Goldberg, Miles & McDermid Vaz, 2008; Nuechterlein, Barch, Gold, Goldberg, Green, & Heaton, 2004).

Indeed, patients tend to show similar impairments on both measures of crystallized intelligence (as indexed by intelligence quotient, IQ) and specific cognitive abilities (as measured by neurocognitive test batteries; e.g., processing speed, verbal memory, attention; Reichenberg & Harvey, 2007). However, estimates of IQ and neurocognitive tests that measure specific cognitive processes are independent measures of cognitive abilities (Reichenberg & Harvey, 2007), and it has been suggested that only specific cognitive processes can be potentially improved by treatment (Nuechterlein et al., 2004).

To address the gap in the literature, therefore, the current study investigated smoking status as it relates to both specific cognitive processes and cortical thickness in individuals with schizophrenia and IQ-matched nonpsychiatric controls. Specifically, the study's aim was to examine whether or not smoking status had a differential association with illness-specific cognitive processes and regional cortical thickness in smoking and nonsmoking patients and controls.

Since patients on average tend to perform 1 standard deviation (SD) below that of healthy controls on several neurocognitive measures (reviewed in Dickinson & Harvey, 2009), it was predicted that there would be a main effect of psychiatric status (patient vs. control) such that IQ-matched controls would outperform patients on all measures of specific cognitive abilities. It was further hypothesized that there would be a main effect of smoking status whereby nonsmokers would demonstrate better performance on cognitive tasks than smokers. This hypothesis was developed based on previous findings that it is rather acute nicotine consumption that may enhance cognitive performance (Jasinska et al., 2014), and the present research study did not examine the immediate effects of nicotine on cognitive performance.

Lastly, an interaction effect was anticipated such that poorer performance was expected with the presence of psychiatric illness and being a smoker, with the greatest impairment expected with psychiatric illness. Therefore, patient smokers were expected to have the poorest performance on cognitive tasks than the other groups (patient nonsmokers, control smokers, and control nonsmokers), and control nonsmokers were expected to have best performance. Control smokers were hypothesized to outperform patient nonsmokers. It was also examined whether or not psychiatric and smoking status may similarly relate to cortical thickness as with cognitive functioning. The study design may thus address whether or not there is a relationship between both psychiatric and smoking status on cognitive performance and neural substrates as indexed by cortical thickness.

## Method

### Participants

Individuals with schizophrenia or schizoaffective disorder were recruited from outpatient mental health clinics and services within Hamilton, Ontario. These services include: Cleghorn Early Intervention in Psychosis Program (St. Joseph's Healthcare Hamilton), Community Schizophrenia Service (St. Joseph's Healthcare Hamilton), Hamilton Program for Schizophrenia, Schizophrenia Society of Canada (Hamilton Chapter), and Path for Employment Services. Controls were recruited from the Hamilton region through advertisements on Kijiji, posted flyers, and word-of-mouth.

Inclusion criteria were limited to male and female participants between 18-65 years old who were fluent in English and had normal or corrected vision. Furthermore, individuals were screened to ensure they did not have any past or existing neurological or endocrine condition (e.g., epilepsy, head trauma, or Cushing’s disease, etc.), developmental disability, or substance

abuse (according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV; American Psychiatric Association, 2000). Healthy control participants were excluded if they reported a diagnosed psychiatric illness within the past 6 months. Diagnosis was confirmed for patients using the Structured Clinical Interview for DSM-IV Axis I Disorder-Patient Edition (SCID; First et al., 1996) prior to testing. This research study was approved by the institutional research ethics board at York University and St. Joseph's Healthcare Hamilton. All participants provided written informed consent and were compensated for their participation.

Following eligibility requirements, a total of 71 patients (43 males and 28 females) and 63 controls (39 males and 24 females) participated in the study. Patient charts confirmed that all patients were taking antipsychotic medications. Patient and control groups comprised of individuals between 18 and 65 years of age (patients had a mean age of 41.49, SD = 10.29, and control participants had a mean age of 39.27, SD = 11.85). The average time since first onset of characteristic signs and symptoms of the illness reported for patient nonsmokers was 17.67 (SD = 9.4) and 16.71 (SD = 12.5) for patient smokers, which was not significantly different.

**Smoking Status**

Thirty patients and 24 controls were smokers and 41 patients and 39 controls were nonsmokers. Smoking status was assessed using self-reports of number of cigarettes smoked daily. Upon commencing the study, participants were not provided with time during the session for tobacco consumption.

**Clinical Measures**

Patients' current symptom severity was measured using the Positive and Negative Syndrome Scale (PANSS; Opler, Kay, Lindenmayer, & Fiszbein, 1999), a semi-structured interview which contains subscales to examine positive, negative, and general psychopathology

symptoms commonly found among those with the disorder. The positive scale captures symptoms present among individuals with schizophrenia not usually found among the general population such as hallucinations, delusions, grandiosity, persecutory ideation, and conceptual disorganization. The negative scale assesses the absence of normative features found among healthy individuals, which include social and emotional withdrawal, rigidity of attitudes and beliefs, poor rapport and blunted affect. Lastly, the general psychopathology scale evaluates overall illness severity encompassing abnormal mannerisms, bizarre thought content, disturbance of volition, somatic preoccupation, disorientation and insight, guilt, depression, anxiety and tension. PANSS is a 30-item measure assesses symptom severity using a 7-point Likert rating scale ranging from the absence of symptoms to the presence of extreme pathological symptoms. PANSS has proven internal reliability and homogeneity among the items (.73 to .83, $p < .001$), test-retest reliability where testing intervals are between 3-6 months, and high construct validity supporting the Positive, Negative, and General Psychopathology scales as mutually exclusive dimensions (Kay, Fiszbein, & Opler, 1987).

**Neurocognitive Measures**

Participants' verbal and non-verbal abilities were measured using the Vocabulary and Matrix Reasoning subtests of the Wechsler Abbreviation Scale of Intelligence (WASI; Wechsler, 1997) respectively, and are robust estimates of general intelligence (or intelligence quotient (IQ); Alwin & McCammon, 2001). Verbal ability tends to be less susceptible to psychiatric illness such as schizophrenia and is supposed to be a measure of crystallized intelligence (Sheppard, & Vernon, 2008). The Reading subtest of the Wide Range Achievement Test (WRAT-4) is also a measure of verbal ability, and is linked to premorbid functioning (Wilkinson & Robertson, 2006).

Cognitive function was also measured using the MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) Consensus Cognitive Battery (MCCB; Nuechterlein et al., 2008), which is a battery of tests developed by experts that is sensitive to the impairments commonly found among individuals with schizophrenia that can be targeted for treatment (August, Kiwanuka, McMahon, & Gold, 2012). The battery of tests include measures of processing speed (Category fluency, Symbol coding, Trail Making A), attention/vigilance (Continuous Performance Test, Identical Pairs [CPT-IP]), working memory (Letter-Number Sequencing [WAIS-III], Spatial Span [Wechsler Memory Scale III]), verbal learning (Hopkins Verbal Learning Test-Revised), visual learning (Brief Visuospatial Memory Test-Revised), reasoning and problem solving (Mazes (Neuropsychological Assessment Battery [NAB]), and social cognition (Mayer-Salovey-Caruso Emotional Intelligence Test [MSCEIT]). Social cognitive functioning was also independently measured using the Reading the Mind in the Eyes and the Faux Pas Theory of Mind test (ToM; Baron-Cohen et al., 1997; Stone et al., 1998).

**Neuroimaging**

Imaging was conducted at the Brain Imaging Research Centre, Brain-Body Institute, St. Joseph's Healthcare Hamilton. Data were gathered from a high-resolution 3-Tesla GE HD Signa MR whole body short bore scanner (General Electric, Milwaukee, WI), with an 8-channel parallel receiver head coil (Invivo Corporation, Gainesville, FL). A T1-weighted axial anatomical scan was acquired using a three-dimensional fast spoiled gradient echo sequence with inversion recovery preparation. The anatomical image had 152 slices (2 mm thick with 1 mm overlap) with the following imaging parameters: time to repetition (TR)/ echo time (TE) = 7.5/2.1 ms, TI = 450 ms, field of view (FOV) = 24 cm, matrix = 512 x 512, flip angle = $12^{o}$, receiver bandwidth (rBW) = +/-62.5 kHz, and number of excitations (NEX) = 1.

