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Demographic Differences in Resting State EEG in Healthy Controls and Patients with Schizophrenia

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and Patients with Schizophrenia

by

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Each person whose signature appears below certifies that this thesis in his/her opinion is adequate, in scope and quality, as a thesis for the degree Doctor of Philosophy.

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ABBREVIATIONS

DMN	Default Mode Network
HC	Healthy Controls
Sz	Schizophrenia
fMRI⁻	Functional Magnetic Resonancy Imaging
EEG	Electroencephalogram
ADHD	Attention Deficit Hyperactivity Disorder
BOLD	Blood Oxygen-Level Dependent
ERP	Event Related Potential
WCST	Wisconsin Card Sorting Test
PANSS	Positive and Negative Symptom Scale
ICD	Independent Component Analysis
ANOVA	Analysis of Variance
Fz	Frontal Midline Region
FCz	Frontal-Central Midline Region
Cz	Midline Region
SD	Standard Deviation
CI	Confidence Interval

ABSTRACT OF THE THESIS

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Doctor of Philosophy, Graduate Program in Clinical Psychology
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The default mode network (DMN) is composed of neural nodes that are

synchronously activated when the brain is at rest and displays a decrease in activation

when the brain is involved in a task. Disruptions in the DMN can potentially serve as

assessment/screening for individuals with neuropsychological disorders. Many studies

use electroencephalography (EEG) to study the brain at rest because of its high temporal

resolution and its ability to provide a time sensitive measure of large-scale neural activity.

Previous studies examining the brain at rest have found differences when comparing

patients with Schizophrenia (Sz) and healthy controls (HC). While many studies have

identified the impact of demographic variables on neuropsychological disorders, none of

these studies have examined the impact of demographic variables on resting state EEG in

either HC or Sz. The current study investigated whether demographic variables (i.e. age

and sex) impacted theta (4-7 Hz), alpha (8-12Hz), beta (12-24Hz), and gamma (30-50

Hz) band power during resting state in 124 HC and 117. There were a total of 123 (38%

women) HC with a mean age of 37.45 (SD = 11.12), and 117 Sz (34% women) with a

mean age of 38.92 (SD = 11.13). An ANOVA revealed that patients with Sz had greater

theta and gamma power at site Fz. Multiple linear regression analyses revealed that being

female predicted more beta power and being older with a diagnosis of schizophrenia

predicted less beta power. The importance of considering demographic variables when

examining resting state EEG activity is discussed, with specific emphasis on the beta

frequency band.

CHAPTER ONE

INTRODUCTION

Research has focused on elucidating the neurological mechanisms involved in the brain's baseline functioning. One way to measure the brain at baseline is to examine the default mode network (DMN; (Raichle et al., 2001). The default mode network (DMN) is one of the resting state networks that is associated with the largest increase of activation when the brain is at rest (Guo et al., 2014). Activation of the DMN resembles patterns of activation observed in the brain when an individual is engaged with a stimulus. This activation is persistent across different behavioral states and has been associated with the intrinsic function of the brain when not performing a specific task (Wen & Liu, 2016). Disruption in the DMN has been reported in a wide range of neurological and psychiatric diseases, including generalized anxiety disorder, post-traumatic stress disorder, depression, autism, Alzheimer's, Parkinson's, chronic pain, attention-deficit hyperactivity disorder and schizophrenia (Broyd et al., 2009; Buckner, Andrews-Hanna, & Schacter, 2008; Wang et al., 2013). Recent research using Functional magnetic resonance imaging (fMRI) has provided evidence that the brain at rest uses more energy than when involved in a goal oriented task (Raichle et al., 2001).

The integration of fMRI with EEG data affords a better understanding of the relationship between structure and function in the brain. EEG provides a relatively precise localization of neuronal sources along with information about brain activity on a millisecond basis and the ability to track ordered connectivity that sustains a given function (Luck, 2005). This information can be incorporated with functional and structural information provided by fMRI (Rossini, Rossi, Babiloni, & Polich, 2007)**.**

While there are hundreds of different EEG paradigms and decades of research that indicate differences in EEG activity due to age (Clarke, Barry, McCarthy, & Selikowitz, 2001; Lorenzo-López, Amenedo, & Cadaveira, 2008; Lorenzo-López, Amenedo, Pascual-Marqui, & Cadaveira, 2008) and sex (Armitage & Hoffmann, 2001; Barriga-Paulino, Flores, & Gómez, 2011; Davidson, Schwartz, Pugash, & Bromfield, 1976; Plante et al., 2012; Rilea, Roskos-Ewoldsen, & Boles, 2004), the impact of these demographic features has not been investigated in resting state EEG. The current study examined the relationship between age and sex and resting state EEG in a large sample of participants. Knowledge of these demographic factors will add to the growing body of literature of the brain at rest, and potentially impact assessment of neuropsychiatric disorders and treatment.

CHAPTER TWO

LITERATURE REVIEW

Established EEG Use

Hans Berger is credited with first using the electroencephalogram (EEG) on humans in 1924, when he used his device to study individuals with skull defects (Schomer & Lopes da Silva, 2011). Electrical activity generated by neurons is recorded by placing electrodes on the scalp, amplifying the resulting signals and finally plotting the changes in voltage over time (Luck, 2005). EEG research has continued to expand, and today EEG is used to study typical and atypical brain development, epilepsy, perception, and a variety of psychological disorders such as depression (Grin-Yatsenko, Baas, Ponomarev, & Kropotov, 2009) and schizophrenia (Andreou et al., 2015).

Clinical use of electroencephalography (EEG) experienced a breakthrough in 1934 with studies of epilepsy (Luck 2005). Research with clinical EEG began to expand outside of epilepsy to observing EEG variants in sleep, effects of tumors and lesions on EEG patterns, and establishing norms in EEG patterns using "healthy" controls (Schomer & Lopes da Silva, 2011). Early clinical researchers used photic stimulation (waving cardboard in front of a lamp), and hyperventilation, which were meant to activate the brain (Schomer & Lopes da Silva, 2011). EEG has expanded to include not only goal directed task EEG recordings, but observing what the brain does while at rest (Raichle 2001). Resting state is characterized by a lack of imposed stimuli or salient events, and recording can take place with the eyes closed or open (Snyder & Raichle, 2012). This state of rest results in the activation of what researchers have identified as resting state networks (Raichle 2001). While there have been six resting state networks identified

(Dante Mantini & Vanduffel, 2013), this paper will focus on the default mode network (DMN). The DMN is identified in the literature as representing the baseline functioning of the brain, is present in non-human primates, and can be recorded in humans from infancy through adulthood (Fair et al., 2007). The default mode network has been found to be anatomically and functionally different from other networks, such as the executive and sensory networks (Buckner et al., 2008). This network has been used to provide clinically relevant information for disorders such as ADHD (Mohan et al., 2016), multiple sclerosis (Pinter et al., 2016), bipolar disorder (Clementz, Sponheim, Iacono, & Beiser, 1994) depression (Qin et al., 2015), and schizophrenia (Razavi et al., 2013). In brief, the use of resting state EEG provides clinically relevant information about the baseline functioning of the brain via the DMN.

Experimental EEG Use

EEG has been experimentally used to better understand both neurological and psychological disorders (Schomer & Lopes da Silva, 2011). Because of the dissimilar time scales of EEG and fMRI, it has been questioned whether or not these two techniques measure the same resting state phenomenon (Chen, Feng, Zhao, Yin, & Wang, 2008). For instance, blood oxygen-level dependent or (BOLD) signals are produced in fMRI and represent a measure of the increased cerebral blood flow needed for neural activity, while EEG represents the electrical signals associated with neural activity. Musso, Brinkmeyer, Mobascher, Warbrick, and Winterer (2010) found a high correlation between EEG and BOLD activation patterns consistent with resting state networks. Scheeringa et al. (2008) found frontal theta activity (3-8 Hz) to be negatively correlated with fMRI-measured

DMN activity. These and other authors have attributed lowered resting state theta activity to reflect activation of the DMN (Massar, Kenemans, & Schutter, 2014; Razavi et al., 2013). Finally, in a study conducted by Knyazev, Slobodskoj-Plusnin, Bocharov, and Pylkova (2011) using data analytic methods generally used for PET and fMRI studies, they found EEG was able to produce some spatial features and reveal functional correlates of the DMN. These studies suggest that EEG recorded at rest and identified DMN activity gathered from fMRI are indeed measuring the same phenomenon. Numerous studies have also examined the value in using EEG to explain the variance in the DMN across different clinical populations, the consensus being that EEG provides valuable temporal information about the DMN not otherwise identified using other methods (Chen, Feng, Zhao, Yin, & Wang 2008).

