An Investigation into Caffeine Intake, Cognition, and Symptomatology in Schizophrenia Patients

by

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I am very blessed and thankful for the family that I have- I would not be here without them. I dedicate this work to each of my three siblings and to my wonderful parents.

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ABSTRACT

Patients with schizophrenia consume significantly more caffeine than the general population. Despite this, few studies report on caffeine use, and even fewer on the association between caffeine intake and how it might affect cognition. In healthy (non-psychiatric) controls, caffeine use has been associated with better cognitive performance on many of the cognitive domains typically impaired in schizophrenia patients. This cross-sectional study assessed moderate versus high caffeine users on measures of cognitive functioning and symptomatology in 19 participants diagnosed with schizophrenia or schizoaffective disorder. Primary analysis compared moderate versus high caffeine users on measures of working memory, attention/vigilance, processing speed, verbal learning, and visual learning. Secondary analysis compared moderate versus high caffeine users on positive symptoms, negative symptoms, and cognitive symptoms (i.e., cognitive deficits). This study also used open-ended survey questions to better understand the role of caffeine for schizophrenia patients, and themes from their responses were reported. Measures included the Cogstate battery and the Positive and Negative Syndrome Scale (PANSS). Participants were placed into one of two caffeine groups based on self-reported daily caffeine intake: moderate dose (0-250 mg/day) or high dose (251 mg or more/day). T-tests for independent samples were carried out to assess for differences between the two groups on demographic and illness-related variables and on measures of cognitive functioning and symptomatology. Results found that, with respect to demographic and illness-related variables, high caffeine users were prescribed higher antipsychotic doses and were more dependent on nicotine than moderate caffeine users. For cognitive measures, executive function was significantly different between groups such that moderate caffeine users demonstrated a better performance than high caffeine users on the Groton Maze Learning Test. There was a trending difference for a measure of verbal learning and memory, such that moderate caffeine users performed better than high caffeine users on the International Shopping List Test. Assessments of symptoms discovered a significant group difference for the negative factor, such that high caffeine users demonstrated fewer negative symptoms than moderate caffeine users. These results appear to suggest that moderate, rather than high, caffeine consumption is associated with better cognitive functioning, but that high caffeine consumption, rather than moderate, is associated with fewer negative symptoms in schizophrenia outpatients, without necessarily exacerbating positive symptoms. However, given the few studies that are available, additional research is warranted.

LIST OF ABBREVIATIONS AND SYMBOLS USED

ADHD	Attention Deficit Hyperactivity Disorder
AS	Asperger Syndrome
CATIE	Clinical Antipsychotic Trials of Intervention Effectiveness
CSB	Cogstate Schizophrenia Battery
CPZE	Chlorpromazine Equivalents
CYP1A2	Cytochrome P450 1A2
d	Cohen's d
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
FTND	Fagerstrom Test for Nicotine Dependence
FGA	First-Generation Antipsychotics
GABA	Gamma-Amino Butyric Acid
GAD	Generalized Anxiety Disorder
GMLT	Groton Maze Learning Test
ISLT	International Shopping List Test
M	Mean
MATRICS	Measurement and Treatment to Improve Cognition in Schizophrenia
MCCB	MATRICS Consensus Cognitive Battery
n	Group Size
N	Total Sample Size
NIMH	National Institute of Mental Health (NIMH)
NSHA	Nova Scotia Health Authority
NSEPP	Nova Scotia Early Psychosis Program

OCD	Obsessive Compulsive Disorder
p	p-value
PANSS	Positive and Negative Syndrome Scale
REB	Research Ethics Board
SCI-PANSS	Structured Clinical Interview for the PANSS
SD	Standard Deviation
SGA	Second-Generation Antipsychotics
SUD	Substance Use Disorder
t	t-value
<	Less Than
>	More Than
≤	Equal to or Less Than
=	Equals

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Chapter 1

Introduction

1.1. Schizophrenia

Schizophrenia is a severe mental disorder that affects the way a person thinks, acts, and expresses emotion, with a lifetime prevalence of approximately 1% (Simeone, Ward, Rotella, Collins, & Windische, 2015). Although the remission rate for schizophrenia patients is approximately 36% (AlAqeel & Margolese, 2012), schizophrenia remains, for some, an incurable disorder with its treatment relying on the management of symptoms (Avramopoulos, 2018). Three core categories of symptoms associated with schizophrenia include positive, negative, and cognitive deficits (Ross, Margolis, Readings, Pletnikov, & Coyle, 2006). Positive symptoms can be described as feelings, experiences, and behaviours that are added or increased as a result of the illness (e.g., delusions), while negative symptoms can be described as feelings, experiences, and behaviours that are absent or reduced as a result of the illness (e.g., apathy; Buchanan, 2007). Cognitive deficits describe impairments in cognitive functioning that are typically associated with schizophrenia, such as poor memory and attention (Ross et al., 2006). The typical age of onset for schizophrenia is late adolescence to early adulthood (Lara, Dall'lgna, Ghisolfi, & Brunstein, 2006).

According to the Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition; DSM-5; American Psychiatric Association, 2013), an individual who is diagnosed with schizophrenia must have had at least two of the following symptoms (and at least one of the two has to be the first, second, or third on the list): delusions, halluncinations, disorganized speech, grossly disorganized or catatonic behaviour, or negative symptoms. Moreover, patients must have impairment in at least one major area of functioning (e.g., work) since the onset of

disturbance. Signs or symptoms of the disorder must be continuous for at least six months, and at least one of those symptoms must meet the list previously mentioned (e.g., delusions) for at least one month. Schizoaffective, bipolar, and depressive disorders with psychotic features must be ruled out, and the symptoms cannot be a result of a substance or medical condition. A diagnosis of schizoaffective disorder is similar to that of schizophrenia, except that the diagnostic criteria for schizoaffective disorder has an additional mood component (e.g., having mood symptoms present for the majority of the illness). In fact, patients diagnosed with schizophrenia and schizoaffective disorder appear to have similar symptomatology (Pini et al., 2004) and cognitive functioning (Smith, Barch, & Csernansky, 2009), and it has been common practice to combine the two groups of patients in research studies (Thompson, Pennay, Zimmermann, Cox, & Lubman, 2014; de Leon, & Diaz, 2005). For more information on the DSM-5 diagnostic criteria of schizophrenia and schizoaffective disorder, please see American Psychiatric Association, 2013.

Schizophrenia is among the top 15 leading causes of disability worldwide (GBD 2016 Disease and Injury Incidence and Prevalence Collaborato, 2017). Patients with schizophrenia have an increased risk of premature mortality, losing on average 29 years of their life relative to the general population (Olfson, Gerhard, Huang, Crystal, & Stroup, 2015). Five-percent of patients with schizophrenia die by suicide (Palmer, Pankratz, & Bostwick, 2005), and patients are at the highest risk of suicide during the first five years after onset (Byrne, 2007). Other co-occurring medical conditions also complicate their health and contribute to their high rate of premature mortality, such as heart disease and diabetes (Olfson et al., 2015). Unhealthy behaviours such as their high rate of smoking along with the weight gain associated with

particular antipsychotics, and the sedantary behaviours associated with negative symptoms, undoubtably contributes to the problem of premature death (Kelly et al., 2011; Gury, 2004).

1.2. Cognitive Deficits in Schizophrenia

In an attempt to better understand the scope of cognitive impairment and to what extent treatment can impact on these deficits in schizophrenia, the National Institute of Mental Health (NIMH) undertook the Measurement and Treatment to Improve Cognition in Schizophrenia (MATRICS) initiative. In this investigation, a group of experts reached a consensus on the seven cognitive domains typically impaired in schizophrenia patients (Green et al., 2004), including speed of processing (e.g., time it takes to complete a task), attention/vigilance (e.g., maintaining attention and a readiness to respond), working memory (e.g., ability to hold and manipulate information for a brief amount of time), verbal learning and memory (e.g., encoding and retaining verbal information), visual learning and memory (e.g., encoding and retaining visual information), reasoning and problem solving (e.g., volition, planning, and purposeful action), and social cognition (e.g., perceiving, understanding, and managing emotions).

While cognitive deficits affect up to 75% of schizophrenia patients (Palmer et al., 1997), the severity and breadth of these deficts in any one individual can vary considerably (Bowie & Harvey, 2006). In general, patients with schizophrenia have moderate (i.e., 0.5 to 1.5 standard deviations [SD] below what is expected) to severe (more than 1.5 SD below what is expected) deficits on domains such as attention/vigilance, working memory, verbal learning and memory, exectuive function, and processing speed (Harvey, 2013). In other words, results from cognitive assessments reveal that schizophrenia patients score approximately one to two standard deviations below the general population on measures of these cognitive domains (Dickinson, Ramsey, & Gold, 2007; Bilder, 2014; Harvey, 2013).