**Testing Sessions**

Testing took place in Hamilton, Ontario where participants were recruited. Individuals with schizophrenia participated in 4 sessions on separate days. In the first session, participants were administered the SCID, PANSS, and WASI, which lasted no more than 3 hours in duration. The second session consisted of the cognitive batteries and the additional measure of verbal ability (MCCB and WRAT, respectively) and took approximately 2.5 -3 hours to complete. Social cognition was assessed in the third session (1.5 hours to complete), and imaging completed in the last session (with a duration of 20 minutes). Controls participated in 3 sessions given that diagnosis and symptom severity did not need to be assessed with the SCID and PANSS. Thus, control participants were administered the measures of cognition, verbal and non-verbal abilities (MCCB, WASI, and WRAT) in the first session with an average time to completion of approximately 2.5 hours. In the second session, social cognition was assessed and completed in 1.5 hours. Lastly, imaging data was collected in the third and final session and had a total duration of approximately 20 minutes.

**Statistical Analyses**

Neurocognitive behavioural data was analyzed using the Statistical Package for the Social Sciences 21 (SPSS). A two-way analysis of variance was conducted with both psychiatric and smoking status as independent variables and cognitive performance as the dependent variable; differences with a $p$ value less than 0.05 were considered significant. Post hoc $t$ tests were used for significant interactions using the Bonferonni-adjusted $p$. Lastly, chi-squared analysis was used to measure the difference between group frequencies for such categorical variables as sex, handedness and first language spoken.

The T1-weighted images collected for each participant were pre-processed in order to segment the brain and to align cortical structures across the subjects using FreeSurfer image analysis (http://surfer.nmr.mgh.harvard.edu/). Cortical thickness was defined as the distance between pial surface to the gray/white matter border at each vertex. Surface maps were smoothed with a 15 mm full-width-half-maximum Gaussian kernel. A main effect of psychiatric status was examined using ANCOVA with sex and age as covariates and cortical thickness as the dependent variable. Similarly, ANCOVA was conducted to examine a main effect of smoking status using sex and age again as covariates. I further examined whether or not there was an interaction between smoking status and psychiatric status on cortical thickness. A *t* value of 3.5 was used as the cut-off for significance such that only brain regions that had values of 3.5 or greater were considered for interpretation, with a *p* value less than 0.05.

## Results

### Demographic Characteristics and Clinical Profile

Demographic profiles comparing smoking and nonsmoking individuals with schizophrenia and nonpsychiatric controls can be found in Table 1. When comparing the four experimental groups (patient nonsmokers, patient smokers, control nonsmokers and control smokers), there was no significant difference in age, sex, handedness, or first language learned. Group compositions were such that the majority of participants were right-handed males who spoke English as their first language. However, there was a significant main effect of years of education obtained. Post hoc analysis revealed that years of education obtained was significantly different when comparing control smokers to both patients and controls who were nonsmokers such that control smokers had fewer years of schooling, $p = 0.001$. No other group differences were observed for this variable.

There was no significant difference with respect to the frequency of smoking per day between patients and controls (see Table 1). Lastly, symptom severity was examined between patient nonsmokers and patient smokers using PANSS and there were no significant group differences on any subscales (see Table 2). This suggests that the clinical profiles of the patient groups were indistinguishable.

**Performance on Neurocognitive Measures**

A two-way ANOVA revealed no main effect of psychiatric status on estimates of IQ and premorbid functioning (i.e., WASI and WRAT-4, respectively; refer to Table 4); that is, there was no significant difference between individuals with schizophrenia and healthy controls on these measures. However, there was a main effect of smoking status on both the WASI (measuring verbal and non-verbal abilities; $p < 0.001$) and WRAT (an independent measure of verbal ability; $p < 0.001$). Here, smokers scored significantly lower than nonsmokers. On all other measures of specific cognitive abilities using the MCCB (i.e., processing speed, attention/ vigilance, working memory, verbal learning, visual learning, reasoning and problem-solving, and social cognition) and independent measures of social cognition a two-way ANOVA confirmed a main effect of psychiatric status, a main effect of smoking status, and an interaction between both independent variables and the reasoning and problem-solving subscale of the MCCB (see Table 3).

Specifically, examining MCCB cognitive domain scores, the main effect of psychiatric status revealed that patients had slower speed of processing than controls ($p < 0.001$) and demonstrated diminished attention ($p = 0.008$). Patients also scored lower on tests of working memory ($p = 0.016$), verbal learning ($p < 0.001$), visual learning ($p = 0.002$), reasoning and problem solving ($p < 0.001$), and social cognition ($p = 0.017$). The MCCB composite score is an

overall score, which is comprised of all other domain scores. Here, the composite score similarly reveals that patients were significantly outperformed by controls ($p < 0.001$). With respect to the additional measures of social cognition, patients were less able to detect faux pas in the social situations presented ($p = 0.001$) and emotional expression as captured by the Reading the Mind in the Eyes task, ($p = 0.001$).

Similarly, the main effect of smoking status revealed that nonsmokers' scores significantly exceeded that of smokers on all but the MCCB's measure of social cognition. In fact, smokers had significantly lower scores on measures of attention ($p = 0.036$), processing speed ($p < 0.001$), working memory ($p = 0.002$), verbal and visual learning ($p < 0.001$ and $p = 0.008$, respectively), reasoning and problem solving ($p = 0.040$). Smokers also had an overall lower MCCB composite score when compared to nonsmokers. Although the MCCB measure of social cognition was not significant, the two independent measures of social cognition (faux pas and reading the mind in the eyes) revealed significant differences between smokers and nonsmokers, with nonsmokers again having higher scores than smokers (faux pas, $p = 0.043$ and reading the mind in the eyes $p < 0.001$).

There was a significant interaction between smoking status and psychiatric status on the reasoning and problem solving task, $p = 0.003$. Post hoc analysis revealed that control nonsmokers ($M = 53.46$, $SD = 9.20$) had superior reasoning and problem solving scores when compared to patient smoker ($M = 42.17$, $SD = 9.67$), patient nonsmoker ($M = 40.71$, $SD = 9.27$) and control smoker ($M = 45.33$, $SD = 7.55$), ($p < 0.001$). No other significance differences were found.

**Neuroimaging Data**

The ANCOVA revealed a main effect of psychiatric status on cortical thickness such that there was widespread cortical thinning in patients (Figures 1 and 2). For example, in the right hemisphere, cortical thickness reductions in patients were observed in the superior frontal gyrus ($t$ = -3.69), superior and inferior parietal gyri ($t$ = -3.75 and ($t$ = -5.81, respectively), and insula ($t$ = -5.35). Individuals with schizophrenia also had greater reductions in the left hemisphere in the following regions: precentral and postcentral gyri ($t$ = -3.56 and $t$ = -5.89, respectively), superior temporal gyrus ($t$ = -4.22) and fusiform ($t$ = -5.19). Lastly, there was significant reduction in cortical thickness found bilaterally in the precuneus (left hemisphere, $t$ = -6.29 and right hemisphere, $t$ = -4.94).

It was further examined whether or not there was a main effect of smoking status on cortical thickness and found no significant reductions in the left hemisphere. However, there was a significant main effect found in the right hemisphere such that nonsmokers had greater thickness than smokers in the middle temporal gyrus ($t$ = 5.32) and banks of the superior temporal sulcus ($t$ = 3.66), see Figure 3. The inferior temporal gyrus was marginally significant ($t$ = 3.24).

Lastly, a significant interaction was found between smoking status and psychiatric status (refer to Figure 4). Patient smokers and control nonsmokers had greater cortical thickness in the left parahippocampal gyrus ($t$ = 4.04), and bilateral medial orbitofrontal gyri (left hemisphere $t$ = 3.89 and right hemisphere $t$ = 4.19) than patient nonsmokers and control smokers.

## Discussion

Cognitive impairments are a core feature of schizophrenia that significantly impact quality of life. Although there is considerable research in this area aimed at better understanding

the neural mechanisms of illness-specific cognitive functions to target for treatment, they are not well understood. Furthermore, mixed findings of nicotine's effect on cognition suggest that further research is needed to better understand the relationship between smoking status and the pathophysiology of schizophrenia (Brody et al., 2004; Ernst et al., 2001; Tregellas et al., 2007).

The goal of the current study was to examine the effect of smoking status on the potentially modifiable treatment relevant cognitive processes and on regional cortical thickness among individuals with schizophrenia and nonpsychiatric controls. Although studies tend to report findings of lower IQ among individuals with schizophrenia as compared to nonpsychiatric controls, patients and controls were matched on this variable in the current study.

It was not surprising that verbal ability (as measured by the WRAT) was not significantly different between the two groups given previous findings that verbal ability remains relatively intact among those with schizophrenia and is less affected by the illness (Heinrichs & Zakzanis, 1998). Given that patients' verbal ability and general intelligence matched that of controls our data provides an opportunity to detect the effects of smoking status and diagnosis on specific cognitive abilities and cortical thickness.