Oscillations recorded by EEG, including those recorded during the resting state, reflect synchronous electrical activity of neurons. These oscillations are characterized by the number of cycles per second, or frequency (in humans, theta, alpha, beta, and gamma frequencies are the most typically studied), and amplitudes, which reflect the collective strength of neural firing within a specific frequency band (refer to Figure 1).
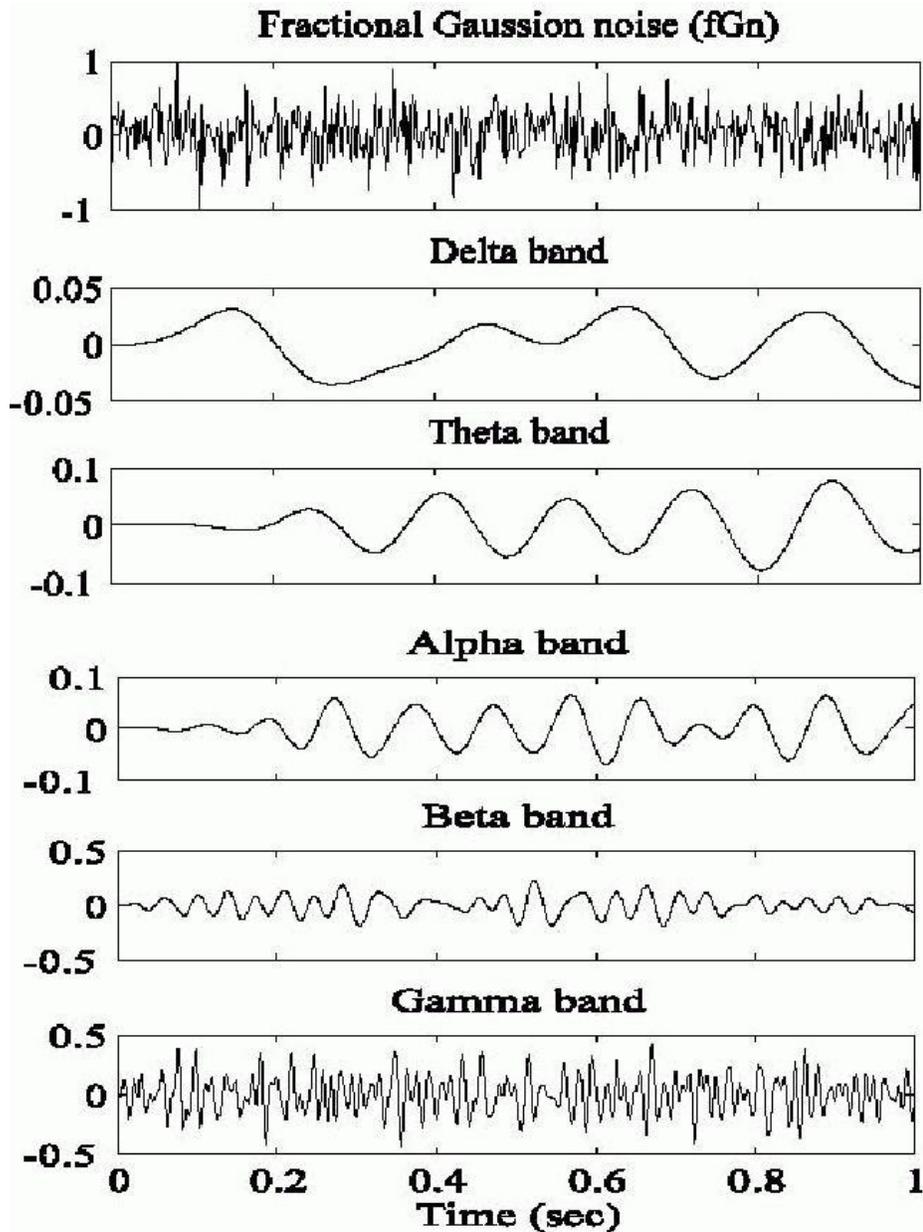
Figure 1. An example of EEG data broken down into the components of delta, theta, alpha, beta and gamma frequencies.

Early research identified that EEG was organized into oscillatory systems that control integrative brain functions on both cognitive and sensory levels (Herrmann, Strüber, Helfrich, & Engel, 2016). This led to cognitive processes being linked to synchronous or desynchronous neuronal oscillations (Linkenkaer-Hansen et al., 2005).

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Interpretation of these oscillations provides relevant information about neural functioning in clinical disorders when abnormal patterns are observed. A detailed breakdown of EEG oscillations is beyond the scope of this paper; however, below is a brief synopsis.

Alpha activity is typically measured as oscillations between 8-12 Hz, and is present during relaxed wakefulness (Schomer & Lopes da Silva, 2011). Alpha rhythms increase in amplitude largely in the posterior region of the brain, when eyes are closed (Laufs, Kleinschmidt, et al., 2003). Researchers have correlated the increase in alpha during resting state with internal mental processing and social cognition (Knyazev et al., 2011). Beta activity is typically measured as oscillations between 12-30 Hz. Beta rhythms are found chiefly over central and frontal regions in healthy adults. Beta activity decreases in posterior regions and increases in frontal areas in resting state (Barry, Clarke, & Johnstone, 2003). Research on beta frequencies in resting state is fairly new, and while many hypotheses about its meaning exist, a prominent one is that beta activity reflects spontaneous cognitive processes such as self-reflection, episodic memory and related imagery, stimulus independent thought, and conceptual processing (Laufs, Krakow, et al., 2003). Theta activity is measured in the 4-8 Hz range and a healthy, awake adult typically presents a small, unorganized amount of theta activity (Schomer & Lopes da Silva, 2011). There is an observed decrease in frontal and midline theta when examining the DMN. Researchers identify theta as normal "background noise" that indicates a decrease in vigilance and early sleep stages. Finally, gamma rhythms, between 30-50 Hz, typically demonstrate lower amplitudes compared to other frequency bands. Researchers have identified an increase in gamma activity in the prefrontal region within the DMN as being related to self-referential processing (Berkovich-Ohana, Glicksohn, &

Goldstein, 2013) and working memory (Hoptman et al., 2010). When observing different frequencies, it is not likely that a single rhythm is linked with a specific cognitive process. However, the amalgamation of frequencies can generally be ascribed to neural operations and these operations compose networks that are associated with different cognitive states (D Mantini, Perrucci, Del Gratta, Romani, & Corbetta, 2007). This basic understanding of frequencies during resting state EEG is useful in conceptualizing and assessing the relationship between resting state and demographic variables.

EEG Differences Based on Age

Age-related cognitive impairments incur financial, personal, and social costs (Drop, Jędrych, Barańska, Firlej, & Janiszewska, 2016). With a better understanding of how the brain ages we may delay, ameliorate, or prevent age-related cognitive impairments from occurring. EEG may help determine how the aging process affects structure, function, and oscillatory activity within and across the brain. While the aging process is heterogeneous and complex, EEG studies have identified distinctive neuronal correlates associated with the aging brain (Polich, 1997). The DMN has also been linked with executive functioning, processing speed, and memory deficits exhibited by elderly individuals (Geerligs, Renken, Saliasi, Maurits, & Lorist, 2015; Greicius, Srivastava, Reiss, & Menon, 2004). Nelson et al (2015) examined the DMN in healthy young adults (18-31) and found that age and memory performance predicted activation in the DMN, such that as an individual ages they deactivate regions of the DMN less than younger individuals when engaged in attention demanding tasks. Furthermore, the findings suggest that early memory decline may be dependent on DMN failure to regulate activity.

Successful encoding has also been linked to the amount of activation in the DMN. Polich (1997) examined the effects of age on resting state EEG and the P3 event related potential (ERP). He concluded that age produces correlated changes in EEG and ERPs; in particular, EEG power decreases are correlated with decreased P3 ERP amplitude. These findings suggest that there is an age-related variability that contributes to EEG power shifts. Therefore, an increase in age is associated with a corresponding decrease in DMN regulation.

Recent research has turned to graph theory, which is a measure of functional connectivity that assumes different areas of the brain work together to produce different behaviors and cognitive processes (Bullmore, Sporns, & Solla, 2009). Functional connectivity is measured by examining modules and efficiency. Modules are organized networks in the brain, and the directness of the paths in these modules determines the level of efficiency. Shorter paths represent a more efficient module. Graph theory analysis is based on the concept of "random activity," and implies that there is a level of organization within and across neural structures (Bassett & Bullmore, 2006). Furthermore, the process of random-to-organized neural activity is a result of maturation and pruning, where the brain decreases connections between neurons creating shorter paths for faster communication between neuronal networks (Smit, Stam, Posthuma, Boomsma, & De Geus, 2008). In younger adults, graph theory analyses have demonstrated that a number of separate networks contain smaller pathways to other networks, creating optimal communication in the brain (Boersma et al., 2011). As an individual ages, these functional networks become less distinct due to an increase in

pathways between networks and a decrease in intranetwork pathways (Vecchio, Miraglia, Bramanti, & Rossini, 2014).