Cognitive decline in schizophrenia patients is thought to begin prior to the onset of overt psychotic symptoms (Salva, Moore, & Palmer, 2008; Bilder et al., 2006). However, cognitive functioning in patients remains stable after the first several years of illness onset (Salva et al., 2008; Heaton et al., 2001). In a longitudinal study with a moderately large sample (N = 142), Heaton and colleagues (2001) compared cognitive functioning in different subgroups of chronic schizophrenia outpatients. The subgroups were defined based on demographic variables (e.g., elderly patients vs younger patients), clinical variables (late onset vs early onset patients; low, middle, or high symptoms), a baseline measure of cognitive functioning (low global cognition score vs high global cognition score), and anticholinergic use (receiving vs not receiving). Regardless of the patient subgroup, cognitive functioning remained stable in schizophrenia patients (Heaton et al., 2001). Cognitive deficits also appear to remain stable during changes in positive and negative symptoms (Heaton et al., 2001; Carbon & Cornell, 2014).

While cognitive deficits in schizophrenia patients have been heavily supported in the literature as independent from negative and positive symptoms (Heaton et al., 2001; Carbon & Cornell, 2014; Bilder et al., 2006; Kaneko, 2018), there is research that has reported a modest relationship between cognitive deficits and negative symptoms (r = -0.13 to -0.27; Keefe et al., 2006) and between cognitive deficits and positive symptoms (r = -0.08 to -0.29; Rhinewine et al., 2005). This inconsistency appears to be a result of differences in how symptoms are measured (Hughes et al., 2003). For instance, Hughes and colleagues (2003) found that while a decrease in the PANSS negative subscale (N1-N7) significantly predicted an increase in tasks measuring verbal fluency (ß = -0.31) and immediate verbal memory (ß = -0.30), a significant prediction of the same cognitive measures was not discovered when using a specific negative factor structure (N1-N4 and N6).

Poor functional outcome has consistently been associated with cognitive deficits in schizophrenia patients (Schaefer, Giangrande, Weinberger, & Dickinson, 2013). Functional outcome is defined as social performance (basic interpersonal relationships), occupational status (whether a person can hold a job), and quality of life (Lepage, Bodnar, & Bowie, 2014). Cognitive functioning in schizophrenia patients may explain between 20% to 60% of the variance in functional outcome (Green, Kern, Braff, & Mintz, 2000). For instance, patients with schizophrenia who are employed full-time demonstrate significantly better cognitive performance on measures of executive functioning, working memory, and vigilance (McGurk & Meltzer, 2000). Similarly, in schizophrenia patients, total wages and total work hours has moderate to large correlations with working memory (r = 0.49 and 0.51, respectively), processing speed (r = 0.58 and 0.60), and attention (0.37 and 0.34; McGurk & Mueser, 2006). Moreover, schizophrenia patients who are neuropsychologically normal (i.e., T-scores ≥ 40; see Carey et al., 2004) are more likely than patients who are neuropsychologically impaired (i.e., T-score < 40) to be living independently and financially responsible (Leung, Bowie, & Harvey, 2008). As a result, schizophrenia patients with cognitive deficits are more likely to be dependent on family and government support due to difficulties with employment and independent living (Holthausen et al., 2007). Additionally, evidence suggests that cognitive deficits have also been associated with difficulties in social functioning and in adherence to medication (Kitchen, Rofail, Heron, & Sacco, 2012). Poor functional outcome in patients with cognitive deficits may be due to the relationship between cognitive impairments and the ability to carry out basic living skills (Salva et al., 2008).

1.3. Pharmacological Treatment of Cognitive Deficits in Schizophrenia

There are currently no approved or widely accepted treatments for cognitive deficits in schizophrenia patients (Kitchen et al., 2012; Bilder, 2014). While current pharmacological treatment modalities are effective in the relief of positive symptoms associated with schizophrenia, pharmacotherapy is not as successful at diminishing negative symptoms nor improving cognitive deficits (Boison, Singer, Shen, Feldon, & Yee, 2012; Tripathi, Kar, & Shukla, 2018). Despite the ongoing efforts to produce effective and tolerable treatment options for cognitive deficits, including adjunctive (e.g., caffeine), pharmacological, and nonpharmacological options, the heterogenity of the samples and methodologies employed has made it difficult to replicate research discoveries (Bilder, 2014).

The advent of second-generation antipsychotics (SGA) led many people to believe that these medications would be better than first-generation antipsychotics (FGA) at improving cognition in schizophrenia (Mackenzie et al., 2018). Indeed, this idea was supported with early research which demonstrated that SGAs were superior to FGAs for the improvement of cognition in schizophrenia (e.g., attention, processing speed, verbal fluency, and learning; Keefe, Silva, Perkins, & Lieberman, 1999; Woodward, Purdon, Meltzer, & Zald, 2005). However, recent literature has suggested otherwise, contending that both FGAs and SGAs have modest benefits on cognition, with neither category of medication demonstrating superiority (Davidson et al., 2009; Keefe et al., 2007). The biggest trial comparing SGA and FGA medication on measures of cognitive functioning in schizophrenia patients was the CATIE Trial (N = 817; Keefe et al., 2007). The CATIE Trial, conducted in the early 2000s, was a randomized, double-blind, and between-subject study that compared cognition in patients after two months of either FGA or SGA treatment. A composite score was used to report cognitive functioning by using a standardized average taken from measures of processing speed, working memory,

attention/vigilance, verbal memory, and executive function. The results found that both categories of antipsychotics modestly improved cognition after two months, but neither category was superior (Keefe et al., 2007).

There are a number of methodological factors that could help explain the previous notion of SGA superiority. For instance, Keefe and colleagues (2007) claim it is problematic that some previous studies used small sample sizes, short durations of treatment, and/or no comparator treatments. Some other studies did not account for anticholinergic treatments, which have previously been discovered to negatively affect working memory (Mori, Yamashita, Nagao, Horiguchi, & Yamawaki, 2002; McGurk, Lee, Jayathilake, & Meltzer, 2004). Finally, some previous research used a high dose FGA comparator (Keefe et al., 2007; Wang et al., 2013), which is associated with an increased use of anticholinergic medications (Casey, 1991), and hence could negatively affect cognition (Salva et al., 2008; Mori et al., 2002).

1.4. General Substance Use and Cognition in Schizophrenia

Nearly half of all individuals with schizophrenia will fulfill the criteria of a comorbid substance use disorder (SUD) at some point during their life (Regier et al., 1990; Kavanagh, McGrath, Saunders, Dore, & Clark, 2002). SUD is a diagnosable illness in the DSM-5 (American Psychiatric Association, 2013) and can be described as a pattern of symptoms that emerge as a result of substance use (e.g., cravings/urges), but which an individual continues to use despite experiencing problems that are a result of its use (see the DSM-5 for more information; American Psychiatric Association, 2013). Schizophrenia patients are six times more likely than the general population to be diagnosed with a SUD (McLellan, 2017). The most commonly used substances by schizophrenia patients include nicotine (80%; Lohr & Flynn, 1992), caffeine (59%; Gurpegui et al., 2006), cannabis (40%; Rathbone, Variend, & Mehta,

2008), and alcohol (32%; Uludag & Güleç, 2016). When assessing substance use in general, schizophrenia patients with a history of substance use, compared to patients without a history of substance use, are more likely to be male (Uludag & Güleç, 2016), younger at the time of illness onset (Barnes, Mutsatsa, Hutton, Watt, & Joyce, 2006), younger at first hospitalization (Uludag & Güleç, 2016), treatment noncompliant (intentional refusal, e.g., patient has low expectation of treatment effectiveness; Janssen et al., 2006), treatment nonadherent (unintentional refusal, e.g., patient feels helpless; Higashi et al., 2013), unemployed (Uludag & Güleç, 2016), self-harming (Uludag & Güleç, 2016), and homeless (Swartz et al., 2006). Moreover, schizophrenia patients with a history of substance use are more likely to have predominant positive symptoms (Pencer & Addington, 2003), experience relapse and hospitalizations (Linszen, Dingemans, & Lenior, 1994; Cantor-Graae, Norström, & McNeil, 2001), suffer a lower quality of life (Potvin, Sepehry, & Stip, 2006), but have fewer negative symptoms (Potvin et al., 2006) than patients without a history of substance use.

There are several hypothesized and self-reported reasons that attempt to explain the high rate of substance use in schizophrenia patients. The most prominent hypothesis comes from Khantzian's self-medication hypothesis (1985) which claims patients use substances because they are gaining some benefit from its use. Khantzian (1985) added to this by stating that "the drugs that addicts select are not chosen randomly. Their drug of choice is the result of an interaction between the psychopharmacologic action of the drug and the dominant painful feelings with which they struggle" (p. 1259). The self-medication hypothesis is supported with discoveries that suggest patients may be using substances to counteract medication induced side-effects such as sedation (Thompson et al., 2014), to reduce psychotic symptoms such as paranoia (Greg, Barrowclough, Haddock, 2007), to relax (Thoma & Daum, 2013), or possiblly due to its

association with better cognitive functioning (Núñez et al., 2015) and fewer negative symptoms (Lucas et al., 1990). However, schizophrenia patients are also thought to overvalue the beneficial effects of drug use and devalue the adverse/harmful effects (Krystal et al., 2006), such as when they devalue the onset or increase in positive symptoms after using drugs (Pencer & Addington, 2003). Other experts attribute their high rate of substance use to institutalization (Gurpegui, Aguilar, Martinez-Ortega, Diaz, & de Leon, 2004), boredom (Hughes, McHugh, & Holtzman, 1998), and poor judgement (Koczapski, Ledwidge, Paredes, Kogan, & Higenbottam, 1990).