Using a battery of neurocognitive tests specifically designed to capture potentially modifiable cognitive processes vulnerable to schizophrenia, I replicated previous findings that patients have impairments in attention, working memory, processing speed, verbal and visual learning, social cognition, and reasoning and problem solving in comparison to controls. These deficits have been consistently shown and have led to the recognition that deficits in cognition are characteristic of the illness (see Heinrichs & Zakanis, 1998; Dickinson & Harvey, 2009; and Winterer, 2010 for reviews). Widespread reduction in cortical thickness was also observed in patients as compared to controls in areas previously found to be implicated in the

pathophysiology of the disorder and the corresponding cognitive deficits (i.e., superior frontal, superior temporal, inferior parietal, precuneus, insula, and fusiform; Ehrlich et al., 2012; Fossati et al., 1999; Goldman et al., 2009; Mjellem & Kringlen, 2001, Nestor et al., 2007; Onitsuka, Shenton, Salisbury, Dickey, Kasai, Toner, Frumin, Kikinis, Jolesz & McMarley, 2004; Pearlson & Marsh, 1999; Tregellas et al., 2007).

Examining the relationship between smoking status and measures of general intelligence revealed that smokers were more likely to have lower general intelligence than nonsmokers. Smokers also tended to have greater deficits on all neurocognitive measures (i.e., speed of processing, attention, working memory, visual and verbal learning, reasoning and problem solving, and independent measures of social cognition). These findings are in line with previous reports that smoking impairs cognition (Brody et al., 2004; Ernst et al., 2001; Gallinat et al., 2006). It may be that individuals with characteristics such as lower general intelligence may have less support in their quitting attempts and thus may be less successful despite the possible link between smoking and impaired cognitive functioning (and consequently, day-to-day functioning; Kotz & West, 2009).

Neuroimaging results revealed that nonsmokers had greater cortical thickness than smokers in the inferior and middle temporal gyri as well as the banks of the superior temporal sulcus of the right hemisphere. These areas are involved in semantic memory and language processing (inferior and middle temporal gyrus; Nestor et al., 2007) and integration of visual, auditory and somatosensory information as well as face processing (banks of the superior temporal sulcus; Seltzer & Pandya, 1978). It is important to note that the inferior temporal area was only marginally significant.

The main purpose of this study was to examine the relationship between smoking status, cognition, and cortical thickness in both patients and controls. The sole interaction effect found in the behavioural data was on measures of reasoning and problem solving where control nonsmokers outperformed control smokers, patient smokers and patient nonsmokers. Interestingly, control smokers were indistinguishable from both patient groups suggesting that they had impaired reasoning and problem solving abilities. It has been suggested that those who abstain from smoking for approximately 3 hours can induce nicotine-withdrawal symptoms, which may affect cognitive performance (see Sacco, Bannon & George, 2004). In our study, the neurocognitive battery administered had a duration of approximately 2-3 hours, and participants were not given smoke breaks. However, Bell et al. (1999) found that nicotine-deprivation in smokers did not affect performance on a logical reasoning task. Therefore, these results cannot be attributed to nicotine-deprivation.

Problem solving skills are crucial for functional capacity in daily living. In fact, among people with schizophrenia, problem solving abilities are highly correlated with other cognitive functions (e.g., processing speed, working memory, and verbal memory), negative symptoms (e.g., flat affect and emotional withdrawal), and functional outcome (Revheim, Schechter, Kim, Silipo, Allingham, Butler & Javitt, 2006). Indeed, inpatients demonstrate significantly lower problem solving skills than outpatients (Revheim et al., 2006). It is understandable that these variables may correlate and affect overall functioning, as activities of daily living require attention to social cues, reasoning and problem solving skills, and efficient processing of information.

Research examining the effects of nicotine on cognition has relied to some extent on contrasting both smoker and nonsmoker patients to nonsmoking controls, which will inevitably

allow for larger effects. However, the greater issue may lie in cognitive research where smoking status is not measured. That is, if nicotine consumption alters information processing and possibly the neural pathways involved, failure to assess smoking status may impede data interpretation in general, and in understanding illness-specific impairments and the pathophysiology of schizophrenia. Our findings suggest that it is especially important to take into consideration smoking status when collecting neuroimaging data given the distinct differences in cortical thickness as a function of both illness and smoking status.

Indeed, patient smokers and control nonsmokers had similar patterns of cortical thickness in the left parahippocampal gyrus and bilateral medial orbitofrontal gyrus. The parahippocampal gyrus is important for integrating sensory information and the processing of communication cues (McDonald, Highley, Walker, Herron, Cooper, Esiri, & Crow, 2000) while the medial orbitofrontal gyrus is involved in decision-making and emotional perspective-taking (Elliott, Dolan, & Frith, 2000; Hynes, Baird & Grafton, 2006). The neuroimaging results, therefore, suggest smoking status is differentially correlated with cortical thickness patterns among patients and controls. These particular areas where patient smokers and control nonsmokers have similar neurobiological profiles seem to be especially important for executive functions and social cognition. Here, the data also lend support for the interconnectedness of various brain regions involved in the pathophysiology of schizophrenia. Thus, it may well be that impairments result from faulty connections (Goldman et al., 2009; Oertel-Knochel et al., 2013).

Taken together, our data suggest that smoking status and schizophrenia are both independently correlated with cognition and brain structure. These results have serious implications as failure to take into account smoking status in cognitive research may explain some of the variability in schizophrenia research. In particular, smoking prevalence among the

schizophrenia population tends to be 2-3 times that of the general population (Goldberg & Van Exan, 2008), which may further obscure results if smoking status is not assessed.

**Limitations**

The behavioural neurocognitive data do not lend support for nicotine enhancement of cognitive deficits within the patient group as previously found in the literature. However, studies have found that it is the acute consumption of nicotine or nicotinic agents that may improve performance on cognitive measures, and impairments or a lack of effect are seen when smokers (particularly psychiatric participants) abstain and perform cognitive tasks (George et al., 2002; Sacco, Bannon & George, 2004). Thus, it is worth noting that the current study examined the relationship between smoking status (i.e., whether or not an individual smokes) and not the acute consumption of nicotine. While it may be argued that a limitation of the present study is that it did not assess cognition in smokers following tobacco consumption, the goal of the study was to examine the effect of smoking status on cognitive performance and brain structure. Given that cognitive studies do not commonly assess smoking status of participants, our findings provide support for its inclusion as a variable of interest as it is independently correlated with both neurocognitive performance and neuroimaging results.

Another limitation of the study is the concern of generalizability given that the patient sample did not show lower general intelligence when compared to controls, which would normally be expected from random sampling. Indeed, patients tend to demonstrate poorer performance on neurocognitive measures (reviewed in Dickinson & Harvey, 2009). However, that patients and controls were matched on general intelligence and had similar educational attainment allowed for better comparison of specific cognitive abilities and regional cortical thickness between the groups.

Additionally, patient smokers tend to have reduced negative symptoms compared to patient nonsmokers as measured by lower overall PANSS score (Zhang, Liang, Chen, Xiu, He, Cheng, Wu, Yang, Haile, Sun, Lu, Kosten & Kosten, 2012). However, in the current study clinical profiles of patient smokers and patient nonsmokers were not significantly different. Given that analyses of smoking status would include data from both patient and control groups, this finding is beneficial for interpreting the current findings. That is, if patient smokers were significantly less symptomatic than patient nonsmokers the results of the neurocognitive measures may have been skewed as symptom severity is highly correlated with cognitive functioning (such as, problem solving; Revheim et al., 2006).

## Conclusion

Cognitive impairments are well documented among the schizophrenia population and are predictive of functional outcome. There has been some support for the self-medication hypothesis that nicotine enhances cognitive performance among individuals with schizophrenia in the extant literature. The higher prevalence of smoking in this clinical population has been suggested as an attempt by patients to counteract illness-specific cognitive impairments and psychotropic medication side effects. However, there are inconsistencies in the literature with respect to the effect of nicotine on cognition and structural brain changes in both people with schizophrenia and nonpsychiatric controls. Whether nicotine enhances or impairs cognitive performance, smoking status should be seriously considered in cognitive research to minimize confounds to data interpretation.