Geerligs, Renken, Saliasi, Maurits, and Lorist (2015) examined age-related changes using graph theory in functional connectivity and concluded that there was a decrease in modularity and local efficiency in the DMN in elderly adults. They interpreted these results to indicate a general inefficiency in the neural networks of aging brains. An important finding of the above study is that the functional connectivity changes observed in elderly adults were not found when investigating global network measures (global modularity). This finding demonstrates that as people age networks within the brain become less specific or less differentiated due to more internetwork connection, whereas younger adults demonstrate more intranetwork connections contributing to networks being more specific or more differentiated. A study by Boersma et al. (2011) examined resting state functional connectivity in the developing brain. They found that path length increased with age, which is representative of the brain moving from "random" topography to more organized networks, and which was interpreted as the brain undergoing maturation by creating more functional segregation and consistent networks. The above studies examined the effect of age on resting state using fMRI. Given the high level of correlation between fMRI and EEG activity (Jorge, Van der Zwaag, & Figueiredo, 2014), we expect that if age differences in patterns of functional connectivity are present, they can be assessed via EEG.

One of the most basic goals of neuroscience is providing an understanding of the relationship between the function and structure of the brain. Small world network analyses allow researchers to use the topographical information from organized networks

in the brain to determine how the relationship between and within network pathway organization impacts neural communication (Vecchio et al., 2014). EEG is useful to study functional connectivity because of its high temporal resolution. A study comparing healthy twins using small world network analyses provides further evidence that small world networks can be used to help identify brain organization differences (Smit et al., 2008). Research using EEG in older individuals shows a trend for a decrease of alpha frequency activity over temporal, parietal, and occipital regions, along with a decrease in delta power in the occipital region (Duffy, Mcanulty, & Albert, 1996; Rossini et al., 2007). Particularly, decreased resting state alpha has been found to be a reliable predictor of declining cognitive performance in elderly individuals (van der Hiele et al., 2008). Gaal, Boha, Stam, and Molnar (2010) examined age-dependent features of EEG and concluded that elderly individuals demonstrated a decreased reactivity to alpha blocking (opening and closing one's eyes) and an overall observed decrease in alpha compared to younger adults. In brief, the effect of age on the default mode network indicates structural and functional changes. However, this work represents a variety of paradigms that primarily focused on older adults. The present study will use a dimensional approach to specifically address the impact of age on resting state EEG. Given the increasing interest in the DMN and its potential as a biomarker in clinical studies, knowing the impact of age is essential to the interpretation of differences between clinical groups.

EEG Differences Based on Sex

Sex affects the structure and function of the brain (Yao et al 2014). Resting state research has shown that sex impacts tasks involving general intelligence, cognitive

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functioning, episodic and working memory, and emotional and language processing (Jausovec and Jausovec 2005; Yao et al 2014). Differences in alpha and beta activity between males and females become more distinct as individuals age (Aurlien et al 2004). However, research on the DMN and sex has received little attention. In a study examining sex differences in DMN activity in those with autism, Jung et al. (2015) found that there was a negative correlation between functional connectivity and a measure of Autistic characteristics, and the amount of DMN functional connectivity was associated with more autistic traits in males, but not in females. Researchers interpreted this as support of the "male brain theory" of autism, such that autistic traits are associated with extreme characteristics of the male brain. For example, men typically exhibit decreased levels of empathy compared to women and are less able to make correct social judgements, and individuals with autism are disabled in these areas no matter the sex. In addition, men tend to excel at detail-oriented processing and individuals with autism are extremely good at perceiving detail, while showing impairments in "big picture" processing (Baron-Cohen, 2002). These findings could potentially provide a biomarker for diagnosing autistic traits in males. Brenner, Ulrich, and Reynolds III (1995) compared healthy elderly women and men using a resting EEG paradigm and found that women demonstrated increased beta activity compared to men, while men exhibited increased alpha and theta activity. Jausovec and Jausovec (2005) reported differences between male and female resting state EEG activity as it related to general intelligence. Specifically, males exhibited a negative relationship between alpha band power and intelligence, while women exhibited a positive relationship. There were also topographical differences between males and females, with females showing more synchronous alpha activity in

frontal areas, while men showed asynchronous activity that was equally distributed in both hemispheres.

In addition to measures of resting state power, sex differences have also been observed using global field power, defined as the quantified amount of activity across all electrode sites simultaneously, and coherence, or the degree of oscillatory pairing between two signals that is independent of power. In a more recent study conducted by Jausovec and Jausovec (2010), approximated entropy (defined as the relative number of neuronal assemblies oscillating concurrently and the degrees of freedom in the competitive interface between them) and power within the beta and gamma bands was greater in females than males, with the largest differences found in the parieto-occipital regions. The increase in approximate entropy observed in women was attributed to females having more complex brain activity than males. Briere, Forest, Chounard, and Godbout (2003) found that women generally exhibit greater global field power compared to men. Nikulin and Brismar (2005) found that alpha and beta oscillations were negatively correlated with age in females at the anterior temporal location.

In general, the current literature suggests differences in alpha and beta activity between men and women, in that women tend to produce more alpha activity, and greater gamma and beta power. However, interpretations of these inconsistent findings are difficult for several reasons. First, some recorded EEG activity in a resting state paradigm, while others selected resting state segments in between cognitive trials. This could impact the frequency composition of the resting state data. Second, the measures employed varied considerably, with some studies reporting power (or the magnitude of response within a specific frequency band), while others reported coherence (the

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relationship between oscillations recorded at different electrode sites), and still others reported approximate entropy. Third, as there is no standard cut-off or agreed-upon range to define frequency bands, studies differed on the frequencies included in each idiosyncratically defined "band" (e.g., alpha activity broken down into "low beta" defined as 12-20 Hz and "high beta" defined as 20-30 Hz). Finally, the data on gender differences in resting state EEG thus far have been taken from secondary analyses; there has not been a purposeful evaluation of the impact of gender on resting state EEG in a large sample of well-matched healthy controls and those with psychological disorders.

Schizophrenia

Symptoms

One of the clinical disorders sensitive to differences in resting state EEG is schizophrenia. Schizophrenia is a lifetime psychological disorder and affects approximately 1% of the population world-wide according to *The Diagnostic and Statistical Manual of Mental Disorders* (5th ed; DSM-5; American Psychiatric Association, 2013) A diagnosis of schizophrenia includes positive, negative, and cognitive symptoms. Symptoms include delusions, hallucinations, thought disorder, reduced feelings of pleasure in everyday life, difficulty beginning and sustaining activities, "flat" affect, and reduced speaking. For some individuals with schizophrenia cognitive symptoms can be subtle, but for others they may be more severe where there is noticeable change in memory and other aspects of thinking (National Institute of Mental Health, 2016).

General Effects of Sex and Age on Schizophrenia

Age effects in patients with schizophrenia are well documented; however, the information is far from conclusive. As a person with schizophrenia ages, brain volume and cortical thickness decrease. This has led some to propose that schizophrenia is associated with rapid aging of the brain such that the brains of individuals with schizophrenia seem "older" than their chronological age (Schnack et al. 2016; Zhang et al. 2015).

Age also impacts schizophrenia symptomology. Earlier age of onset is associated with a more severe symptom course, and predicts worse disorganization and negative symptoms (Abel, Drake and Goldstein 2010). Gur, Petty, Turetsky, and Gur (1996) found that age ameliorated some positive symptoms; however, negative symptoms increased in severity. Conversely, Schultz et al. (1997) found that age had no effect on negative symptoms; however, they found that age was associated with a decrease in delusions, hallucinations, inappropriate affect, and bizarre behavior.

Bellino et al. (2004) found that individuals with an earlier age of onset self-reported high severity of depressive and negative symptoms, and were cognitively impaired, as measured by the Wisconsin Card Sorting Test (WCST) and Continuous Performance Test (CPT). Conversely, others have found that age of onset did not significantly affect neuropsychological functioning (Friedman et al. 2001; Heaton et al. 1994; Zorrilla et al. 2000). A more recent study conducted by Mosiolek, Gierus, Koweskzko and Szulc (2016) examined cognitive impairments across age groups in schizophrenia and concluded that cognitive impairments, compared to age matched groups, were present in all age groups. Specifically, patients with schizophrenia aged 26-

35 exhibited significantly worse performance on tasks of attention and working memory compared to those aged 18-25. With regard to how age impacts treatment outcomes, Targum et al (2016) found that age did not affect response to treatment and that all ages demonstrated the same progressive improvement, based on the Positive and Negative Symptom Scale(PANSS), a scale used to measure symptom severity in patients with schizophrenia.