The association between general substance use and cognitive functioning in schizophrenia patients has been controversial. While some research describes comparable cognitive functioning between schizophrenia patients with and without a history of substance use (Barnes et al., 2006; Pencer & Addington, 2003), others have described both better (Potvin et al., 2005; Thoma, Wiebel, & Daum, 2007) and worse cognitive functioning in schizophrenia patients with a history of substance use (Addington & Addington, 1997). The heterogeniety of these results can be attributed to the variability in samples and methodologies employed. For instance, some studies do not control for potential confounders such as sex, type of medication, severity of symptoms, and phase of illness (e.g., chronic or acute; Thoma & Daum, 2013). Some studies also fail to collect information related to the duration and frequency of the participant's substance use (Thoma & Daum, 2013; Núñez et al., 2015). Similarly, some researchers combine data from both chronic and acute substance users (Thoma & Daum, 2013) despite the possibility that the effects of both types of substance use could be different (Donoghue & Doody, 2012). Finally, some studies do not exclude participants using multiple substances or who suffer from a learning disability (Donoghue & Doody, 2012; Verdejo-Garcia & Pérez-Garcia, 2007).

1.5. Caffeine Use and Cognition in Schizophrenia

Caffeine (1,3,7-trimethylxanthine) is the most widely used psychoactive substance in the world. Approximately 85% of the general population consumes caffeine, in one form or another, with an average daily intake of 165 mg among caffeine users (Mitchell, Knight, Hockenberry, Teplansky, & Hartman, 2014). In healthy controls, caffeine is associated with better attention (Kelemen & Creeley, 2001), processing speed (Mackay, Tiplady, & Scholey, 2002), working memory (Smillie & Gokcen, 2010), and verbal memory (Jarvis, 1993). These domains typically are those affected in schizophrenia patients (Green et al., 2004).

Some researchers make the case for an inverted-U relationship between caffeine dose and cognitive performance in healthy (non-psychiatric) controls. Kaplan et al. (1997) conducted a double-blind, three-way cross-over design study using healthy controls, comparing a placebo and two caffeine doses (placebo, 250 mg, 500 mg). That study found that while 250 mg of caffeine increased performance on a working memory task, 500 mg of caffeine decreased performance. Kaplan et al. (1997) also suggests that caffeine has positive subjective effects up to 250 mg (e.g., peacefulness, elation, relaxation) while higher doses (> 500 mg) had unpleasant effects (e.g., tension, anxiety). In a literature review assessing caffeine's effects on cognitive performance, McLellan, Caldwell, and Lieberman (2016) support the notion of an inverted-U relationship, suggesting that caffeine doses up to ~300 mg enhances cognitive performance by preventing decrements to alertness and attention. Additionally, research suggests that while caffeine can help with mood and energy at lower doses (~200 mg/day; Brice & Smith, 2001; Lara, 2010), caffeine may be associated with a depressive mood following excessive caffeine consumption (Hedges, Woon, & Hoopes, 2009; Rizkallah et al., 2011). Therefore, to consider whether these

findings carry over into a schizophrenia population, it is important to categorize caffeine in a way that allows for the assessment of different dosages.

Caffeine is the second most commonly used substance for schizophrenia patients (59%; Gurpegui et al., 2006). Although there are fewer caffeine users among schizophrenia patients relative to the general population (59% vs. 70%, respectively; Gurpegui et al., 2006), caffeine consumption (i.e., dose) is significantly higher in schizophrenia patients compared to the general population (Strassnig, Brar, & Ganguli, 2006). The mean caffeine consumption among caffeine-using and non-using schizophrenia patients is approximately 500 mg per day (Strassnig et al., 2006), while 33% of caffeine-using patients consume more than 550 mg per day (Mayo, Falkowski, & Jones, 1993).

Despite the high usage of caffeine by individuals with schizophrenia, only one study has examined the association between caffeine intake and cognition in individuals with schizophrenia (Núñez et al., 2015). In a regression analysis, this study found that caffeine use (as measured by cups) was associated with better performance on tasks requiring visual memory, working memory, semantic fluency, and processing speed, but only in male patients (n = 34). The latter result could have been due to the small number of female patients that were included in the study (n = 18; Núñez et al. 2015), or because there may be sex differences related to the impact of caffeine (Adan, Prat, Fabbri, & Sànchez-Turet, 2008; Botella & Parra, 2003). Nevertheless, these findings suggest that caffeine use is associated with better functioning in cognitive abilities that are typically affected in schizophrenia patients.

1.5.1. Caffeine and Sedation in Schizophrenia

It is also possible that patients are using caffeine to offset side-effects induced by their medication (Deckert et al., 2003). For instance, approximately 40% of clozapine users report

experiencing sedation (Safferman, Lieberman, Kane, Szymanski, & Kinon, 1991), which is significant since antipsychotic-induced sedation can impair cognitive functioning (Harvey et al., 2007). Therefore, since caffeine is known to counteract sedation, it is possible that schizophrenia patients consume caffeine as a countermeasure to sedation (Williams & Gandhi, 2008). This notion is supported with a qualitative study which assessed the role of caffeine for schizophrenia patients from their perspective (Thompson et al., 2014). In this latter study, the authors asked 20 patients in-depth questions related to their caffeine intake and then thematically analyzed their responses. The study found that, among other reasons, patients were using caffeine to offset sedation induced by their medication (Thompson et al., 2014). Patients also reported using caffeine for its stimulating properities, to satisfy cravings, and to help facilitate social interactions (Thompson et al., 2014). The suggestion that caffeine can be used as an avenue to reduce sedation in schizophrenia patients is shared by some physicians (Miller, 2004). This finding by Thompson et al. (2014) as well as the supportive suggestion by Miller (2004) provides support to the notion that caffeine may be exerting beneficial effects on some schizophrenia patients and warrants further research.

1.5.2. Caffeine and Positive Symptoms

Prior research investigating the impact of caffeine on schizophrenia patients primarily reported adverse effects, such as exacerbations in positive symptoms, but used high doses of caffeine (Lucas et al., 1990; Peng, Chiang, & Liang, 2014). For instance, Lucas and colleagues (1990) described an increase in positive symptoms after administering 10 mg of caffeine per kilogram to 13 patients with schizophrenia. To put this in perspective: if a participant weighed 100 kilograms, that individual was administered 1000 miligrams of caffeine in one sitting. Indeed, there are reports of delusions and hallucinations in patients with (Zaslove, Russell, &

Ross, 1991) and without (Rush, Sullivan, & Griffiths, 1995) schizophrenia after consuming large amounts of caffeinated beverages. Only one published article reports an increase in positive symptoms following the consumption of a low dose caffeine beverage- however, that was based on a case study (Wang, Woo, Bahk, & 2015). Future research investigating caffeine use in schizophrenia patients should assess various caffeine doses and its association with cognition and symptomatology. Please see Appendix A for a paper discussing recent findings and future directions for caffeine research in schizophrenia.

1.5.3. Pharmacology of Caffeine

Caffeine is a stimulant that functions as an adenosine antagonist, primarily blocking the adenosine A_1 and A_{2A} receptors (Fisone, Borgkvist, & Usiello, 2004). Adenosine is a neurotransmitter that promotes feelings of sleep and sedation due to its inhibiting effects on neuronal activity (Ferré, 2008). In fact, it has been suggested that there are comparable effects of adenosine agonists and antipsychotics; by inhibiting neuronal activity such as dopamine, both adenosine agonists and antipsychotics can induce feelings of sleep and sedation (Ribeiro & Sebastião, 2010). Caffeine exerts its effects by blocking adenosine from performing its function, and hence is indirectly associated with the release of neurotransmitters such as dopamine, glutamate, norepinephrine, serotonin, and GABA (Daly, Shi, Nikodyivic,, & Jacobson, 1999). Caffeine is primarily metabolized by cytochrome P450 1A2 (CYP1A2; Ribeiro & Sebastião, 2010) and reaches peak plasma concentrations approximately 45 minutes after consumption (Benowitz, 1990).

1.5.4. Metabolic Interactions of Caffeine

Smokers are thought to consume more caffeine than non-smokers due to CYP1A2 metabolic interactions (Williams & Gandhi, 2008). That is, tobacco is an inducer of CYP1A2

while caffeine is a substrate of CYP1A2. As a result, tobacco can increase caffeine metabolism by approximately 60% (Zevin & Benowitz, 1999). In support of this is the finding that smokers require approximately 2-3x more caffeine than non-smokers in order to experience the same effects (Gurpegui et al., 2004). Since up to 80% of schizophrenia patients use nicotine (Lohr & Flynn, 1992), smoking schizophrenia patients may have higher levels of caffeine consumption in order to seek the level of caffeine benefit that they desire.

Some antipsychotics such as clozapine, olanzapine, and haloperidol are also metabolized by CYP1A2 (Carrillo & Benitez, 2000). Since caffeine is also metabolized by CYP1A2, the use of caffeine and these particular antipsychotics competes for CYP1A2 metabolism which leads to a slower clearance of them both. This in turn requires a lower dose of antipsychotic to avoid clinical consequences to the patient, such as nausea or exacerbated symptoms (Carrillo & Benitez, 2000; Hägg, Spigset, Mjörndal, & Dahlqvist, 2000; Vainer & Chouinard, 1994). On the other hand, nicotine is an inducer of CYP1A2 which leads to a quicker clearance of antipsychotics and hence requires a higher dose of medication to remain effective (Šagud et al., 2018; Mayerova et al., 2018). As a result, for antipsychotics that are metabolized by CYP1A2, clinicians should consider increasing the antipsychotic dose for smokers by a factor of approximately 1.5 while decreasing the dose for caffeine users by a factor of approximately 0.6 (de Leon, 2004). More research is required to understand what occurs during a metabolic interaction among caffeine, nicotine, and antipsychotics (e.g., since nicotine is an inducer of CYP1A2, will it still lead to a quicker clearance of both caffeine and antipsychotics?).