The current data point to the importance of assessing smoking status in cognitive research in general as well as in schizophrenia research in particular. The goal is to understand the neuroanatomical abnormalities and their relationship to cognitive deficits as a function of the

illness separately from other confounds (such as tobacco consumption). Given the current findings, it follows that smoking status may be an artifact in the interpretation of cognitive research data. Thus, the use of schizophrenia control comparisons in the existing literature is of questionable value. Measuring smoking status is of great utility as future treatment may be more effective in targeting illness-specific deficits to possibly establish significant change in quality of life.

References

Alwin, D. F. & McCammon, R. J. (2001). Aging, cohorts, and verbal ability. *Journal of Gerontology: Social Sciences, 56B,* S151-S161.

American Psychiatric Association. (2000). Diagnostic And Statistical Manual Of Mental Disorders DSM-IV-TR Fourth Edition (Text Revision) Author: American Psychiatric Association.

American Psychiatric Association. (2013). DSM 5. American Psychiatric Association.

Andreasen, N. C. (2010). The lifetime trajectory of schizophrenia and the concept of neurodevelopment. *Dialogues in clinical neuroscience, 12,* 409-415.

August, S. M., Kiwanuka, J. N., McMahon, R. P., & Gold, J. M. (2012). The MATRICS Consensus Cognitive Battery (MCCB): clinical and cognitive correlates. *Schizophrenia research, 134,* 76-82.

Baliunas, D., Patra, J., Rehm, J., Popova, S., & Taylor, B. (2007). Smoking-attributable morbidity: acute care hospital diagnoses and days of treatment in Canada, 2002. *BMC Public Health, 7,* 247-254.

Barch, D. M., Bustillo, J., Gaebel, W., Gur, R., Heckers, S., Malaspina, D., ... & Carpenter, W. (2013). Logic and justification for dimensional assessment of symptoms and related clinical phenomena in psychosis: relevance to DSM-5. *Schizophrenia research, 150*(1), 15-20.

Bell, S. L., Taylor, R. C., Singleton, E. G., Henningfield, J. E., & Heishman, S. J. (1999). Smoking after nicotine deprivation enhances cognitive performance and decreases tobacco craving in drug abusers. *Nicotine Tobacco Research, 1,* 45–52.

Breese, C. R., Lee, M. J., Adams, C. E., Sullivan, B., Logel, J., Gillen, K. M., ... & Leonard, S. (2000). Abnormal regulation of high affinity nicotinic receptors in subjects with schizophrenia. *Neuropsychopharmacology*, *23*(4), 351-364.

Brody, A. L., Mandelkern, M. A., Jarvik, M. E., Lee, G. S., Smith, E. C., Huang, J. C., ... & London, E. D. (2004). Differences between smokers and nonsmokers in regional gray matter volumes and densities. *Biological psychiatry*, *55*, 77-84.

Chan, R. C., Di, X., McAlonan, G. M., & Gong, Q. Y. (2011). Brain anatomical abnormalities in high-risk individuals, first-episode, and chronic schizophrenia: an activation likelihood estimation meta-analysis of illness progression. *Schizophrenia bulletin*, *37*, 177-188.

Cobia, D. J., Smith, M. J., Wang, L., & Csernansky, J. G. (2012). Longitudinal progression of frontal and temporal lobe changes in schizophrenia. *Schizophrenia research*, *139*, 1-6.

Counotte, D. S., Goriounova, N. A., Li, K. W., Loos, M., Van Der Schors, R. C., Schetters, D., ... & Spijker, S. (2011). Lasting synaptic changes underlie attention deficits caused by nicotine exposure during adolescence. *Nature neuroscience*, *14*, 417-419.

Dalack, G. W., Healy, D. J., & Meador-Woodruff, J. H. (1998). Nicotine dependence in schizophrenia: clinical phenomena and laboratory findings. *American Journal of Psychiatry*, *155*, 1490-1501.

de Leon, J., & Diaz, F. J. (2005). A meta-analysis of worldwide studies demonstrates an association between schizophrenia and tobacco smoking behaviors. *Schizophrenia research*, *76*(2), 135-157.

Dickinson, D., & Harvey, P. D. (2009). Systemic hypotheses for generalized cognitive deficits in schizophrenia: a new take on an old problem. *Schizophrenia bulletin*, *35*(2), 403-414.

Ehrlich, S., Brauns, S., Yendiki, A., Ho, B. C., Calhoun, V., Schulz, S. C., ... and Sponheim, S. R. (2012). Associations of cortical thickness and cognition in patients with schizophrenia and healthy controls. *Schizophrenia bulletin*, *38*, 1050-1062.

Elliott, R., Dolan, R. J., & Frith, C. D. (2000). Dissociable functions in the medial and lateral orbitofrontal cortex: evidence from human neuroimaging studies. *Cerebral cortex*, *10*(3), 308-317.

Ernst, M., Heishman, S. J., Spurgeon, L., & London, E. D. (2001). Smoking history and nicotine effects on cognitive performance. *Neuropsychopharmacology*, *25*(3), 313-319.

Flaum, M., O'Leary, D. S., Swayze, V. W., Miller, D. D., Arndt, S., and Andreasen, N. C. (1995). Symptom domains and brain morphology in schizophrenia and related psychotic disorders. *Journal of Psychiatry Research*, *29*, 261–276.

Fossati, P., Amar, G., Raoux, N., Ergis, A. M., and Allilaire, J. F. (1999). Executive functioning and verbal memory in young patients with unipolar depression and schizophrenia. *Psychiatry research*, *89*, 171-187.

Freedman, R. (2014). α7-nicotinic acetylcholine receptor agonists for cognitive enhancement in schizophrenia. *Annual review of medicine*, *65*, 245-261.

Gallinat, J., Meisenzahl, E., Jacobsen, L. K., Kalus, P., Bierbrauer, J., Kienast, T., ... & Staedtgen, M. (2006). Smoking and structural brain deficits: a volumetric MR investigation. *European Journal of Neuroscience*, *24*, 1744-1750.

Garey, L. (2010). When cortical development goes wrong: schizophrenia as a neurodevelopmental disease of microcircuits. *Journal of anatomy*, *217*, 324-333.

George, T. P., Termine, A., Sacco, K. A., Allen, T. M., Reutenauer, E., Vessicchio, J. C., & Duncan, E. J. (2006). A preliminary study of the effects of cigarette smoking on prepulse

inhibition in schizophrenia: involvement of nicotinic receptor mechanisms. *Schizophrenia research, 87*, 307-315.

George, T. P., Vessicchio, J. C., Termine, A., Sahady, D. M., Head, C. A., Pepper, W. T., ... & Wexler, B. E. (2002). Effects of smoking abstinence on visuospatial working memory function in schizophrenia, *Neuropsychopharmacology, 26*, 75-85.

Glahn, D. C., Laird, A. R., Ellison-Wright, I., Thelen, S. M., Robinson, J. L., Lancaster, J. L., ... & Fox, P. T. (2008). Meta-analysis of gray matter anomalies in schizophrenia: application of anatomic likelihood estimation and network analysis. *Biological psychiatry*, *64*, 774-781.

Glassman, A. H. (1993). Cigarette smoking: implications for psychiatric illness. *The American journal of psychiatry*, *150*, 546-553.

Goeree, R., Farahati, F., Burke, N., Blackhouse, G., O'Reilly, D., Pyne, J., & Tarride, J. E. (2005). The economic burden of schizophrenia in Canada in 2004. *Current Medical Research and Opinion*, *21*, 2017-2028.

Gogtay, N., Greenstein, D., Lenane, M., Clasen, L., Sharp, W., Gochman, P., ... & Rapoport, J. (2007). Cortical brain development in nonpsychotic siblings of patients with childhood-onset schizophrenia. Archives of General Psychiatry, 64, 772-780.

Goldberg, J. O., & Van Exan, J. (2008). Longitudinal rates of smoking in a schizophrenia sample. *Tobacco control*, *17*, 271-275.

Goldman, A. L., Pezawas, L., Mattay, V. S., Fischl, B., Verchinski, B. A., Chen, Q., ... & Meyer-Lindenberg, A. (2009). Widespread reductions of cortical thickness in schizophrenia and spectrum disorders and evidence of heritability. *Archives of general psychiatry*, *66*, 467-477.

Green, M. F., Kern, R. S., & Heaton, R. K. (2004). Longitudinal studies of cognition and functional outcome in schizophrenia: implications for MATRICS. *Schizophrenia research*, *72*, 41-51.

Hahn, B., Harvey, A. N., Concheiro-Guisan, M., Huestis, M. A., Holcomb, H. H., & Gold, J. M. (2013). A test of the cognitive self-medication hypothesis of tobacco smoking in schizophrenia. *Biological psychiatry*, *74*(6), 436-443.