In summary, research findings are mixed with respect to the impact of age on schizophrenia symptoms and cognitive abilities. This could be due to the grouping of individuals into age brackets instead of examining age as a continuous variable, resulting in the loss of potentially valuable information. The current study will address this issue by investigating the relationship between resting state EEG and age as a continuous variable in a large sample of healthy controls and individuals with schizophrenia, providing clarification of the effect of age on the DMN.

Sex differences in schizophrenia are extensively documented. Females with schizophrenia have a later onset of the illness (Lindamer, Lohr, Harris, McAdams, & Jeste, n.d.). Some have attributed this later onset in females as the result of estrogen being a protective factor; however, it is important to note that these findings are inconsistent (Castle, Abel, Takei, & Murray, 1995). With regard to schizophrenia symptoms, Tang et al. (2007) found that women commonly present with more positive symptoms and the paranoid subtype of schizophrenia, attempt suicide more often, have higher global assessment of functioning (GAF) scores, are more likely to be married, have later onset, and have lower daily doses of antipsychotic medications when compared to men with schizophrenia. Maric, Krabbendam,Vollebergh, de Graaf, and van Os (2003) found that

males exhibit more negative symptoms while females tended to exhibit more depression. Likewise, Xiang et al. (2010) also found that males tended to be single, have fewer positive symptoms, and more thought deterioration compared to women with schizophrenia. Importantly, Nowrouzi et al. (2015) found that early onset was associated with being White and male, and having a family history of psychiatric disorders and cannabis abuse.

Differences in cognitive abilities between the sexes have been documented in healthy controls (Hanlon, Thatcher, & Cline, 1999), and researchers have investigated whether similar differences exist in those with schizophrenia. Bozikas et al. (2010) examined sex differences in neuropsychological function in healthy controls and patients with schizophrenia. They found that, with the exception of psychomotor speed, individuals with schizophrenia performed poorly and that significant sex differences were observed in verbal learning and memory, where women outperformed men. These findings supported previous research in that healthy women outperform healthy men in the domains of verbal learning and memory (Collaer & Hines, 1995). Furthermore, in a study conducted by Longenecker, Dickinson, Weinberger, and Elvevlag (2010), females with schizophrenia showed less cognitive impairment in verbal memory, processing speed, executive functioning (measured by the WCST), and visual memory. With regard to illness course, females have a more favorable course of illness in the short- (2-5 years after onset) and middle term (5-10 years after onset), with less substance use (Leung & Cheu, 2000). Moreover, females also tend to respond better to treatment, which results in improved occupation and social outcomes compared to males with schizophrenia (Gogos,

Joshua, & Rossell, 2010). Thus, when comparing patients with schizophrenia, women tend show less deficits compared to men.

EEG Use in Schizophrenia

It is hypothesized that schizophrenia may be due to a functional imbalance between brain regions (Uhlhaas, 2013). Therefore, the study of functional changes in the brain via EEG may provide a better understanding of the underlying mechanisms of the disorder, lead to the development of better outcome measures for therapeutic interventions, and shift the focus of outcome measures to the core underlying neural mechanisms of this disorder, rather than the symptoms that change over time. It is possible that resting state EEG data may eventually be used to predict treatment response in those with schizophrenia (Boutros et al., 2008).

Resting state EEG activity of individuals with schizophrenia differs from individuals with other psychiatric disorders and healthy controls (Clementz et al., 1994). Studies of individuals with schizophrenia show more low frequency activity (less than 8 Hz) and less alpha activity (Clementz et al., 1994). Furthermore, Kam, Bolbecker, O'Donnell, Hetrick, and Brenner (2013) found increased coherence in delta and theta frequencies within and across hemispheres in individuals with schizophrenia compared to individuals with bipolar disorder. Kam et al. (2013) also found that alpha coherence was greater both inter- and intra-hemisphere in those with schizophrenia compared to healthy controls.

Goldstein, Peterson, Sanguinetti, Tononi, and Ferrarelli (2015) examined resting state alpha activity and found that, compared to healthy controls, individuals with

schizophrenia demonstrated a decrease in alpha EEG power in occipital and frontal areas. Additionally, Goldstein et al. (2015) found that schizophrenia chronicity was proportionally related to peak alpha frequency and not alpha power. Garrity et al. (2007) reported that there is impaired communication between other brain regions and the default mode network in patients with schizophrenia compared with healthy controls using fMRI data. Garrity et al. (2007) also interpreted the higher frequency BOLD signal oscillations found in schizophrenia patients to indicate that there was less temporal synchronicity between the brain regions involved in the default mode network. Researchers have consistently found increased beta, as well as increased slow wave and alpha waves, in patients with schizophrenia (Boutros et al., 2008). Furthermore, Mitra, Nizamie, Goyal, and Tikka (2015) found that gamma oscillations were higher in patients with schizophrenia compared to controls, particularly in frontal (30-70 Hz) and parieto-temporal (70-100 Hz) regions at rest. These results were interpreted as possibly representing a trait marker for schizophrenia, as these findings endured despite symptom improvement. In summary, schizophrenia produces changes in resting state EEG, particularly in alpha, beta, and gamma frequencies.

The Current Study

There are documented sex differences in resting EEG in healthy controls, such that females tend to produce more alpha activity and produce greater beta and gamma power. Age affects resting EEG in HC, such that greater age is associated with decreased activity in higher frequency ranges (i.e., beta and gamma). To date, no studies have purposefully examined the effects of sex and age on resting EEG in Schizophrenia.

Specific Aim and Hypotheses

The main aim of this study was to examine the effects of sex and age on resting state EEG in a large, well-matched group of healthy controls and patients with schizophrenia.

Hypothesis One

Based on the current literature, we hypothesized an overall group difference between HC and patients with Sz, such that patients with Sz will demonstrate decreased alpha frequency and increased theta and gamma resting state EEG power compared to HC.

Hypothesis Two

We hypothesized that HC females will have increased alpha, beta, and gamma frequency power and decreased theta frequency power compared to HC males. Similarly, we hypothesize that Sz females will have increased alpha, beta, and gamma frequency power and decreased theta frequency power compared to Sz males.

Hypothesis Three

We also hypothesize that older HC adults will have increased delta and decreased alpha, beta, and gamma frequency power compared to younger adults. Similarly we hypothesize that older adult patients with Sz will have increased delta and decreased alpha, beta and gamma frequency power compared to younger adult patients with Sz. These analyses will allow us to investigate whether age and sex impact resting state EEG similarly in HC and those with Sz.

CHAPTER THREE

METHODOLOGY

Participants

Healthy controls were recruited from the community via online and newspaper advertisements, and patients with schizophrenia were recruited from the inpatient psychiatric unit at Larue Carter Hospital in Indianapolis, Indiana and from Gastown Vocational Services in Vancouver, British Columbia. EEG recording systems, set up, and instructions were identical between the two recording sites. The control group consisted of 123 (45% White) healthy adults, including 76 men and 47 women with a mean age of 37.45 (SD = 11.12). The patient group consisted of 117 (36% White) adults with schizophrenia, including 77 men and 40 women with a mean age of 38.92 (SD = 11.13). No participants reported learning disorders or neurological problems, and none reported a serious head injury or loss of consciousness greater than five minutes. None reported current substance use or abuse, and for controls none had been diagnosed with an Axis I disorder. All participants provided written informed consent and received $10 per hour for participation.

Electrophysiological Data Collection and Processing

Participants were instructed to sit in a dimly lit room with their eyes closed for three minutes (van Diessen et al., 2015). Using Ag/AgCl electrodes with a nose reference (Falk-Minow Services, Munich, Germany) and Neuroscan SYNAMPS recording system (Neuroscan, Inc., El Paso, TX, USA), 32 channels of EEG were recorded. Using a .10Hz high pass filter and a 200 Hz low pass-filter, EEG signals were digitized at 1000 Hz.

Impedance from the electrode were kept below 10k. Horizontal and vertical electroculograms (EOGs) located on the right and left outer canthus, respectively, inferior to the right eye were monitored.