1.6. Rationale For The Current Study

The current study compared moderate caffeine users to high caffeine users on cognitive functioning, symptomatology, and demographic and illness-related variables in schizophrenia

patients. Although it was our initial intention to research whether there was a dose relationship between caffeine intake and cognitive functioning, as was previously discovered in healthy controls (Kaplan et al., 1997), this plan had to be amended due to the small sample size and, as a result, two caffeine groups were compared rather than three. Patients were also asked questions regarding their motivations for using caffeine. There is currently a void in our understanding about the impact of caffeine on schizophrenia patients, especially with respect to cognition. Given the high rate of caffeine intake in this population (Strassnig et al., 2006), additional research needs to be conducted so that clinicians have a better understanding of the potential impact of caffeine on schizophrenia patients.

1.7. Objectives and Hypotheses

The primary objective of this study was to compare moderate versus high caffeine users on measures of working memory, attention/vigilance, processing speed, visual learning, and verbal learning in patients with psychotic disorders. Secondary objectives included a comparison of the two caffeine groups with respect to positive symptoms, negative symptoms, and cognitive deficits, as measured by symptomatic rating scales. We also wished to better understand patients' motivations for caffeine use and hence asked patients two open-ended questions about the aspects of caffeine they like/enjoy and the aspects they dislike/do not enjoy. Based on literature from healthy (non-psychiatric) controls that suggest caffeine dosages of up to ~250 mg benefit cognition while doses above that may be detremental or have no additional effect (McLellan et al., 2016; Kaplan et al., 1997), it was hypothesized that $\boldsymbol{H_1}$. moderate caffeine users would demonstrate better cognitive performance than high caffeine users on measures of processing speed, executive function, verbal learning and memory, visual learning and memory, and sustained attention. Moreover, based on the study by Lucas et al. (1990) which

found an increase in positive symptoms and a decrease in negative symptoms after the acute administration of a high caffeine dose (10 mg/kilo), we hypothesized that $\boldsymbol{H_2}$. high caffeine users would demonstrate fewer negative symptoms than moderate caffeine users and $\boldsymbol{H_3}$. high caffeine users would demonstrate more positive symptoms than moderate caffeine users.

Chapter 2

Methods

2.1. Participants

This study was approved by the Nova Scotia Health Authority Research Ethics Board (NSHA REB File # 1023131). Participants were recruited for this study through the Nova Scotia Early Psychosis Program (NSEPP), as well as via advertisements throughout the hospital, community note boards, and Kijiji.com. The inclusion and exclusion criteria were as follows: Participants must have had a DSM-5 (American Psychiatric Association, 2013) diagnosis of schizophrenia or schizoaffective disorder, 18-55 years of age, on a stable medication regime for at least 4 weeks, an outpatient, (corrected to-) normal vision, fluent in English, and must not have had recent illicit substance use (3+ months; caffeine, nicotine, alcohol, and cannabis are permitted). The principal investigator obtained verbal consent to contact the patients physician or nurse and confirm their diagnosis and medication regime.

2.2. Materials

Materials for this study included questionnaires, neuropsychological testing, and a clinical interview. Descriptions of the materials that were used in this study are found below.

Demographic and Illness-Related Questionnaire. The demographic and illness-related questionnaire consists of nine questions created by the principal investigator. These questions query for age, sex, diagnosis, medication (type and dosage), highest level of educational acheivement, employment status, marital status, ethnicity, and smoking status. The demographic and illness-related questionnaire took approximately five minutes to complete. See Appendix B for the demographic and illness-related questionnaire.

Nicotine Questionnaire. The Fagerstrom Test for Nicotine Dependence (FTND) measures patients' nicotine use and level of dependence (Heatherton et al., 1991). The FTND consists of six questions and takes approximately five minutes to complete. The FTND is among the most commonly used measures of nicotine dependence (Korte, Capron, Zvolensky, & Schmidt, 2013). The FTND is a valid measure of nicotine dependence in smokers (Lim et al., 2016) and has been used in studies measuring nicotine dependence in schizophrenia patients (Gurpegui et al., 2004). A score of 0 was applied for non-smokers. The highest score for this scale is 10 and higher scores are indicative of higher levels of dependence. See Appendix C for the FTND.

Cogstate Battery. The Cogstate Schizophrenia Battery (CSB) included a series of six computerized tasks and takes approximately 30 minutes to complete (Lees et al., 2015). The six tasks include the Detection Test (processing speed), Identification Test (attention/vigilance), One Back Test (working memory), One Card Learning Test (visual learning and memory), International Shopping List Test (verbal learning and memory), and Groton Maze Learning Test (executive function Pietrzak et al., 2009). Raw outcome scores were reported, which is consistent with previous literature (Pietrzak et al., 2009), and a composite score was not reported given the interest of this current study was in the outcome of individual tests (listed above) rather than a global cognitive score. For the One Back Test, which included two outcome measures (i.e., average speed of correct responses and proportion of correct responses), only the latter was reported, which is consistent with previous literature assessing the cogstate battery (Pietrzak et al., 2009). See Appendix D for the Cogstate Battery. The battery was consistently administered by the principal investigator. The CSB measures cognitive domains that are typically impaired in schizophrenia as per the consensus from the MATRICS (Green et al., 2004). Moreover, while

the MATRICS Consensus Cognitive Battery (MCCB) takes approximately 90 minutes to administer (Nuechterlein et al., 2008), the Cogstate battery takes approximately 30 minutes to complete and measures the same cognitive domains (Lees et al., 2015). When comparing the CSB to the MCCB, the CSB proved to be a reliable and valid measure of the cognitive domains outlined by MATRICS (Lees et al., 2015). This is in contrast to the previous study (Núñez et al., 2015) which did not use cognitive measures that were tailored for schizophrenia patients, and which included shallow/deep measures for each cognitive domain without providing references for their distinctions.

Positive and Negative Syndrome Scale. The Positive and Negative Syndrome Scale (PANSS) is a 30-item clinical scale measuring positive symptoms, negative symptoms, and general psychopathology (Kay et al., 1987). The purpose is to detect the presence and severity of psychotic symptoms. PANSS is administered in the form of a clinical interview which takes approximately 40 minutes to complete (Kay et al., 1987). The PANSS is a reliable and valid measure of symptoms for schizophrenia patients (Kay, Opler, & Lindenmayer, 1988), and is a widely used clinical scale (Núñez et al., 2016; Opler, Yavorsky, & Daniel, 2017). The principal investigator was trained to administer the PANSS and followed standardized instructions outlined in Structured Clinical Interview for the PANSS (SCI-PANSS; Kay et al., 1987). See Appendix E for more details on the PANSS. The author used individual items from the PANSS to derive the positive factor (P1 [delusions], P3 [hallucinatory behaviour], P5 [grandiosity], G9 [unusual thought content]), negative factor (N1 [blunted affect], N2 [emotional withdrawal], N3 [poor rapport], N4 [passive/apathetic withdrawal], N6 [lack of spontaneity & flow of conversation], G7 [motor retardation]), and cognitive factor (P2 [conceptual disorganization], N5 [difficulty in abstract thinking], G11 [poor attention]; Wallwork, Fortgang, Hashimoto,

Weinberger, & Dickinson, 2012), and these factor scores were then used when comparing symptoms between the two caffeine groups. Analysis of a specific factor structure was used in this study for two reasons: the factors (rather than the subscales positive, negative, and general psychopathology) better characterize the data collected by PANSS (Wallwork et al., 2012), and also because it was necessary to assess cognitive deficits independently, while in the three subscales in PANSS cognitive items are interspersed within. Moreover, this specific factor structure was selected because it is referred to as the "consensus model" as a result of its high reliability and concurrent validity (Rodriguez-Jimenez et al., 2013; Wallwork et al., 2012).