Hartberg, C. B., Lawyer, G., Nyman, H., Jönsson, E. G., Haukvik, U. K., Saetre, P., ... and Agartz, I. (2010). Investigating relationships between cortical thickness and cognitive performance in patients with schizophrenia and healthy adults. *Psychiatry Research: Neuroimaging*, *182*, 123-133.

Heinrichs, R. W. (2005). The primacy of cognition in schizophrenia. *American Psychologist, 60*, 229-242.

Heinrichs, R. W., Goldberg, J. O., Miles, A. A., & McDermid Vaz, S. (2008). Predictors of medication competence in schizophrenia patients. *Psychiatry research*, *157*, 47-52.

Heinrichs, R. W., & Zakzanis, K. K. (1998). Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. *Neuropsychology*, *12*, 426-455.

Heishman, S. J., Kleykamp, B. A., & Singleton, E. G. (2010). Meta-analysis of the acute effects of nicotine and smoking on human performance. *Psychopharmacology*, *210*, 453-469.

Ho, B. C., Andreasen, N. C., Nopoulos, P., Arndt, S., Magnotta, V., & Flaum, M. (2003). Progressive structural brain abnormalities and their relationship to clinical outcome: a longitudinal magnetic resonance imaging study early in schizophrenia. *Archives of General Psychiatry*, *60*, 585-594.

Honea, R. A., Meyer-Lindenberg, A., Hobbs, K. B., Pezawas, L., Mattay, V. S., Egan, M. F., ... & Callicott, J. H. (2008). Is gray matter volume an intermediate phenotype for schizophrenia? A voxel-based morphometry study of patients with schizophrenia and their healthy siblings. *Biological psychiatry*, *63*, 465-474.

Hong, L. E., Wonodi, I., Lewis, J., & Thaker, G. K. (2007). Nicotine effect on prepulse inhibition and prepulse facilitation in schizophrenia patients. *Neuropsychopharmacology*, *33*(9), 2167-2174.

Hynes, C. A., Baird, A. A., & Grafton, S. T. (2006). Differential role of the orbital frontal lobe in emotional versus cognitive perspective-taking. *Neuropsychologia*, *44*(3), 374-383.

Jaaro-Peled, H., Ayhan, Y., Pletnikov, M. V., & Sawa, A. (2010). Review of pathological hallmarks of schizophrenia: comparison of genetic models with patients and nongenetic models. *Schizophrenia bulletin*, *36*(2), 301-313.

Jacobsen, L. K., D'Souza, D. C., Mencl, W. E., Pugh, K. R., Skudlarski, P., & Krystal, J. H. (2004). Nicotine effects on brain function and functional connectivity in schizophrenia. *Biological psychiatry*, *55*(8), 850-858.

Jasinska, A. J., Zorick, T., Brody, A. L., & Stein, E. A. (2014). Dual role of nicotine in addiction and cognition: a review of neuroimaging studies in humans. *Neuropharmacology*, *84*, 111-122.

Kalman, D., Morissette, S. B., & George, T. P. (2005). Co-Morbidity of Smoking in Patients with Psychiatric and Substance Use Disorders. *The American Journal on Addictions*, *14*, 106-123.

Kašpárek, T., Mareček, R., Schwarz, D., Přikryl, R., Vaníček, J., Mikl, M., & Češková, E. (2010). Source-based morphometry of gray matter volume in men with first-episode

schizophrenia. *Human brain mapping*, *31*, 300-310.

Kay, S. R., Flszbein, A., & Opler, L. A. (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia bulletin*, *13*, 261.

Kotz, D., & West, R. (2009). Explaining the social gradient in smoking cessation: it's not in the trying, but in the succeeding. *Tobacco control*, *18*(1), 43-46.

Kumari, V. (2005). Nicotine use un schizophrenia: The self-medication hypothesis. *Neuroscience and biobehavioural reviews, 29*, 1021-1034.

Kumari, V., Soni, W., & Sharma, T. (2001). Influence of cigarette smoking on prepulse inhibition of the acoustic startle response in schizophrenia. *Human Psychopharmacology: Clinical and Experimental*, *16*(4), 321-326.

Lawrence, N. S., Ross, T. J., & Stein, E. A. (2002). Cognitive mechanisms of nicotine on visual attention. *neuron*, *36*(3), 539-548.

Lesh, T. A., Niendam, T. A., Minzenberg, M. J., & Carter, C. S. (2011). Cognitive control deficits in schizophrenia: mechanisms and meaning. *Neuropsychopharmacology*, *36*, 316-338.

Marutle, A., Zhang, X., Court, J., Piggott, M., Johnson, M., Perry, R., ... & Nordberg, A. (2001). Laminar distribution of nicotinic receptor subtypes in cortical regions in schizophrenia. *Journal of chemical neuroanatomy*, *22*(1), 115-126.

Marwaha, S., & Johnson, S. (2004). Schizophrenia and employment. *Social psychiatry and psychiatric epidemiology*, *39*(5), 337-349.

McClernon, F. J. (2009). Neuroimaging of Nicotine Dependence: Key Findings and Application to the Study of Smoking–Mental Illness Co-morbidity. *Journal of dual diagnosis*, *5*, 168-178.

McDonald, B., Highley, J. R., Walker, M. A., Herron, B. M., Cooper, S. J., Esiri, M. M., & Crow, T. J. (2000). Anomalous asymmetry of fusiform and parahippocampal gyrus gray matter in schizophrenia: a postmortem study. *American Journal of Psychiatry*, *157*(1), 40-47.

McGrath, J., Saha, S., Chant, D., & Welham, J. (2008). Schizophrenia: a concise overview of incidence, prevalence, and mortality. *Epidemiologic reviews*, *30*(1), 67-76.

Mitchell, J. E., & Dahlgren, A. (1986). Prevalence of smoking among psychiatric outpatients. *American Journal of Psychiatry*, *143*, 993-997.

Minzenberg, M. J., Laird, A. R., Thelen, S., Carter, C. S., & Glahn, D. C. (2009). Meta-analysis of 41 functional neuroimaging studies of executive function in schizophrenia. *Archives of general psychiatry*, *66*, 811-822.

Mjellem, N., and Kringlen, E. (2001). Schizophrenia: a review, with emphasis on the neurodevelopmental hypothesis. *Nordic journal of psychiatry*, *55*, 301-309.

Mueser, K. T. & McGurk S. R. (2004). Schizophrenia. *Lancet*, *363*, 2063–2072.

Nestor, P. G., Onitsuka, T., Gurrera, R. J., Niznikiewicz, M., Frumin, M., Shenton, M. E., and McCarley, R. W. (2007). Dissociable contributions of MRI volume reductions of superior temporal and fusiform gyri to symptoms and neuropsychology in schizophrenia. *Schizophrenia research*, *91*, 103-106.

Niendam, T. A., Bearden, C. E., Johnson, J. K., McKinley, M., Loewy, R., O'Brien, M., ... & Cannon, T. D. (2006). Neurocognitive performance and functional disability in the psychosis prodrome. *Schizophrenia research*, *84*, 100-111.

Nuechterlein, K. H., Barch, D. M., Gold, J. M., Goldberg, T. E., Green, M. F., & Heaton, R. K. (2004). Identification of separable cognitive factors in schizophrenia. *Schizophrenia research*, *72*, 29-39.

Oertel-Knöchel, V., Knöchel, C., Rotarska-Jagiela, A., Reinke, B., Prvulovic, D., Haenschel, C., ... and Linden, D. E. (2013). Association between psychotic symptoms and cortical thickness reduction across the schizophrenia spectrum. *Cerebral Cortex*, *23*, 61-70.

Olincy, A., Young, D. A., & Freedman, R. (1997). Increased levels of the nicotine metabolite cotinine in schizophrenic smokers compared to other smokers. *Biological Psychiatry*, *42*, 1-5.

Onitsuka, T., Shenton, M. E., Salisbury, D. F., Dickey, C. C., Kasai, K., Toner, S. K., ... & McCarley, R. W. (2004). Middle and inferior temporal gyrus gray matter volume abnormalities in chronic schizophrenia: an MRI study. *American Journal of Psychiatry*, *161*, 1603-1611.

Opler, L. A., Kay, S. R., Lindenmayer, J. P., & Fiszbein, A. (1999). Structured Clinical Interview: The Positive and Negative Syndrome Scale (SCI-PANSS) Multi-Health Systems Inc. *North Tonawanda, NY*.

Orellana, G., & Slachevsky, A. (2013). Executive functioning in schizophrenia. *Frontiers in Psychiatry*, *4*, 1-15.