Brain Vision Analyzer software (Brain Products, GmbH, Gilching, Germany) was used to process EEG data offline. To attenuate low frequency artifacts, we used a 0.5Hz high pass digital filter with a 24 dB/octave roll-off and a 60Hz notch filter to remove line noise. Blinks were corrected using an algorithm, and activity that exceeded +/- 100uV was removed. Participants were only included if their EEG data contained at least 50 s of artifact-free data.

Corrected EEG data were transferred into a reference-free dataset using current source density (CSD) estimates by applying a spherical Laplacian algorithm (Mima & Hallett, 1999), which addresses coherence confounds between two scalp electrodes. The common reference approaches such as the nose, linked earlobe or mastoid, and average reference have, in varying degrees, produced incorrect coherence estimates. The use of this reference- free measure bypasses the issues that are associated with the choice of reference (Mima & Hallett, 1999).

To further correct for ocular artifacts, such as microsaccades, we utilized independent component analysis (ICA). ICA provides a more stringent method to eliminate ocular artifacts like microsaccades that may have been overlooked by the reference-free algorithm. Only reference-free CSD estimates corrected for artifacts were used for subsequent computations.

EEG Power

Using a Hanning window with 10% taper length, we conducted fast Fourier transformations with non-overlapping 2.048 s epochs of corrected data. Participant data were individually averaged across the epochs for each electrode site and for the following frequency bands the mean absolute power was computed: alpha(8-12Hz), beta (12-20 Hz), gamma (30-50 Hz), and theta (4-8Hz) (See Appendix A for frequency examples). Frontal and central midline sites (Fz, FCz, Cz) were examined and included in the analysis. In order to better approximate a normal distribution, a natural log transform was computed for each site at each frequency (refer to figure 2).
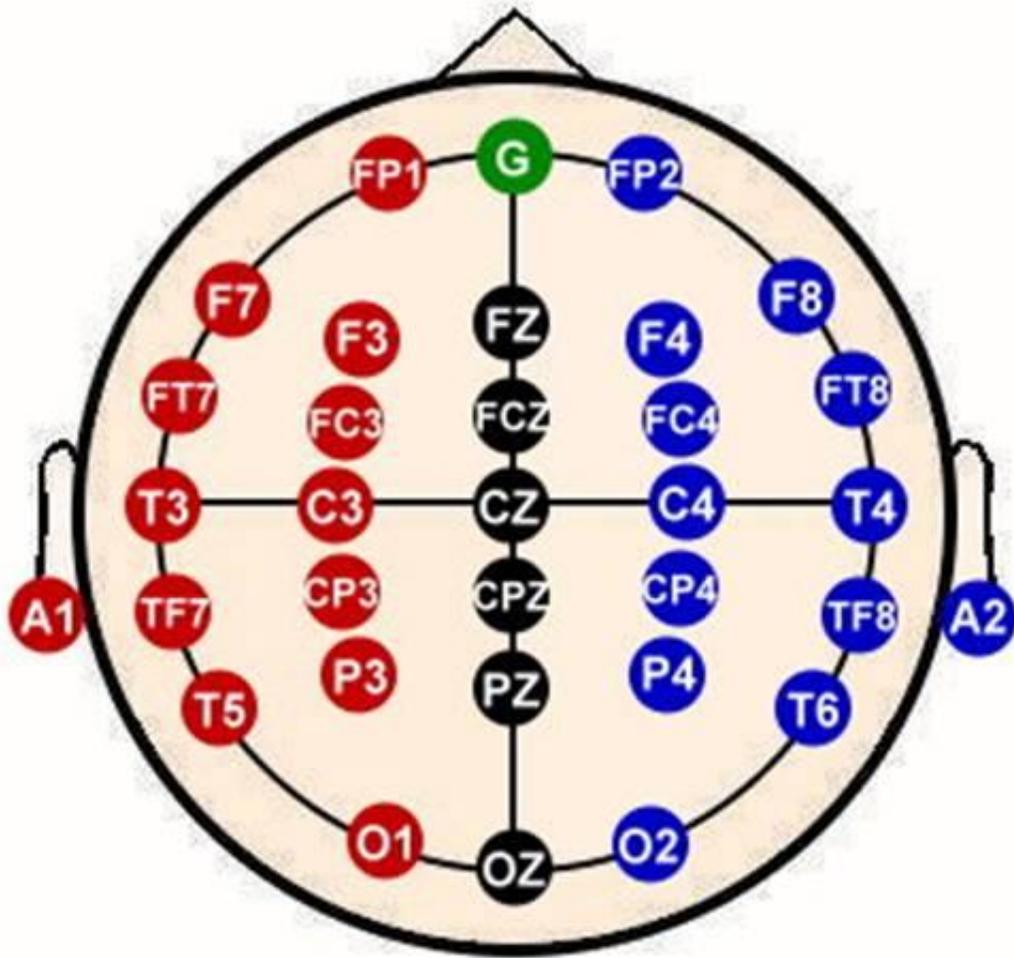
Figure 2. An example of electrode placements of the 10-20 system (standard placement for EEG studies).

Preliminary Analysis

Residual scatterplots were used for tests of normality, linearity, homoscedasticity, and detecting outliers. As is common with resting EEG, data violated assumptions of normality. Therefore, a natural log transform was computed for data from each electrode. In the search for outliers we evaluated data points on three properties: leverage, discrepancy and influence. Individual cases that were deemed an outlier on these measures (n = 18) were excluded from further analyses.

Data Analytic Plan

A Chi-Square analysis was used to examine whether the number of males and females in each group was different from what is expected by chance. An ANOVA was used to examine overall group differences between HC and patients with Sz. Prior to running our analyses we conducted a power analysis which indicated that we have approximately 95% power (or chance) to detect a truly significant effect of $R^2 = .08$ at $\alpha = .05$, with three predictors and a sample size of 235. To test our hypotheses, a hierarchical multiple linear regression analysis was used to examine (a) whether age predicts resting state EEG, (b) whether sex predicts resting state EEG, (c) whether group predicts resting state EEG (d) whether the interaction of age and sex predicts resting state EEG, (e) whether the interaction of age and group predicts resting state EEG and (f) whether the interaction of sex and group predicts resting state EEG. We ran regression analysis that included age, sex, group, age x group interaction, age x sex interaction and group x sex interaction to predict resting state EEG in each frequency band using the entire sample. Sex and group were contrast coded and age was centered for the regression analysis. Based on a power analysis we have about 60% power (or chance) to detect a truly significant effect of $R^2 = .08$ at $\alpha = .05$ in our regression analyses, with six predictors and a sample size of approximately 117 for HC and 113 for patients with Sz.

CHAPTER FOUR

RESULTS

A *t*-test revealed no significant difference in age between the HC and Sz groups: $t(235) = -.825, p = .410, d = 0.051649; M = 37.72, SD = 11.39$ for HC; $M = 38.92, SD = 11.12$ for Sz. A chi-square test indicated that the ratio of males to females did not differ between groups $X^2(1, N = 237) = .159, p = .786$.

While this study focused on the effect of demographic variables on resting state EEG, previous literature has demonstrated differences between groups. Therefore, to be consistent with previous resting state studies, data was first analyzed using a mixed-design ANOVA using within subject factors of frequency (gamma, beta, alpha, theta) and electrode site (Fz, FCz, Cz) and a between-subjects factor of group (HC vs Sz). Mauchly's test indicated that the assumption of sphericity had been violated $[X^2(5) = 724.24, p < .001; X^2(2) = 24.47, p < .001; X^2(20) = 1754.85, p < .001;$ respectively], therefore degrees of freedom were corrected using a Greenhouse-Geisser estimates of sphericity ($\square = .646, \square = .904, \square = .544$ respectively). Main effects of frequency $[F(1.94, 422.54)=132.07, p < .001 \; \square_p^2 = .38]$ and site $[F(1.807, 393.975) = 5.090, p = .008, \square_p^2 = .02]$, were qualified by interactions between frequency and group $[F(1.938, 422.539) = 3.086, p=.048, \square_p^2 = .01]$, site and group $[F(1.830, 398.896) = 5.712, p = .005, \square_p^2 = .03]$, and frequency and site $[F(3.262, 711.142) = 11.788, p < .001, \square_p^2 = .05]$. Post hoc analyses using a Bonferroni correction indicated: theta and alpha were larger than gamma (p < .001, p < .001 respectively) and beta (p < .001, p < .001, respectively); beta was significantly larger than gamma power (p < .001); power at FCz was larger than that at Fz (p < .001) and there was a trend for larger power at FCz than

Cz ($p = .052$). Power at Fz did not differ from power at Cz ($p = .241$); gamma and theta

power at sites Fz and FCz did not significantly differ from one another ($p = .135$, $p = .761$

respectively) but both were larger than at site Cz ($p < .001$ and $p = .031$, respectively);

beta and alpha power at sites FCz and Cz did not significantly differ from one another (p

$= .676$ and $p = .713$ respectively), but both were larger than at site Fz ($p < .001$ and $p <$

$.001$, respectively).