Caffeine Questionnaire. The caffeine questionnaire required participants to complete eight questions regarding their caffeine consumption. Open-ended questions were concerned with their average daily caffeine intake, the time of day they use caffeine the most, the aspects of caffeine they enjoy and/or do not enjoy, how long they think they can abstain from caffeine, whether their use of caffeine has changed in the past three months (and if so, why/how has it changed?), and finally the questionnaire asks what time of day they typically awaken from sleep. These questions were created and administered by the principal investigator; the questionnaire took approximately 10 minutes to complete. While Núñez and colleagues (2014) measured caffeine in cups, and without distinguishing between coffee, tea, and other caffeinated beverages, this current study collected specific information about the caffeinated items used by each participant (e.g., coffee, tea, energy drink, chocolate, medication) and documented their caffeine intake based on milligrams (the principal investigator would ask them the brand, amount/size, and, if relevant, the type of roast, e.g., Tim Hortons, medium, dark roast, and then the principal investigator would use resources on the internet to determine the specific caffeine content of the item[s] in question). If participants experienced difficulty remembering specific information, the

researcher provided photographic cues that were used to help the person determine the type and size of caffeineated item they used. Measuring caffeine intake via self-report is considered valid (Addicott, Yang, Peiffer, & Laurienti, 2009) and is a widely used measure of chronic caffeine consumption (Kyle et al., 2010; Harvanko et al., 2015). While measuring caffeine intake via direct drug concentrations are more reliable, this would only capture caffeine intake in the past 24-48 hours, while using a self-report method allows researchers to capture chronic (regular) caffeine consumption. The survey component of our study was included in this questionnaire, in which the principal investigator asked participants: "What are the aspects of caffeine that you like/enjoy and those you dislike/do not enjoy?". The survey question was divided into two questions, such that participants first responded to "What are the aspects of caffeine that you like/enjoy?" followed by "What are the aspects of caffeine that you dislike/do not enjoy?". See Appendix F for the caffeine questionnaire.

2.3. Design and Procedure

This cross-sectional study compared two caffeine use groups, based on literature that assessed healthy controls, suggesting that doses of up to ~250 mg are beneficial to cognitive functioning and mood while doses beyond that may be detremental to both cognition and mood (McLellan, et al., 2016; Lara, 2010; Hedges et al., 2009; Kaplan et al., 1997). Group 1 was a moderate dose group (0-250 mg/day) and Group 2 was a high dose group (251 mg or more/day). Participants self-reported their average daily caffeine intake. Based on the literature from healthy controls which suggested there was a curvilinear relationship among caffeine intake, cognitive functioning, and mood (Kaplan et al., 1997), it was our original intention to compare three caffeine groups in this study: minimal (0-100 mg/day), moderate (101-250 mg/day), and high (251 mg or more/day). However, due to the small sample size, the moderate group would

have had only two participants, and so a decision was made to combine the minimal and moderate dose groups and call it a moderate group (0-250 mg/day), since it has also been previously discovered that moderate doses of up to ~300 mg have a positive impact on cognition functioning while doses above that do not (McLellan et al., 2016). As a result, only two groups were compared in this study.

All participants underwent identical study procedures and assessments. Participants were first screened for inclusionary and exclusionary criteria (see Appendix G). Following this, after obtaining verbal consent, the principal investigator contacted the participant's physician or nurse to confirm the participant's responses (e.g., ensure that the diagnosis is correct). Participants who were caffeine users were asked to consume their regular caffeine dose 45 minutes prior to participating in the study, given that is approximately how long it takes for caffeine to be absorbed and to reach peak plasma concentration (Liguori, Hughes, & Grass, 1997). Initially during their visit, participants were first asked to provide informed consent (see Appendix H). Participants then completed a demographic and illness-related questionnaire followed by a nicotine questionnaire (FTND; Heatherton et al., 1991). Following this, participants underwent cognitive testing (Cogstate Battery; Pietrzak et al., 2009) and then symptom assessment (PANSS; Kay et al., 1987). Finally, participants completed a caffeine questionnaire. Self-reported caffeine intake was how patients were stratified into subject groups. Participants attended Abbie J. Lane once for approximately 90 minutes. Each participant was compensated $20.00 for costs incurred.

2.4. Statistical Analysis

Independent sample t-tests were carried out to compare the moderate caffeine group to the high caffeine group on measures of cognitive functioning, symptomatology, and

demographic and illness-related variables. Alpha was set at $p \leq .05$, and one-tailed tests were employed for a priori hypothesized differences (**H_1, H_2, & H_3**), while two-tailed tests were employed for demographic and illness-related variables. Moreover, a chi-square test was used to assess for sex differences in the frequency of males and females between the two caffeine groups. Several sensitivity analyses were also conducted for our demographic and illness-related variables, cognitive variables, and symptomatology variables to see if this changed our results and could help inform future research. That is, we re-ran the analyses five additional times comparing moderate caffeine users to high caffeine users but either excluded patients in a chronic phase of illness (n = 4), non-caffeine users (n = 2), females (n = 3), or patients diagnosed with schizoaffective disorder (n = 3), and in a fifth sensitivity analysis we compared smokers (n = 8) to non-smokers (n = 11) irrespective of caffeine intake. For the survey data, the principal investigator and his supervisor (Dr. Kimberley Good) independently coded and categorized responses to the open-ended questions (as described in section 2.2; E. G. Marshall, email communication, June 7, 2019; Iversen, Bjertæs, & Skudal, 2014). Following this, the principal investigator and his supervisor met and reached a consensus on any differences that arose from between their codings and categorizations of participant's responses.

2.5. Sample Size Calculations

There is very little data on the effects of caffeine on cognition in patients with schizophrenia. However, Núñez and colleagues (2015) used a regression analysis to predict cognitive test scores from caffeine use. With a sample size of 34 male patients, significant beta coefficients were noted between caffeine intake and semantic fluency, cognitive speed, working memory and visual memory. As such, our aim was to recruit 34 participants per caffeine group (N = 68).

Chapter 3

Results

3.1. Demographic and Illness-Related Data

Nineteen participants were recruited for this study (16 males). On average, participants were 28.8 years old, had a daily caffeine intake of 315.5 mg, were prescribed 283.8 mg of antipsychotics per day (chlorpromazine equivalents; CPZE; Danivas & Venkatasubramanian, 2013), had an FTND score of 2.1, and completed 13.9 years of education. See Table 1 for the demographic and illness-related data for all participants.

Participants identified as White (n = 10), Black (n = 4), Chinese (n = 1), West Asian (n = 1), First Nations (n = 1), and Other (n = 2). Participants were diagnosed with schizophrenia or schizoaffective disorder, according to DSM-5 criteria, for an average of 4.21 years. Thirteen participants had a single diagnosis of schizophrenia or schizoaffective disorder, four participants had two diagnoses, and one participant had three diagnoses. While all of the participants were diagnosed with schizophrenia (n = 16) or schizoaffective disorder (n = 3), some participants were also diagnosed with comorbid generalized anxiety disorder (GAD; n = 2), obsessive compulsive disorder (OCD; n = 1), attention deficient hyperactivity disorder (ADHD; n = 1), and Asperger syndrome (AS; n = 1). Participants in this study were using various antipsychotics such as Aripiprazole (n = 7), Paliperidone (n = 5), Clozapine (n = 3), Quetiapine (n = 2), Olanzapine (n = 1), Risperidone (n = 1), Lurasidone (n = 1), Loxapine (n = 1), Flupentixol (n = 1), and two participants were not currently taking an antipsychotic. While most patients were using only one medication to treat their symptoms (n = 11), others were using two medications (n = 4), three medications (n = 2), four medications (n = 1), or no medication (n = 1). Two out of the 10

participants in the moderate dose group were non-caffeine users (which is 20% of the moderate dose group, or approximately 11% of the whole sample).

Independent sample t-tests were carried out to assess for differences between the two groups with respect to age, education, average daily caffeine intake, FTND score, and antipsychotic dose (CPZE; Danivas & Venkatasubramanian, 2013). As a reliability check, a difference between group means was discovered for caffeine intake ($t(8.3 = 3.2, p < .05, d = 1.5$). Those in the high dose group consumed more caffeine ($M = 593.2$, $SD = 489.3$) than those in the moderate dose group ($M = 65.5$, $SD = 68.3$), as predicted. A difference was also discovered between the two groups for the FTND score ($t(10.8) = 2.4, p < .05, d = 1.1$). High caffeine users were more dependent on nicotine ($M = 3.6$, $SD = 3.4$) than moderate caffeine users ($M = 0.7$, $SD = 1.5$). A difference was also discovered between the two caffeine groups with respect to antipsychotic dose ($t(13.2) = 2.2, p < .05, d = 1.0$). High caffeine users were prescribed higher antipsychotic doses ($M = 413.4$, $SD = 283.7$) than moderate caffeine users ($M = 167.1$, $SD = 178.3$). No other differences were discovered. There were more females in the moderate dose group (n = 3) than the high dose group (n = 0); however, this finding was not significant (X^2 (1) $= 3.2, p > .05, V = 0.4$). See Table 2.

A sensitivity analysis was conducted which excluded patients in a chronic phase of illness (n = 4). The moderate dose group (n = 8) was compared to the high dose group (n = 7) on demographic and illness-related variables. As a reliability check, a difference between group means was discovered for caffeine intake ($t(7.1) = 6.2, p < .05, d = 3.3$). Those in the high dose group consumed more caffeine ($M = 456.7$, $SD = 164.9$) than those in the moderate dose group ($M = 53.7$, $SD = 53.1$). A difference was also discovered between the two groups for the FTND score ($t(13) = 2.7, p < .05, d = 1.3$). High caffeine users were more dependent on nicotine ($M =$

4.4, *SD* = 3.3) than moderate caffeine users (*M* = 0.9, *SD* = 1.6). A difference was also discovered between the two caffeine groups with respect to antipsychotic dose ($t(13) = 2.6$, $p < .05$, $d = 1.3$). High caffeine users were prescribed higher antipsychotic doses (*M* = 371.3, *SD* = 251.6) than moderate caffeine users (*M* = 121.1, *SD* = 93.0). No other differences were discovered. There were more females in the moderate dose group (n = 2) than the high dose group (n = 0); however, this finding was not significant (X^2 (1) = 2.0, $p > .05$, $V = 0.1$). See Appendix I.