Pearlson, G. D., and Marsh, L. (1999). Structural brain imaging in schizophrenia: a selective review. *Biological psychiatry*, *46*, 627-649.

Prochaska, J. J., Hall, S. M., & Bero, L. A. (2008). Tobacco use among individuals with schizophrenia: what role has the tobacco industry played?. *Schizophrenia bulletin*, *34*, 555-567.

Ragland, J. D., Yoon, J., Minzenberg, M. J., & Carter, C. S. (2007). Neuroimaging of cognitive disability in schizophrenia: search for a pathophysiological mechanism. *International Review of Psychiatry*, *19*, 417-427.

Reichenberg, A., & Harvey, P. D. (2007). Neuropsychological impairments in schizophrenia: Integration of performance-based and brain imaging findings. *Psychological bulletin*, *133*, 833-858.

Revheim, N., Schechter, I., Kim, D., Silipo, G., Allingham, B., Butler, P., & Javitt, D. C. (2006). Neurocognitive and symptom correlates of daily problem-solving skills in schizophrenia. *Schizophrenia research*, *83*, 237-245.

Riehemann, S., Volz, H. P., Stützer, P., Smesny, S., Gaser, C., & Sauer, H. (2001). Hypofrontality in neuroleptic-naive schizophrenic patients during the Wisconsin Card Sorting Test–a fMRI study. *European archives of psychiatry and clinical neuroscience*, *251*, 66-71.

Rusted, J. M., Caulfield, D., King, L., & Goode, A. (2000). Moving out of the laboratory: does nicotine improve everyday attention?. *Behavioural Pharmacology*, *11*(7-8), 621-629.

Sacco, K. A., Bannon, K. L., & George, T. P. (2004). Nicotinic receptor mechanisms and cognition in normal states and neuropsychiatric disorders. Journal of Psychopharmacology, 18(4), 457-474.

Sacco, K. A., Termine, A., Seyal, A., Dudas, M. M., Vessicchio, J. C., Krishnan-Sarin, S., ... & George, T. P. (2005). Effects of cigarette smoking on spatial working memory and attentional deficits in schizophrenia: involvement of nicotinic receptor mechanisms. *Archives of general psychiatry*, *62*, 649-659.

Šagud, M., Mihaljević-Peleš, A., Mück-Šeler, D., Pivac, N., Vuksan-Ćusa, B., Brataljenović, T.,

& Jakovljević, M. (2009). Smoking and schizophrenia. *Psychiatria Danubina, 21*, 371-375.

Seltzer, B. & Pandya, D. N. (1978). Afferent cortical connections and architectonics of the superior temporal sulcus and surrounding cortex in the rhesus monkey. *Brain research, 149*, 1-24.

Sheppard, L. D., & Vernon, P. A. (2008). Intelligence and speed of information-processing: A review of 50 years of research. *Personality and Individual Differences, 44*(3), 535-551.

Snitz, B. E., MacDonald, A., Cohen, J. D., Cho, R. Y., Becker, T., and Carter, C. S. (2005). Lateral and medial hypofrontality in first-episode schizophrenia: functional activity in a medication-naive state and effects of short-term atypical antipsychotic treatment. *American Journal of Psychiatry, 162*, 2322-2329.

Strand, J. E., & Nybäck, H. (2005). Tobacco use in schizophrenia: a study of cotinine concentrations in the saliva of patients and controls. *European Psychiatry, 20*, 50-54.

Sun, J., Maller, J. J., Guo, L., & Fitzgerald, P. B. (2009). Superior temporal gyrus volume change in schizophrenia: a review on region of interest volumetric studies. *Brain research reviews, 61*, 14-32.

Swerdlow, N. R., Light, G. A., Cadenhead, K. S., Sprock, J., Hsieh, M. H., & Braff, D. L. (2006). Startle gating deficits in a large cohort of patients with schizophrenia: relationship to medications, symptoms, neurocognition, and level of function. *Archives of General Psychiatry, 63*, 1325-1335.

Tregellas, J. R., Shatti, S., Tanabe, J. L., Martin, L. F., Gibson, L., Wylie, K., & Rojas, D. C. (2007). Gray matter volume differences and the effects of smoking on gray matter in schizophrenia. *Schizophrenia research, 97*, 242-249.

Üçok, A. L. P., Polat, A., Bozkurt, O. Y. A., & Meteris, H. (2004). Cigarette smoking among patients with schizophrenia and bipolar disorders. *Psychiatry and clinical neurosciences*, *58*, 434-437.

Weiss, E. M., Golaszewski, S., Mottaghy, F. M., Hofer, A., Hausmann, A., Kemmler, G., ... & Wolfgang Fleischhacker, W. (2003). Brain activation patterns during a selective attention test—a functional MRI study in healthy volunteers and patients with schizophrenia. *Psychiatry Research: Neuroimaging*, *123*, 1-15.

Wildgust, H. J., & Beary, M. (2010). Review: Are there modifiable risk factors which will reduce the excess mortality in schizophrenia? *Journal of Psychopharmacology*, *24*(4 suppl), 37-50.

Wilkinson, G. S., & Robertson, G. J. (2006). *WRAT 4: Wide Range Achievement Test; professional manual*. Psychological Assessment Resources, Incorporated.

Wing, V. C., Bacher, I., Sacco, K. A., & George, T. P. (2011). Neuropsychological performance in patients with schizophrenia and controls as a function of cigarette smoking status. *Psychiatry research*, *188*, 320-326.

Winterer, G. (2010). Why do patients with schizophrenia smoke?. *Current Opinion in Psychiatry*, *23*, 112-119.

Zhang, X. Y., Liang, J., Chen, D. C., Xiu, M. H., He, J., Cheng, W., . . . Kosten, T. R. (2012). Cigarette smoking in male patients with chronic schizophrenia in a chinese population: Prevalence and relationship to clinical phenotypes. *PLoS ONE*, *7*, e30937.

# Appendices

## Appendix A

Table 1

*Demographic Characteristics of Smoking and Nonsmoking Patients and Healthy Controls*

| | **Patients** | | **Controls** | | |
|---|---|---|---|---|---|
| **Variable** | Nonsmoker (n = 41) | Smoker (n = 30) | Nonsmoker (n = 39) | Smoker (n = 24) | **Test value** |
| **Age, Mean (SD)** | 41.71 (10.56) | 41.55 (10.31) | 39.72 (13.09) | 38.54 (9.74) | $\mathbf{F_{3,133} = 0.55}$ |
| **Sex, Males (%)** | 26 (63%) | 17 (57%) | 23 (59%) | 16 (67%) | $\mathbf{\chi^2 = 0.87}$ |
| **Handedness, Right (%)** | 33 (81%) | 25 (83%) | 36 (92%) | 19 (79%) | $\mathbf{\chi^2 = 0.57}$ |
| **Eng 1st Lang., *n* (%)** | 38 (93%) | 27 (90%) | 37 (95%) | 22 (92%) | $\mathbf{\chi^2 = 0.89}$ |
| **Education, Mean (SD)** | 13.41 (2.44) | 12.41 (1.84) | 13.10 (2.00) | 11.29 (2.33) | $\mathbf{F_{3,133} = 5.44***}$ |
| **Smoke Freq., Mean (SD)** | N/A | 17.04 (8.59) | N/A | 12.47 (8.35) | $\mathbf{t_{49} = 1.91}$ |

*** denotes main effect significance at $p < 0.001$

Appendix B

Table 2

*Clinical Characteristics of Patient Nonsmokers and Patient Smokers*

| Variable | Patient Nonsmoker (n = 41) | Patient Smoker (n = 30) | Test value |
|---|---|---|---|
| PANSS Positive† | 41.02 (7.52) | 44.40 (8.27) | $t_{69} = -1.79$ |
| PANSS Negative† | 37.80 (6.82) | 39.43 (7.06) | $t_{69} = -.98$ |
| Composite T Scores† | 53.12 (7.50) | 54.13 (9.67) | $t_{69} = -0.50$ |
| PANSS General† | 40.02 (7.18) | 43.10 (8.18) | $t_{69} = -1.68$ |
| Anergia† | 42.17 (9.44) | 46.10 (10.40) | $t_{69} = -1.66$ |
| Thought Disturbance† | 40.24 (7.70) | 43.43 (7.58) | $t_{69} = -1.74$ |
| Activation† | 44.15 (7.66) | 44.03 (6.54) | $t_{69} = 0.07$ |
| Paranoid† | 44.02 (6.62) | 44.10 (7.73) | $t_{69} = -0.04$ |
| Depression† | 50.56 (12.56) | 52.27 (12.87) | $t_{69} = -.56$ |