Follow-up One-Way ANOVAs at each electrode site revealed that the frequency

by group interaction reported above was driven by Sz having greater gamma ($p=.028$)

and theta ($p = .013$) power at electrode site Fz, and no group differences at other sites.

Notably, the difference between groups in the gamma frequency was statistically

significant however, the actual values were negligible. All other main effects and

interactions were non-significant.

A multiple linear regression analysis was used to determine the influence of

group, age, sex, and the interactions of these three variables on resting state EEG at

frequencies theta, alpha, beta, and gamma at sites Fz, FCz, and Cz. Overall, the optimal

linear combination of these predictor variables accounted for a significant portion of the

variance for beta at site Fz, Adjusted $R^2 = .041$, $F(6, 225) = 2.637$, $p = .017$; for Beta at

site FCz, Adjusted $R^2 = .091$, $F(6,224) = 4.84$, $p < .001$; and for beta at site Cz, Adjusted

$R^2 = .068$, $F(6,228) = 2.79$, $p = .012$ (see Table's 1, 2, and 3 respectively).

Table 1. Summary of Multiple Regression Analysis for Predicting Beta at Fz

Predictor Variable	B	95% CI	β	sr^2
Diagnosis	.001	[.000, .002]	.124	0.01392
Age Centered	.000	[.000, .000]	-.008	0.00005
Sex	-.001*	[-.002, .000]	-.185	0.03348
Diagnosis X Age Centered	.000*	[.000, .000]	-.130	0.01664
Sex X Age Centered	.000009	[.000, .000]	.017	0.00026
Diagnosis X Sex	.000	[-.002, .001]	-.024	0.00084

Note. CI = confidence interval; * $p < .05$

Table 2. Summary of Multiple Regression Analysis for Predicting Beta at FCz

Predictor Variable	B	95% CI	β	sr^2
Diagnosis	.000	[-.001, .001]	-.063	0.0036
Age Centered	.000007	[.000, .000]	.022	0.0004
Sex	-.002*	[-.003, -.001]	-.195	0.0368
Diagnosis X Age Centered	.000*	[.000, .000]	-.236	0.0547
Sex X Age Centered	.000011	[.000, .000]	.018	0.0002
Diagnosis X Sex	.001	[-.001, .003]	.086	0.0064

Note. CI = confidence interval; * $p < .05$

Table 3. Summary of Multiple Regression Analysis for Predicting Beta at Cz

Predictor Variable	B	95% CI	β	sr^2
Diagnosis	.000	[-.001, .001]	-.006	0.000036
Age Centered	.000017	[.000, .000]	.048	0.002025
Sex	-.001*	[-.002, -.000]	-.156	0.023716
Diagnosis X Age Centered	.000*	[.000, .000]	-.181	0.032041
Sex X Age Centered	.000022	[.000, .000]	.031	0.000841
Diagnosis X Sex	.001	[-.002, .003]	.032	0.0009

Note. CI = confidence interval; * $p < .05$

Females' mean resting state beta at site Fz is on average .001 units higher than males' mean resting state beta at site Fz, regardless of diagnosis (β = .001; t =2.839, p = .005). The interaction of group and age was a significant independent predictor of resting state beta at site Fz, such that having a diagnosis of schizophrenia and being older was associated with a decrease in beta power (β = .000; t =-1.995, p = .047; see Figure 3).

Figure 3. Interaction plot for group (HC and Sz) and age on beta power at site Fz.

Females' mean resting state beta at site FCz is on average .002 units higher than males' mean resting state beta at site FCz, regardless of diagnosis ($\beta = .002$, $t = -3.056$, $p = .003$). The interaction of group and age was a significant independent predictor of resting state beta at site FCz, such that having a diagnosis of schizophrenia and being older was associated with a decrease in beta power ($\beta = -.516$; $t = -3.720$, $p = .000$; see Figure 4).
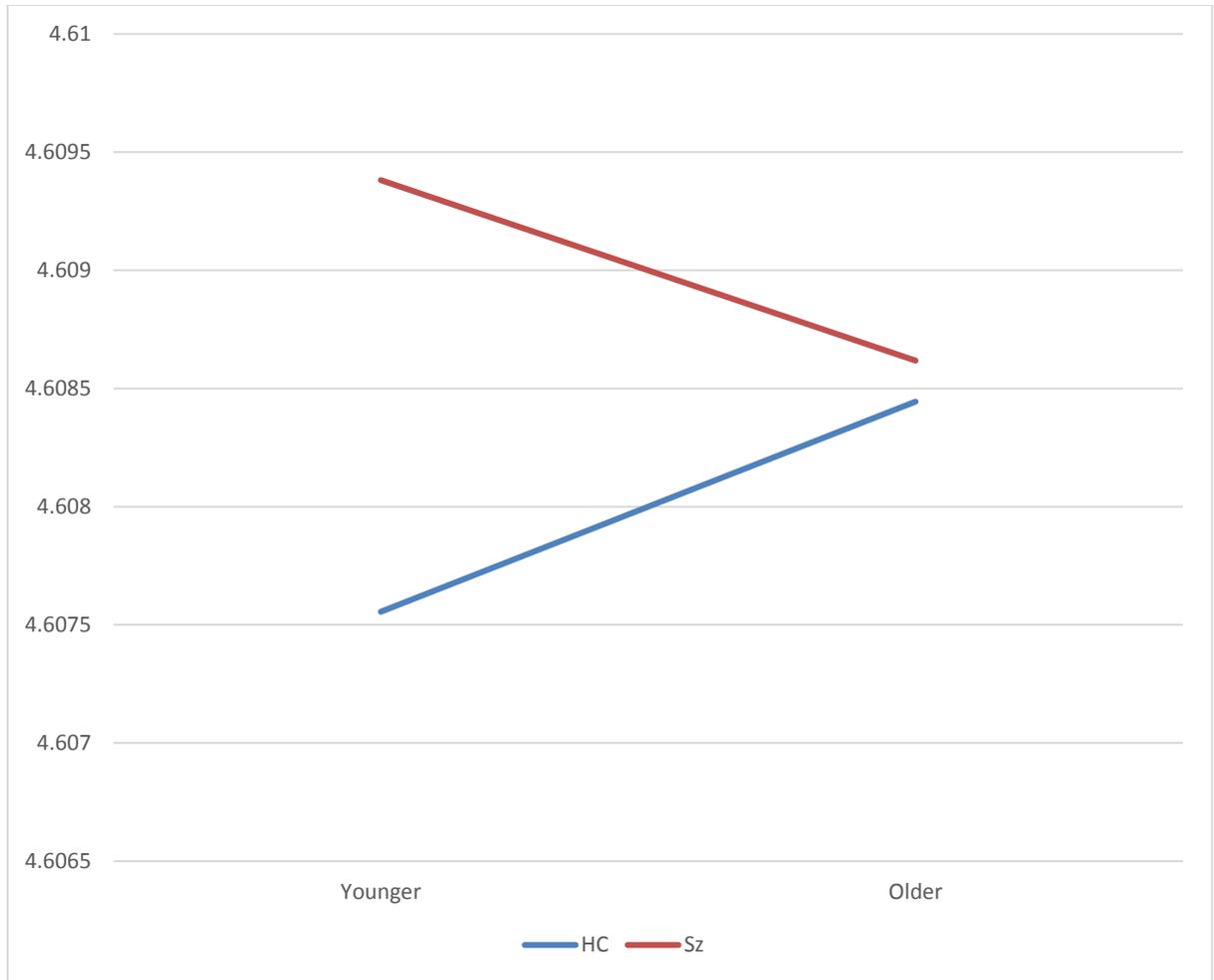
Figure 4. Interaction plot for group (HC and Sz) and age on beta power at site FCz.