A sensitivity analysis was also conducted which excluded non-caffeine users (n = 2). The moderate dose group (n = 8) was compared to the high dose group (n = 9) on demographic and illness-related variables. As a reliability check, a difference between group means was discovered for caffeine ($t(15) = 2.9$, $p < .05$, $d = 1.5$). Those in the high dose group consumed more caffeine (*M* = 593.2, *SD* = 489.3) than those in the moderate dose group (*M* = 81.8, *SD* = 66.8). A difference was also discovered between the two groups for the FTND score ($t(9.8) = 2.7$, $p < .05$, $d = 1.3$). High caffeine users were more dependent on nicotine (*M* = 3.6, *SD* = 3.4) than moderate caffeine users (*M* = 0.4, *SD* = 1.1). No other differences were discovered. There were more females in the moderate dose group (n = 2) than the high dose group (n = 0); however, this finding was not significant (X^2 (1) = 2.6, $p > .05$, $V = 0.1$). See Appendix J.

A sensitivity analysis was conducted which excluded females (n = 3). The moderate dose group (n = 7) was compared to the high dose group (n = 9) on demographic and illness-related variables. As a reliability check, a difference between group means was discovered for caffeine intake ($t(14) = 2.7$, $p < .05$, $d = 1.4$). Those in the high dose group consumed more caffeine (*M* = 593.2, *SD* = 489.3) than those in the moderate dose group (*M* = 88.4, *SD* = 70.1). A difference was trending between the two groups for the FTND score ($t(12.5) = 1.9$, $p > .05$, $d = 0.9$). High

caffeine users were more dependent on nicotine (M = 3.6, SD = 3.4) than moderate caffeine users (M = 1.0, SD = 1.7). No other differences were discovered. See Appendix K.

An additional sensitivity analysis was conducted which excluded participants diagnosed with schizoaffective disorder (n = 3). The moderate dose group (n = 9) was compared to the high dose group (n = 7) on demographic and illness-related variables. As a reliability check, a difference between group means was discovered for caffeine intake (t(7.5) = 5.5, $p < .05$, d = 2.9). Those in the high dose group consumed more caffeine (M = 448.4, SD = 171.6) than those in the moderate dose group (M = 72.7, SD = 68.2). A difference was also discovered between the two groups on the FTND ($t(14) = 3.2$, $p < .05$, d = 1.5). High caffeine users were more dependent on nicotine (M = 4.6, SD = 3.1) than moderate caffeine users (M = 0.8, SD = 1.6). A difference was trending between the two groups for antipsychotic dose ($t(14) = 1.9$, $p > .05$, d = 0.9). High caffeine users were prescribed higher antipsychotic dosages (M = 384.9, SD = 239.5) than moderate caffeine users (M = 185.7, SD = 178.6). No other differences were discovered. There were more females in the moderate dose group (n = 2) than the high dose group (n = 0); however, this finding was not significant (X^2 (1) = 1.8, $p > .05$, V = 0.1). See Appendix L.

A final sensitivity was conducted comparing smokers (n = 8) to non-smokers (n = 11) on demographic and illness-related variables. A difference between group means was discovered for FTND ($t(7 = 5.9$, $p < .05$, d = 2.9). Smokers were more dependent on nicotine (M = 4.9, SD = 2.4) than non-smokers (M = 0.0, SD = 0.0), as predicted. No other differences were discovered. There were more females in the non-smoker group (n = 3) than the smoker group (n = 0); however, this finding was not significant (X^2 (1) = 2.6, $p > .05$, V = 0.1). See Appendix M. None of the correlations between the FTND (or the number of cigarettes smoked per day) and the demographic and illness-related variables were significant. See Appendix N.

3.2. Cognitive Functioning

To test our first hypothesis that moderate caffeine users would demonstrate better cognitive functioning than high caffeine users, independent sample t-tests were carried out to assess for differences between the two caffeine groups on tasks measuring executive function, processing speed, attention/vigilance, verbal learning and memory, visual learning and memory, and working memory. There was a difference between group means for a task measuring executive function ($t(17) = 2.0$, $p < .05$, $d = 0.9$). Moderate caffeine users made fewer errors on the Groton Maze Learning Test (GMLT; $M = 47.6$, $SD = 16.8$) than high caffeine users ($M = 68.7$, $SD = 27.5$). There was also a trending difference between group means for a task measuring verbal learning and memory ($t(17) = 1.6$, $p > .05$, $d = 0.7$). Moderate caffeine users recalled more words from the International Shopping List Test (ISLT; $M = 24.6$, $SD = 3.2$) than high caffeine users ($M = 21.6$, $SD = 5.0$). No differences were discovered between the two caffeine groups on measures of processing speed, attention/vigilance, visual learning and memory, and working memory. There were no outliers on any of the measures (defined as 3 times the interquartile range). See Table 3.

A sensitivity analysis was conducted which excluded patients in a chronic phase of illness (n = 4). The moderate dose group (n = 8) was compared to the high dose group (n = 7) on tasks measuring cognitive functioning. There was a difference between group means for a task measuring verbal learning and memory ($t(13) = 3.1$, $p < .05$, $d = 1.6$). Moderate caffeine users recalled more words from the ISLT ($M = 25.0$, $SD = 3.3$) than high caffeine users ($M = 20.0$, $SD = 3.0$). There was also a trending difference between group means for a task measuring executive function ($t(13) = 1.6$, $p > .05$, $d = 0.8$). Moderate caffeine users made fewer errors on the GMLT ($M = 49.9$, $SD = 18.1$) than high caffeine users ($M = 68.7$, $SD = 28.4$). No other

differences were discovered. There were no outliers on any of the measures (defined as 3 times the interquartile range). See Appendix O.

A sensitivity analysis was also conducted which excluded non-caffeine users (n = 2). The moderate dose group (n = 8) was compared to the high dose group (n = 9) on tasks measuring cognitive functioning. There was a trending difference between group means for a task measuring executive function ($t(15) = 1.6$, $p > .05$, $d = 0.8$). Moderate caffeine users made fewer errors on the GMLT ($M = 50.0$, $SD = 17.9$) than high caffeine users ($M = 68.7$, $SD = 27.5$). No other differences were discovered. There were no outliers on any of the measures (defined as 3 times the interquartile range). See Appendix P.

A sensitivity analysis was conducted which excluded females (n = 3). The moderate dose group (n = 7) was compared to the high dose group (n = 9) on tasks measuring cognitive functioning. No differences were discovered. There were no outliers on any of the measures (defined as 3 times the interquartile range). See Appendix Q.

An additional sensitivity analysis was also conducted which excluded participants diagnosed with schizoaffective disorder (n = 3). The moderate dose group (n = 9) was compared to the high dose group (n = 7) on tasks measuring cognitive functioning. There was a trending difference between group means for a task measuring executive function ($t(14) = 1.6$, $p > .05$, $d = 0.8$). Moderate caffeine users made fewer errors on the GMLT ($M = 48.1$, $SD = 17.7$) than high caffeine users ($M = 67.0$, $SD = 29.6$). No other differences were discovered. There were no outliers on any of the measures (defined as 3 times the interquartile range). See Appendix R.

A final sensitivity analysis was conducted comparing smokers (n = 8) to non-smokers (n = 11) on tasks measuring cognitive functioning. No differences were discovered. There were no outliers on any of the measures (defined as 3 times the interquartile range). See Appendix S.

None of the correlations between the FTND (or the number of cigarettes smoked per day) and cognitive functioning were significant. See Appendix T.

3.3. Symptomatology

Independent sample t-tests were carried out to assess for differences between the two caffeine groups on symptomatology. In order to assess symptoms, the author used the positive factor (P1, P3, P5, G9), negative factor (N1, N2, N3, N4, N6, G7), and cognitive factor (P2, N5, G11; Wallwork et al., 2012). There was a difference between group means for the negative factor ($t(17) = 1.8$, $p \leq .05$, $d = 0.8$). High caffeine users had fewer negative symptoms ($M = 8.9$, $SD = 4.4$) than moderate caffeine users ($M = 12.6$, $SD = 4.7$). No differences were discovered between the two caffeine groups on the positive factor and cognitive factor. There were no outliers on any of the measures (defined as 3 times the interquartile range). See Table 4.

A sensitivity analysis was conducted which excluded patients in a chronic phase of illness (n = 4). The moderate dose group (n = 8) was compared to the high dose group (n = 7) on measures of symptomatology. There was a trending difference between group means for the negative factor ($t(13) = 1.6$, $p > .05$, $d = 0.8$). High caffeine users had fewer negative symptoms ($M = 9.7$, $SD = 4.7$) than moderate caffeine users ($M = 13.5$, $SD = 4.7$). No other differences were discovered. There were no outliers on any of the measures (defined as 3 times the interquartile range). See Appendix U.

A sensitivity analysis was conducted which excluded non-caffeine users (n = 2). The moderate dose group (n = 8) was compared to the high dose group (n = 9) on measures of symptomatology. No differences were discovered. There were no outliers on any of the measures (defined as 3 times the interquartile range). See Appendix V.