† = *t*-scores
no significant differences were found, $p > 0.05$

Appendix C

Table 3

*MATRICS Consensus Cognitive Battery. Specific Cognitive Abilities of Patients vs. Healthy Controls and Smokers vs. Nonsmokers*

| | PT (n = 71) | CN (n = 63) | **Test statistic** | SM (n = 54) | NS (n = 80) | **Test statistic** |
|---|---|---|---|---|---|---|
| MCCB | | | | | | |
| Process. Speed | 34.53 (10.95) | 45.41 (12.73) | **$F_{1,129}$ = 25.24*** ** | 36.87 (12.20) | 41.55 (13.22) | **$F_{1,129}$ = 4.50*** |
| Attention | 35.21 (13.19) | 42.19 (14.23) | **$F_{1,129}$ = 7.26** ** | 34.36 (13.67) | 41.28 (13.75) | **$F_{1,129}$ = 8.20** ** |
| Working Memory | 38.16 (12.65) | 43.60 (12.40) | **$F_{1,129}$ = 6.00*** | 36.43 (12.60) | 43.59 (12.15) | **$F_{1,129}$ = 10.39** ** |
| Verbal Learning | 37.31 (9.73) | 44.98 (10.35) | **$F_{1,129}$ = 17.25*** ** | 36.91 (8.91) | 43.63 (11.00) | **$F_{1,129}$ = 15.20*** ** |
| Visual Learning | 33.66 (11.74) | 40.60 (10.65) | **$F_{1,129}$ = 10.28** ** | 33.74 (11.86) | 39.08 (11.21) | **$F_{1,129}$ = 7.34** ** |
| Reason./ Prob Solv | 41.31 (9.40) | 50.37 (9.43) | **$F_{1,129}$ = 24.46*** ** | 43.60 (8.83) | 46.93 (11.20) | **$F_{1,129}$ = 4.29*#** |
| Social Cognition | 39.63 (12.37) | 45.24 (12.89) | **$F_{1,129}$ = 5.89*** | 40.79 (12.88) | 43.28 (12.87) | **$F_{1,129}$ = 1.06** |
| COMPOSITE | 29.39 (13.40) | 41.22 (14.41) | **$F_{1,129}$ = 21.47*** ** | 29.98 (13.95) | 38.31 (14.92) | **$F_{1,129}$ = 11.71** ** |

Abbreviations: PT = Patient; CN = Control; SM = Smoker; NS = Nonsmoker
***denotes main effect significance at $p$ <.001; ** main effect significance at $p$ < .01; * main effect significance at $p$ < .05;
# denotes interaction effect

Appendix D

Table 4

*Cognitive Profile of Individuals with Schizophrenia vs. Healthy Controls and Smokers vs. Nonsmokers*

| | PT (n = 71) | CN (n = 63) | **Test statistic** | SM (n = 54) | NS (n = 80) | **Test statistic** |
|---|---|---|---|---|---|---|
| WASI IQ Estimate | 96.66 (21.40) | 101.24 (20.35) | **$F_{1,130} = 0.73$** | 89.22 (18.74) | 105.29 (19.97) | **$F_{1,130} = 22.58$***** |
| WRAT-4 Reading | 91.47 (11.50) | 95.27 (11.73) | **$F_{1,127} = 2.44$** | 88.17 (9.81) | 96.78 (11.69) | **$F_{1,127} = 19.46$***** |
| Faux Pas | 38.52 (13.03) | 46.40 (10.29) | **$F_{1,129} = 11.97$**** | 39.51 (13.57) | 43.98 (11.35) | **$F_{1,129} = 4.16$*** |
| Reading the Mind in Eyes | 21.72 (5.19) | 25.24 (5.34) | **$F_{1,129} = 12.50$**** | 21.25 (5.41) | 24.76 (5.19) | **$F_{1,129} = 14.63$***** |

Abbreviations: PT = Patient; CN = Control; SM = Smoker; NS = Nonsmoker;
***denotes main effect significance at $p < .001$; ** main effect significance at $p < .01$; * main effect significance at $p < .05$
# denotes interaction effect

Appendix E

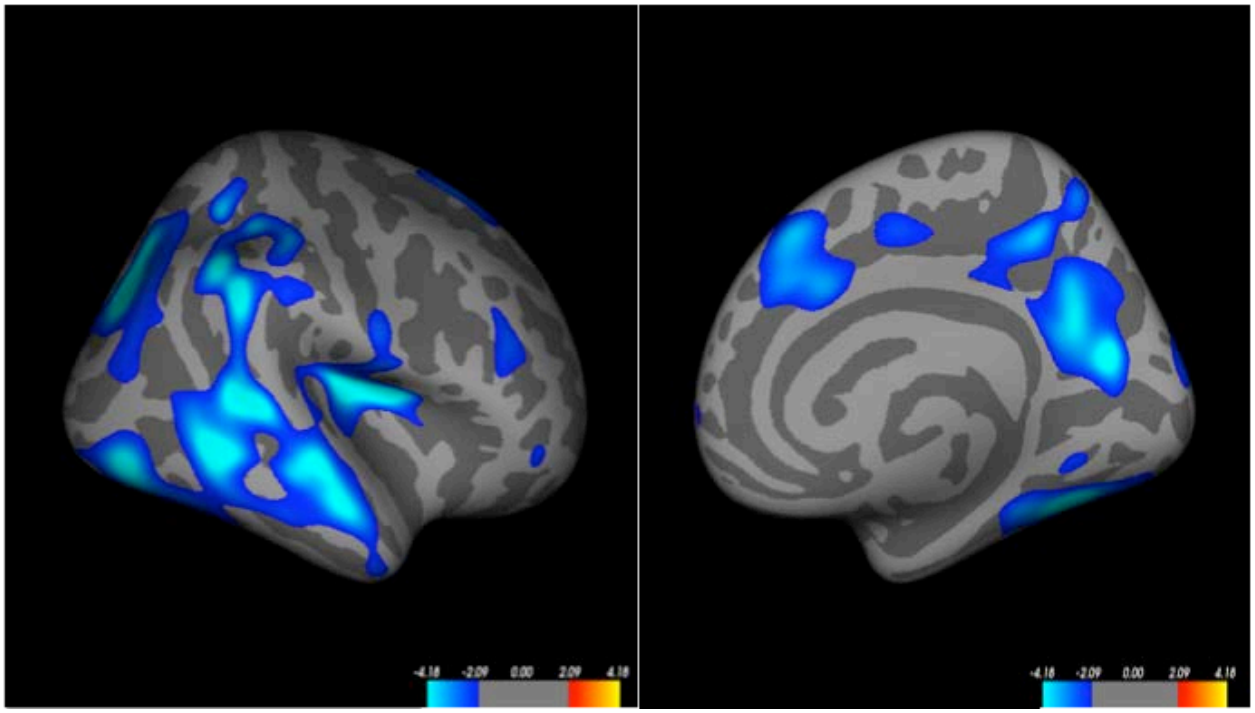


*Figure 1. Widespread Cortical Thinning in Right Hemisphere of Individuals with Schizophrenia vs. Healthy Controls. Blue areas indicate reduced thickness.*