Females' mean resting state beta at site Cz is on average .001 units higher than males' mean resting state beta at site Cz, regardless of diagnosis (β = .001; t = -2.414, p = .017). The interaction of group and age was a significant independent predictor of resting state beta at site Cz, such that having a diagnosis of schizophrenia and being older was associated with a decrease in beta po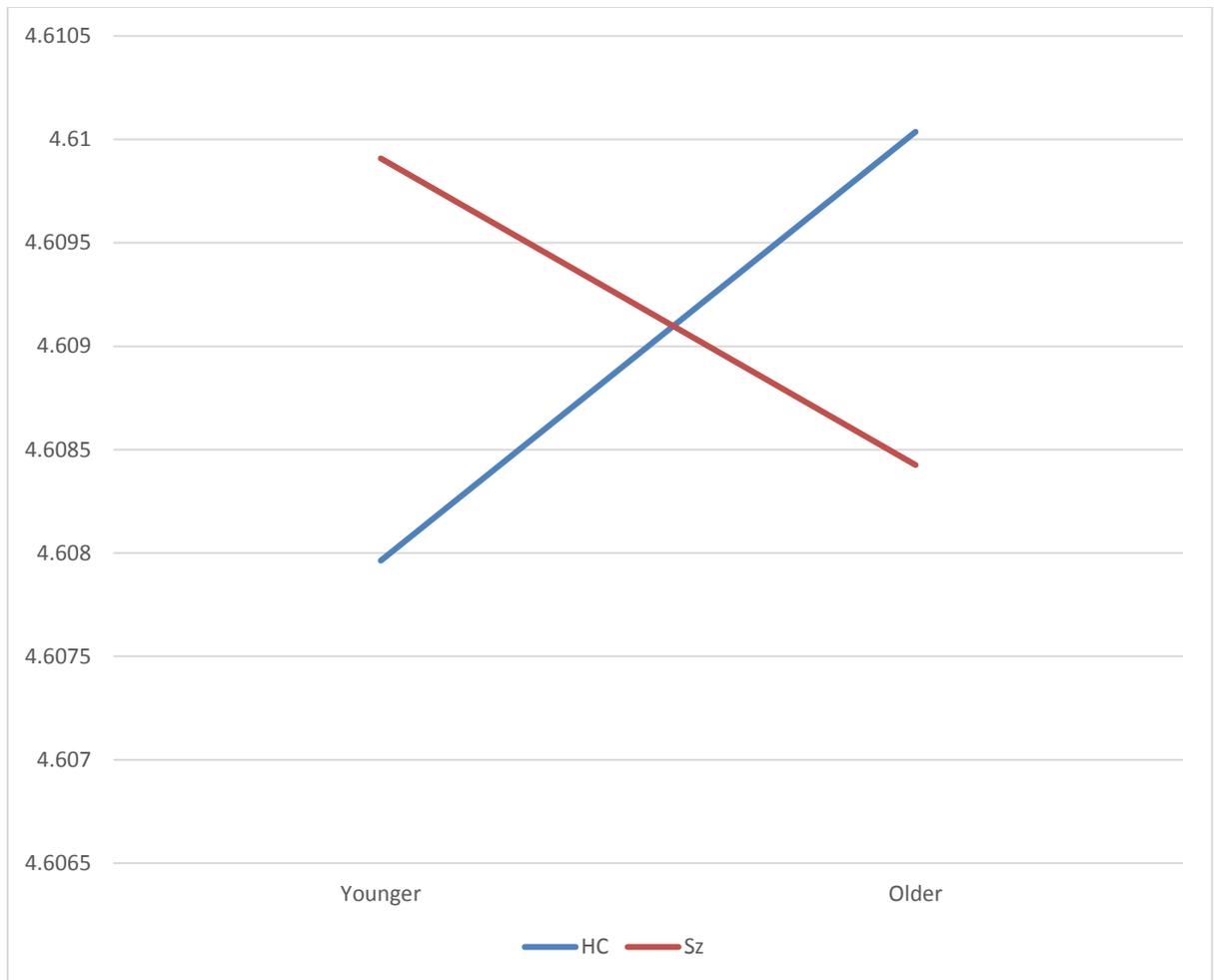wer (β = .000; t = 2.800, p = .006; see Figure 5). For Theta, Alpha, and Gamma there were no significant predictors.
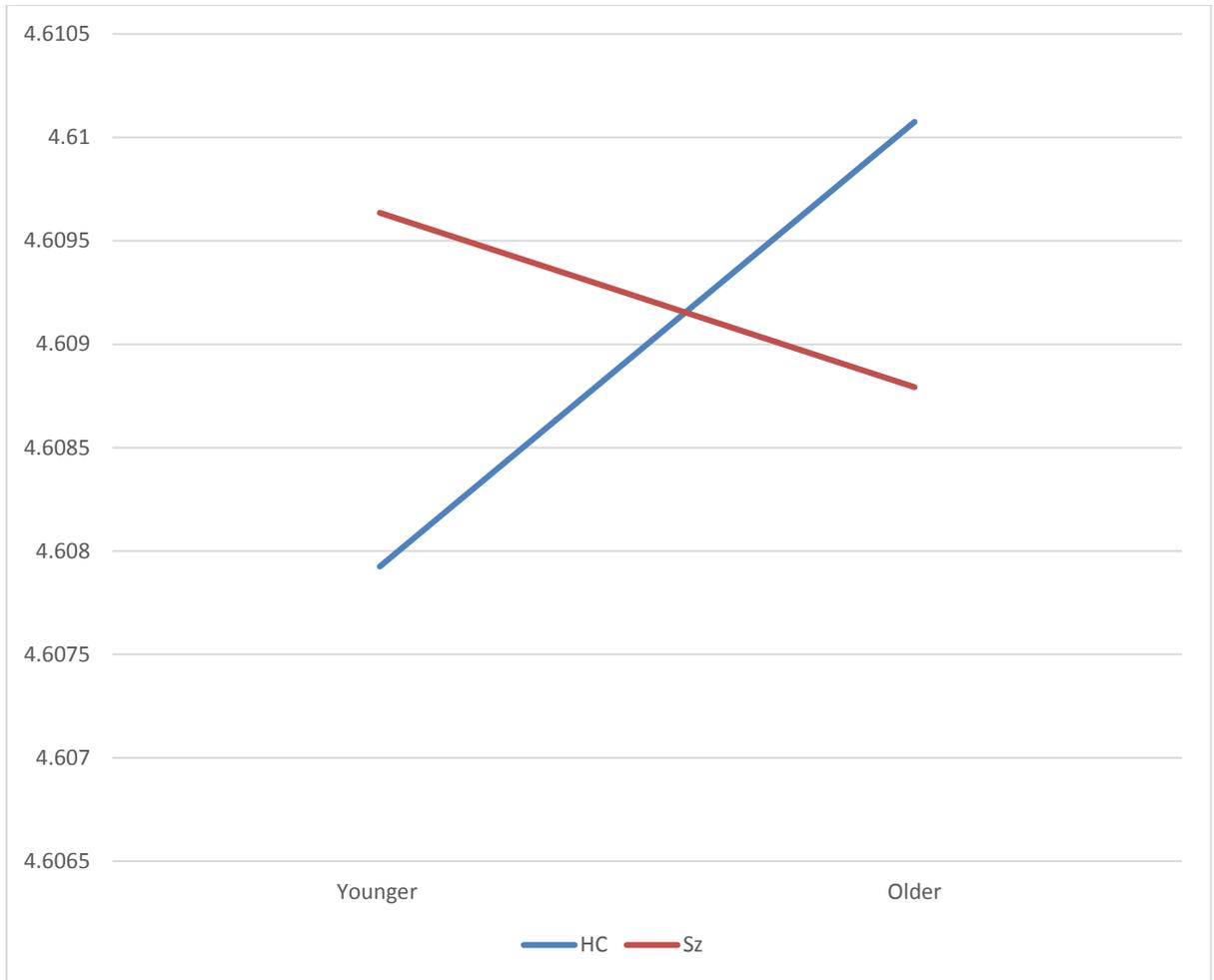
Figure 5. Interaction plot for group (HC and Sz) and age on beta power at site Cz.

CHAPTER FIVE

DISCUSSION

The present study examined resting state EEG power in the gamma, beta, alpha, and theta frequency bands in individuals with schizophrenia and healthy controls. It also investigated whether resting state EEG power was distinct based on age, sex, and diagnosis.

The first hypothesis of this study posited there would be overall group differences between HC and patients with Sz such that patients with Sz would demonstrate decreased alpha frequency and increased theta and gamma resting state EEG power compared to HC. This hypothesis was not supported. Post hoc analysis revealed that patients with Sz had greater gamma and theta power compared to HC. Further analysis revealed these differences were mainly driven by group mean differences in theta. Group mean differences in gamma were negligible.

Our second hypothesis was two-fold and posited that: HC females would have increased alpha, beta, and gamma frequency power and decreased theta frequency power compared to HC males; female patients with Sz would have increased alpha, beta, and gamma frequency power and decreased theta frequency power compared to male patients with Sz. This hypothesis was partially supported in that females, regardless of diagnosis, demonstrated increased beta across all sites.