A sensitivity analysis was conducted which excluded females (n = 3). The moderate dose group (n = 7) was compared to the high dose group (n = 9) on measures of symptomatology. There was a trending difference between group means for the positive factor ($t(14) = 1.4$, $p > .05$, $d = 0.7$). High caffeine users had more positive symptoms ($M = 8.3$, $SD = 3.6$) than moderate caffeine users ($M = 6.1$, $SD = 1.9$). No other differences were discovered. There were no outliers on any of the measures (defined as 3 times the interquartile range). See Appendix W.

An additional sensitivity analysis was conducted which excluded participants diagnosed with schizoaffective disorder (n = 3). The moderate dose group (n = 9) was compared to the high dose group (n = 7) on measures of symptomatology. No differences were discovered. There were no outliers on any of the measures (defined as 3 times the interquartile range). See Appendix X.

A final sensitivity was conducted comparing smokers (n = 8) to non-smokers (n = 11) on symptomatology. No differences were discovered. There were no outliers on any of the measures (defined as 3 times the interquartile range). See Appendix Y. None of the correlations between the FTND (or the number of cigarettes smoked per day) and symptomatology were significant. See Appendix Z.

3.4. Survey Data: Summary of Open-Ended Questions

Participants were first asked to describe the aspects of caffeine they like/enjoy. Participants described they liked/enjoyed caffeine because it helped them with wakefulness (n = 10; 53%), physical energy (n = 7; 37%), cognitive functioning (n = 7; 37%), mood (n = 5; 26%), feeling pleasure (hedonicity e.g., “the taste”; n = 5; 26%), sympathetic arousal (e.g., “the buzz”; n = 2; 11%), and reducing symptoms (n = 1; 5%). One participant described they did not like or enjoy any aspect of caffeine (5%), and two participants did not use caffeine (11%). See Table 5

for the codes and categories that are assigned to each participants response (including the frequency and percent of times a code/category was assigned for this particular question).

Participants were then asked to describe the aspects of caffeine they dislike/do not enjoy. Participants described they disliked/did not enjoy caffeine because of its sympathetic arousal (e.g., "I get agitated"; n = 4; 21%), physical distress (e.g., "makes me feel sick"; n = 4; 21%), sleep disturbance (n = 3; 16%), taste (n = 2; 11%), addictive potential (n = 2; 11%), cost (n = 1; 5%), and because they did not feel anything after caffeine intake (n = 1; 5%). Two participants reported there was nothing they disliked about caffeine (n = 2; 11%), and two participants did not use caffeine (11%). See Table 6 for the codes and categories that are assigned to each participants response (including the frequency and percent of times a code/category was assigned for this particular question).

Chapter 4

Discussion

The potential impact of caffeine on cognition in schizophrenia patients is poorly studied. In fact, there is only one published study that investigated the association between caffeine intake and cognition in schizophrenia patients (Núñez et al., 2015). In that study, caffeine intake was associated with better cognitive functioning in domains typically impaired in schizophrenia patients. This finding was restricted to male schizophrenia patients but not female schizophrenia patients (Núñez et al., 2015). The current study sought to expand on this line of research, but this time including a cognitive battery that is tailored for schizophrenia patients (i.e., Cogstate Battery; Pietrzak et al., 2009) and recording average daily caffeine intake in milligrams rather than cups.

When assessing the demographic data and illness-related data, the two caffeine groups differed on the FTND score and on antipsychotic dose (CPZE). The primary analysis assessing cognitive functioning discovered a difference between the two caffeine groups on a measure of executive function, and there was a trend toward better verbal learning and memory that did not reach statistical significance. In both of these findings, moderate caffeine users performed better than high caffeine users. The secondary analysis assessed symptomatology and discovered a difference between group means for the negative factor, in which the high caffeine group demonstrated fewer negative symptoms than the moderate caffeine group. Our additional secondary analysis assessing the role of caffeine for schizophrenia patients from their perspective found that the leading aspect of caffeine participants like/enjoy is that it helps with wakefulness while the leading aspects of caffeine that participants dislike/do not enjoy are that they feel sympathetic arousal (highness) and physical distress.

4.1. Demographic and Illness-Related Data.

With respect to illness-related variables, differences between the two caffeine groups were discovered for FTND score and for antipsychotic dose (CPZE). High caffeine users (>250 mg/day) were more dependent on nicotine than moderate caffeine users (≤250 mg/day). This is likely the case because of a metabolic interaction at CYP1A2, in which tobacco use leads to a quicker clearance of caffeine (Carrillo & Benitez, 2000). As a result, nicotine users (smokers) need to consume higher doses of caffeine to experience the same effects as non-smokers (Gurpegui et al., 2004). Since approximately 42% of the participants in this study were smokers, this may help explain the high rate of caffeine intake in our sample.

Additionally, high caffeine users (>250 mg/day) were prescribed higher doses of antipsychotics compared to moderate caffeine users (≤250 mg/day). Given that particular antipsychotics are metabolized by CYP1A2, and that caffeine is a substrate of this same enzyme, participants who use caffeine would theoretically have a higher plasma concentration of antipsychotics and would experience additional side-effects as a result (Carrillo & Benitez, 2000; Hägg et al., 2000; Vainer & Chouinard, 1994; de Leon, 2004). However, it is important to note that high caffeine users in this study were also highly dependent on nicotine. As a result, it is possible that high tobacco use leads to the quicker clearance of both caffeine and antipsychotics, which then requires a higher dosage of both caffeine and antipsychotics to experience the same effects (Carrillo & Benitez, 2000; Gurpegui et al., 2004; de Leon, 2004). Unfortunately, the interaction among nicotine, caffeine, and antipsychotics is complex and still not understood. Another hypothesis is that since high doses of antipsychotics are associated with additional side-effects (Salva et al., 2008), it is possible that patients who are prescribed higher doses are using

more caffeine to counteract additional side-effects such as sedation (Thompson et al., 2014; Miller, 2004).

In the sensitivity analysis that excluded patients in a chronic phase of illness (n = 4), group means remained different for caffeine intake, FTND, and antipsychotic dose (CPZE). That is, it appears phase of illness does not have a changing effect on these variables. While the sensitivity analysis that excluded non-caffeine users (n = 2) also found differences between group means on caffeine intake and the FTND, the antipsychotic dose (CPZE) became a non-significant trend. As for the sensitivity analyses excluding females (n = 3), while caffeine intake continued to be different between the two groups, FTND became a non-significant trend and antipsychotic dose (CPZE) became non-significant. Hence, it appears that the women (who were all in the moderate dose group) were the driving factor for the difference between group means, likely because the women were prescribed, on average, lower antipsychotic dosages than the men (61.9 mg vs. 325.4 mg, respectively). Another sensitivity analysis excluded participants diagnosed with schizoaffective disorder (n = 3), and group means remained different for caffeine intake and the FTND score, but the antipsychotic dose (CPZE) became a non-significant trend. It appears the participants diagnosed with schizoaffective disorder were driving the difference previously discovered between the two caffeine groups. However, this non-significant trend had a large effect size (d = 0.9), and hence it is possible a larger sample size would have resulted in a statistical difference. The final sensitivity analysis that compared smokers (n = 8) to non-smokers (n = 11) found that the mean scores for caffeine intake and antipsychotic dose (CPZE) were no longer different between the two caffeine groups. In other words, it appears smoking does not affect these variables.

4.2. Cognitive Functioning.

Our primary analysis of cognitive functioning discovered a between-group difference for a task measuring executive function. High caffeine users (>250 mg/day) performed worse (i.e., made more errors) on the GMLT than moderate caffeine users (≤250 mg/day). The effect size of this difference was considered large by conventional standards ($d > 0.80$; Cohen, 1988). This is consistent with the literature on healthy (non-psychiatric) controls which also describes a positive impact of caffeine on executive function (Soar, Chapman, Levan, Jansari, & Turner, 2016). However, given there was not a healthy (non-psychiatric) control group, it should not be interpreted that moderate caffeine users performed within a normal (healthy) range that is comparative to the general population, but rather that it appears high caffeine-using schizophrenia patients performed worse on a task of executive functioning than moderate caffeine-using schizophrenia patients.

A difference between group means was trending towards significant for a task measuring verbal learning and memory. Moderate caffeine users performed better (i.e., recalled more words) on the ISLT than high caffeine users. This discovery is inconsistent with previous literature assessing the impact of moderate caffeine intake on verbal memory (Warburton, Bersellini, & Sweeney, 2001). Although this finding was not significant ($p = .06$), the effect size of the difference is considered moderate ($d = 0.50$ to 0.80; Cohen, 1988), and hence it is possible that a larger sample size could have resulted in a statistical difference. Using the results of this analysis, a power estimation suggests that a sample size of 23 participants per caffeine group (N = 46) could have potentially resulted in a statistical difference ($p \leq .05$; University of British Columbia, n.d.).