Appendix F

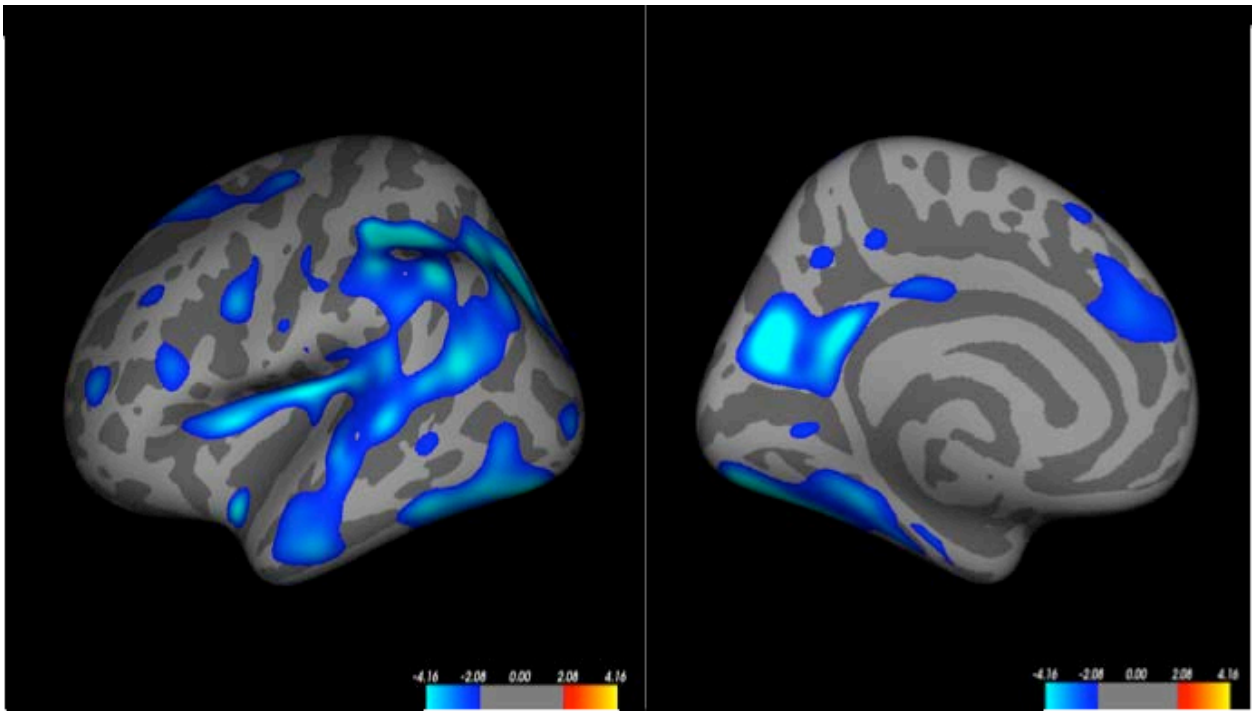


*Figure 2. Widespread Cortical Thinning in Left Hemisphere of Individuals with Schizophrenia vs. Healthy Controls. Blue areas indicate reduced thickness.*

Appendix G

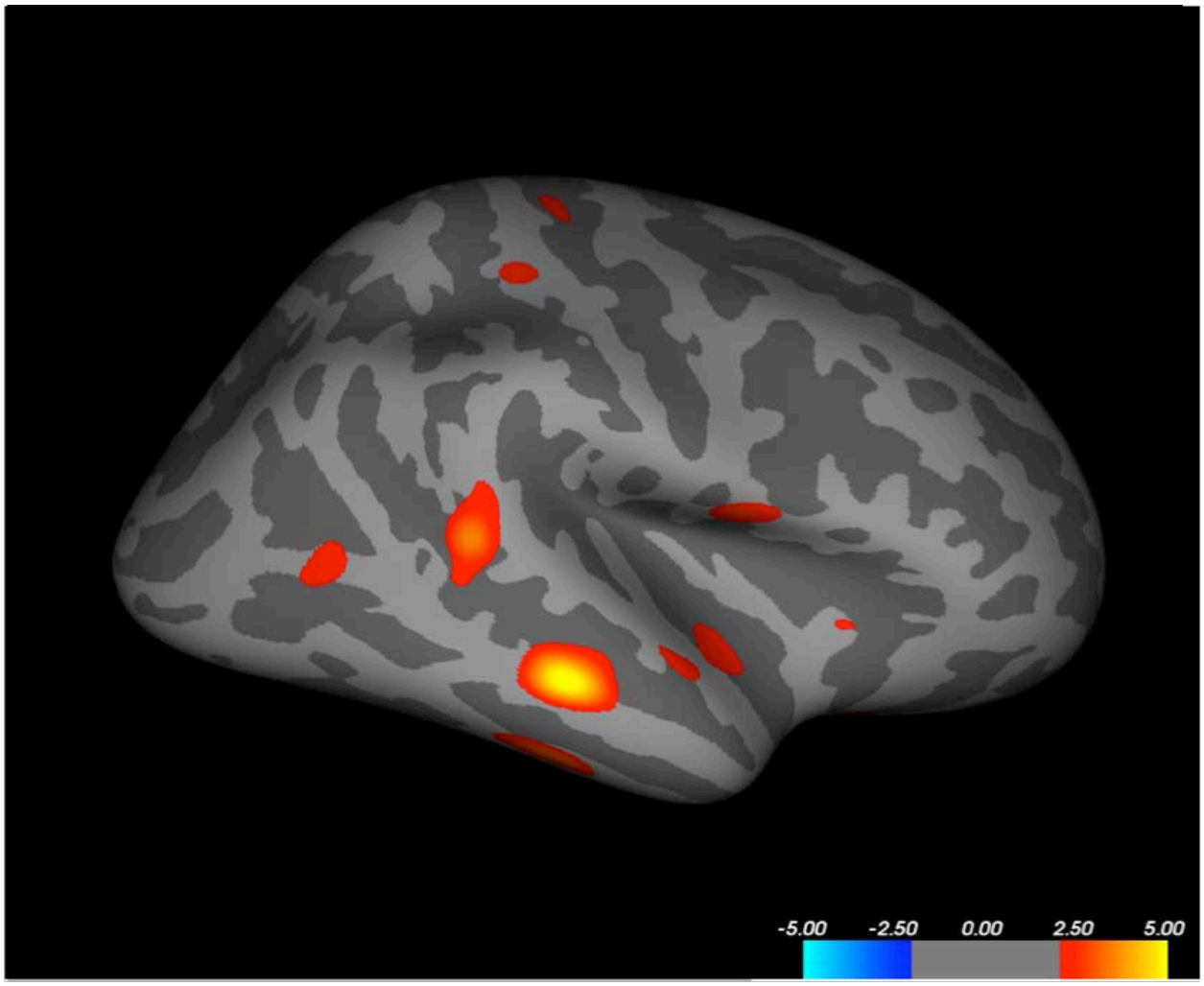


*Figure 3. Greater Cortical Thickness in Right Middle Temporal Gyrus and Banks of Superior Temporal Sulcus of Nonsmokers than in Smokers. Red areas indicate greater thickness.*

Appendix H

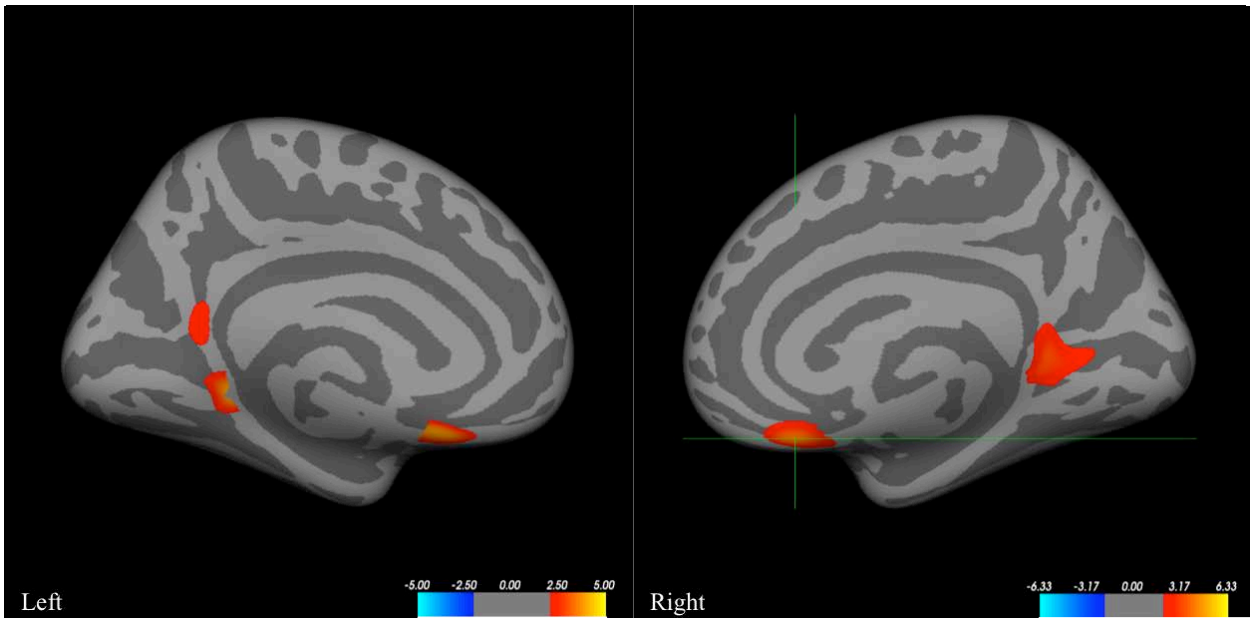


*Figure 4. Interaction between Smoking Status and Psychiatric Status reveals Increased Cortical Thickness in Patient Smokers and Control Nonsmokers in Bilateral Medial Orbitofrontal Gyrus and Left Parahippocampal Gyrus. Red areas indicate greater thickness.*