Our third and final hypothesis was two-fold and posited that: older HC adults would have increased delta and decreased alpha, beta, and gamma frequency power compared to younger adults; that older adult patients with Sz would have increased delta and decreased alpha, beta and gamma frequency power compared to younger adult

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patients with Sz. This hypothesis was not supported. Notably, we found that older age and having a diagnosis of schizophrenia predicted less beta power across all sites. These findings suggest that demographic factors such as age and sex impact resting state EEG, and that these factors may be particularly important when comparing resting state power between healthy controls and individuals with schizophrenia.

Schizophrenia and Resting State EEG

Consistent with the literature, we found increased resting state theta activity in patients with schizophrenia (Lorenzo et al., 2016). Increased theta activity is present in patients with schizophrenia experiencing their first episode and patients with chronic schizophrenia, leading some to suggest that increased theta is a trait marker for the disorder (Lorenzo et al., 2016; Sponheim, Clementz, Iacono, & Beiser, 1994). Theta activity is connected to top down cognitive processes such as working memory (Sauseng, Griesmayr, Freunberger and Klimesch 2009). In patients with schizophrenia, increased resting theta power is indicative of top down cognitive deficits. In a study conducted by Wichniak et al. (2015), less theta power was linked to superior cognitive performance and suggested that theta power is linked to top-down cognitive deficits in patients with schizophrenia. Hanslmayer et al. (2013) used a selective visual attention task in which a monkey (i.e., unexpected salient visual event) was presented and theta activity was observed; they found that patients with schizophrenia demonstrated a lack of task related theta, which was due to the abnormally high levels of resting state theta. A study by Garakh et al. (2014) linked increased resting theta, along with alpha and beta activity, to negative symptoms in first episode patients with schizophrenia. Sponheim et al (1994)

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concluded that increased theta, delta, and decreased alpha was associated with negative symptoms. Moreover, Clementz et al. (1994) demonstrated that resting EEG in patients with chronic schizophrenia and first episode patients with schizophrenia do not differ in showing increased delta, theta, and decreased alpha frequency resting state activity. They interpreted these results to indicate that changes in resting state EEG may represent a biological trait marker for the disorder. Gschwandtner, Zimmermann, Pflueger, Riecher-Rossler and Fuhr (2009) found positive correlations between delta, theta, alpha, and beta and negative symptoms, which led them to suggest that augmented slow-wave power (theta and delta) may represent potential markers for psychosis. Therefore, an increase in theta activity may indicate deficits in cognitive top-down cognitive processing and the presence of negative symptoms.

In the current study, patients with schizophrenia demonstrated an increase in gamma power in frontal regions. Although this finding supported previous studies that patients with schizophrenia have significantly increased gamma power during resting state, our study found negligible mean differences between the groups. A study examined medicated patients with schizophrenia, their first-degree biological relatives, and medicated patients with bipolar disorder and their biological relatives found an increase in gamma activity in patients with schizophrenia during resting state over frontal regions (Venables, Bernat and Sponheim 2008). A study by Spencer (2012) also found elevated gamma activity over frontal regions in patients with schizophrenia (Spencer, 2012). Similar findings of elevated resting state gamma activity over frontal regions compared to healthy controls were reported by Kikuchi et al. (2011), using medication-naive patients. The invariance to medication is one reason that some have proposed resting state gamma

as a potential trait marker for schizophrenia (Mitra et al., 2015). Gamma activity is associated with consciousness, perception, and working memory (Engel, Roelfsema, Fries, Brecht, & Singer, 1997; Howard et al., 2003; Panagiotaropoulos, Deco, Kapoor, & Logothetis, 2012). Basar-Eroglu et al. (2007) found that, when engaged in working memory tasks, patients with schizophrenia displayed consistent gamma oscillations regardless of task difficulty while healthy controls demonstrated a gradual increase of gamma oscillations as the working memory load increased. During visual perception tasks, researchers have found an increase in gamma activity in frontal regions, leading them to conclude that the increase in gamma is linked to perception (Basar-Eroglu et al., 1996). Therefore, increased resting state gamma in patients with schizophrenia may reflect deficits in working memory, perception, consciousness, and the ability to respond to significant stimuli.

Sex and Resting State EEG

Being female predicted increased beta activity in the current study. This finding was consistent with Brenner et al (1995), who also reported that women had higher beta power than men. It was previously stated that differences in brain structure, (i.e., women have larger corpus callosum) contribute to differences found in EEG recordings between men and women. Sex differences in skull thickness were also considered as possibly contributing to EEG differences; however, they did not significantly account for power differences between males and females (Veldhuizen, Jonkman, & Poortvliet, 2017). In a study that examined EEG differences between young men and women, Briere, Forest, Choinard, and Godbout (2003) found that women displayed higher power in left

temporal, parietal, frontal, and central areas. In the aforementioned study, the conclusion was that differences in EEG needed to be broken down further to incorporate time of day, age, and localization of the electrode.

Research has shown that hormonal differences contribute to physiological differences between the male and female brain, such as differences in glucose metabolism in the middle and posterior cingulate gyrus (Allen, Richey, Chai, & Gorski, 1991; Gur et al., 2013). The aforementioned area of the brain has been associated with internally directed cognition, which has also been linked to DMN function (Buckner et al., 2008). Therefore, it is possible that increased beta activity during resting state in women is associated with an increase in metabolic functioning and/or internally directed cognition. Researchers have found that this beta increase observed in women becomes more pronounced as women age (Vogel, 1970).

Age and Resting State EEG

Most notable, our regression analyses indicated that older age and a diagnosis of schizophrenia were associated with less beta power during resting state. Increased beta activity is associated with resting state activity and the default mode network in healthy controls (Jann, Kottlow, Dierks, Boesch, & Koenig, 2010). Previous studies in a healthy aging population suggested that older adults may exhibit a decreased ability to regulate the default mode network (i.e., turning off the default mode network when engaging in a task and/or turning the default mode network on when not engaged in a task; (Nelson et al., 2015). While resting state beta activity has not been extensively explored in patients with schizophrenia, our finding could reflect compounded deficits in beta-mediated DMN

functioning in older patients with schizophrenia. Functionally, beta activity has also been attributed to reflecting spontaneous cognitive processes such as self-reflection and stimulus independent thought, and mediating top down processes involved in the detection of stimuli and the detection of upcoming sensory events (Arnal & Giraud, 2012; Laufs, Krakow, et al., 2003). Therefore, decreased beta power may indicate reduced ability to engage in self-reflection and stimulus independent thought in older patients with schizophrenia.

Interestingly, our study did not find significant differences in theta, alpha and gamma when using age, sex, group and the interaction of these variables to predict resting state EEG activity. One possible explanation for this may be due to decreases in sample size as a result of outliers being removed for each frequency.

Limitations

There are several limitations to this study. First, this study was cross sectional, so differences observed based on age may be the result of cohort effects. Future studies would benefit from a cross sequential design in order to truly assess this variable. Second, we were unable to account for time of day, which may affect power spectral amplitude due to a morning-evening sensitivity. Third, the current study did not incorporate information on menses or menopausal state. Previous studies have provided evidence that the release of hormones during the different phases of menses effect EEG, such that higher levels of progesterone and estrogen are associated with higher activity within the prefrontal cortex (Jaušovec & Jaušovec, 2010). Finally, the current study may have

limited statistical power due to the modest sample size, which may have limited some of the statistical comparisons conducted.

Conclusions and Future Directions

In the current study we found that age impacts beta frequency at rest, and this difference becomes more significant in patients with schizophrenia. This result supports the hypothesis that patients with schizophrenia show progressive functional changes where there is a decrease in top down processing, as measured by beta EEG activity. Women, regardless of their age and group (diagnosis), exhibited more beta power at rest compared to men. Patients with schizophrenia demonstrated increased gamma and theta activity in resting state compared to healthy controls, specifically in frontal regions. This increase in gamma and theta frequency in patients with schizophrenia suggests a robust marker for understanding the pathophysiology of schizophrenia. Also, it is noteworthy that while there were group differences in gamma and theta activity, demographics did not affect gamma and theta activity. In contrast, beta seems to be the only frequency affected by age and sex, and these demographic factors interacted with diagnosis for beta activity only. As the aging population in the United States, including individuals with schizophrenia, continues to grow, it is imperative that we learn how aging and disease impact brain functioning. Furthermore, as the National Institutes of Health are requiring equal representation of the sexes in funded research, explicitly investigating sex differences will ultimately lead to a more detailed understanding of brain functioning. This study provides invaluable information on the impact that both age and sex have on brain functioning in patients with schizophrenia. This information not only influences

basic knowledge, but may be used by the clinical community to enhance treatment in

patients with schizophrenia as they age.

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