No other differences in cognitive functioning were discovered between the two caffeine groups on measures of processing speed, attention/vigilance, visual learning and memory, and

working memory. This lack of differences is inconsistent with the one previous study that assessed the association between caffeine intake and cognitive functioning in schizophrenia patients (Núñez et al., 2015). In a regression analysis, Núñez and colleagues (2015) found caffeine intake was associated with better processing speed, working memory, visual memory, and semantic fluency in male schizophrenia patients. In other words, while Núñez et al. (2015) found higher caffeine intake was associated with better cognitive functioning, this current study found that moderate users demonstrated better cognitive functioning than high caffeine users-hence refuting this previous study. Moreover, while verbal memory was the only measure found to be non-significant in a regression analysis conducted by Núñez et al. 2015, this current study's measure of verbal memory was trending towards significant, and this outcome was in the opposite direction of the previous study, such that moderate caffeine users performed better than high caffeine users on our measure of verbal memory.

Although our results are inconsistent with the one previous study assessing the association between caffeine intake and cognition (Núñez et al., 2015), the literature assessing caffeine intake and cognition in healthy controls is not without controversy. While some research has discovered a positive impact of caffeine on cognitive functioning in healthy individuals (Pasman, Boessen, Donner, Clabbers, & Boorsma, 2017; Smit & Rogers, 2000; Smillie & Gokcen., 2010; Jarvis et al., 1993), others have discovered no impact (Núñez et al., 2015; Harvanko, Derbyshire, Schreiber, & Grant, 2015; Kyle, Fox, & Whalley, 2010; Ullrich et al., 2015; Kuhman, Joyner, & Bloomer, 2015), or perhaps a negative impact (Klaassen et al., 2013). The heterogeneity of these results may be due to the samples differing on important characteristics such as the lack of a standardized methodology in regard to the dose(s) administered, the research setting, and/or how to precisely and exhaustively collect information

on regular caffeine intake. It is also possible that a curvilinear relationship may underlie the association between cognition and caffeine in patients with psychotic disorders. Neither a linear regression (e.g., Núñez et al., 2015) nor a two-group design (e.g., current study) is able to uncover that type of association.

In a sensitivity analysis that excluded patients in a chronic phase of illness (n = 4), the GMLT (executive function) became a non-significant trend and the ISLT (verbal learning and memory) became significant. Since the GMLT had a large effect size (d = .80), it is possible a larger sample size could have resulted in a statistical difference between group means when only assessing participants in an early phase of illness. However, it is also possible that caffeine impacts schizophrenia patients in varying phases of illness differently. For instance, while Núñez et al. (2015) found higher caffeine intake was associated with better cognitive functioning in chronic phase schizophrenia patients, a sensitivity analysis in this current study, which excluded chronic phase patients, found moderate caffeine users (relative to high caffeine users) performed better on measures of verbal memory and executive function (latter finding was trending). No previous study has assessed the impact of caffeine on cognition by comparing early phase to chronic phase schizophrenia patients.

Moreover, when non-caffeine users were excluded (n = 2), the GMLT became a non-significant trend and the ISLT was no longer trending towards significant. However, because the GMLT had a large effect size (d = .80) and the ISLT had a moderate effect size (d = .60), it is possible a larger sample would have resulted in a difference between group means for both measures. Nevertheless, it appears that non-caffeine users in the moderate dose group were driving the difference and trending difference previously discovered. Hence, it is possible that

non-caffeine using schizophrenia patients have better cognitive functioning than both moderate and high caffeine using patients.

The most interesting finding was in the third sensitivity analysis which excluded females (n = 3), in which the group means were no longer different or trending on any of the cognitive measures. Since all three women were in the moderate dose group, it appears their scores were driving the difference between group means for the GMLT and the trending difference between group means for the ISLT, and that this difference does not emerge when comparing group means with only men with schizophrenia. This finding is in contrast to the one previous study by Núñez et al. (2015) who found caffeine was associated with better cognitive functioning in men with schizophrenia but not women.

Another sensitivity analysis excluded participants diagnosed with schizoaffective disorder (n = 3) and found that the task measuring executive function (GMLT) became a non-significant trend and the task measuring verbal learning and memory (ISLT) was no longer trending towards significant. Both of these findings suggest it was the participants diagnosed with schizoaffective disorder that were driving the differences previously discovered. That is, it is possible caffeine affects patients with schizophrenia and schizoaffective disorder differently. Unfortunately, there is no previous study that assessed the impact of caffeine on cognition by comparing patients with schizophrenia and schizoaffective disorder. On the other hand, the tasks measuring verbal memory and executive function had moderate and large effect sizes (d = 0.6 and d = 0.8, respectively), and hence it is possible a larger sample size would have resulted in a difference between group means.

The final sensitivity analysis compared smokers (n = 8) to non-smokers (n = 11) and found no differences between group means on any of the cognitive measures, which appears to

suggest smoking was not the driving factor for the original findings, despite the fact that high caffeine users were more dependent on nicotine than moderate caffeine users. The literature assessing the impact of nicotine on cognition in schizophrenia patients is mixed (Hickling et al., 2018; Iasevoli, Balletta, Gilardi, Glordano, & de Bartolomeis, 2013).

However, findings of no differences between group means in any of the sensitivity analyses conducted in this study should be interpreted with caution. That is, a sample that was already small (N = 19) was even smaller for all sensitivity analyses since participants had to be removed in order to conduct each analysis. This, in turn, made it more difficult to find differences between group means. Therefore, results from any of the sensitivity analysis that were conducted this study should be carefully interpreted- and it may be more helpful to observe effect sizes as they may be more informative than alpha.

4.3. Symptomatology.

Our secondary analysis compared symptomatology between the two caffeine groups using factors derived from the PANSS (Wallwork et al., 2012). There was a statistical difference between group means for the negative factor, and the effect size was considered large ($d > 0.80$; Cohen, 1988). High caffeine users (> 250 mg/day) had fewer negative symptoms than moderate caffeine users (≤ 250 mg). This finding was consistent with a priori predictions. Moreover, lower levels of negative symptoms in high caffeine users is consistent with a previous study that found fewer negative symptoms in schizophrenia patients after the acute administration of a high dose of caffeine (10 mg/kg; Lucas et al., 1990).

Many antipsychotics are dopamine D2 antagonists and hence are associated with exacerbations in negative symptoms and cognitive deficits (Li, Snyder, & Vanover, 2016). Caffeine consumption, on the other hand, is indirectly associated with neuronal activation (e.g.,

dopamine; Daly et al., 1999). As a result, it is possible that high caffeine-using participants had fewer negative symptoms because caffeine was reversing the dopamine D2 antagonism moreso than moderate caffeine-using participants. Interestingly, while high caffeine users demonstrated fewer negative symptoms than moderate caffeine users, moderate caffeine users demonstrated better cognitive performance on tasks measuring executive function and verbal learning and memory (trending). This appears to support the notion that cognitive deficits and negative symptoms are independent features of schizophrenia (Heaton et al., 2001).

However, in contrast to a priori hypotheses, no between-group differences were observed on positive symptoms. Nevertheless, the effect size for this finding was considered moderate (d = 0.50 to 0.80; Cohen, 1988), with high caffeine users demonstrating more positive symptoms than moderate caffeine users. This suggests a larger sample size could have discovered a difference between the two caffeine groups. This finding is inconsistent with previous literature which found a high acute dose of caffeine was associated with the onset of positive symptoms (Wang et al., 2015; Lucas et al., 1990). As the current study assessed the effects of chronic caffeine intake, the differences between these two findings are not unexpected.

No between group differences were observed on the cognitive factor as measured by the PANSS. This is inconsistent with previous literature that demonstrated a moderate correlation between the PANSS cognitive factor and neuropsychological measures (ranging from 0.20 to 0.64; Daban et al., 2002; Bozikas, Kosmidis, Kioperlidou, & Karavatos, 2004; Hofer et al., 2007). In other words, given this current study found moderate caffeine users performed better than high caffeine users on measures of executive function and verbal learning and memory (trending) it was expected that there would be a relationship between caffeine intake and cognitive deficits (measured by PANSS) as well. However, since the PANSS is subjective and is

a more general assessment of cognition than the Cogstate battery, it is possible that the PANSS cognitive factor is not as good a proxy of cognitive functioning as is the Cogstate battery.

In the sensitivity analysis that excluded participants in a chronic phase of illness (n = 4), the negative factor became a non-significant trend. Therefore, it is possible that participants who were in a chronic phase of illness were driving the difference previously discovered for negative symptoms. However, due to its large effect size (d = .80), it is possible a larger sample size would have resulted in a difference between group means. There is currently no previous study that assesses the impact of caffeine on symptomatology by comparing schizophrenia patients in an early versus chronic phase of illness. Further longitudinal research in this area might uncover some interesting trends with regards to caffeine use across the illness course.

The second sensitivity analysis excluded non-caffeine users from the analysis (n = 2), and the negative factor was no longer significant. It appears non-caffeine users were driving the difference between moderate and high caffeine users for the negative factor. On the other hand, the negative factor did have a moderate effect size (d = .60), and hence a larger sample size could have potentially resulted in a significant difference between group means.

The third sensitivity analysis excluded females (n = 3), and the negative factor became non-significant. Interestingly, when females were excluded from the analysis, the positive factor was trending towards significant (p = .09), such that higher caffeine users demonstrated more positive symptoms than moderate caffeine users. It appears that, in the original analysis that included women, it was the women (who were all in the moderate dose group) who were driving the mean positive factor score higher in the moderate caffeine group which led to a non-significant finding.

The fourth sensitivity analysis excluded participants diagnosed with schizoaffective disorder (n = 3) and the negative factor became non-significant. This appears to suggest it was participants diagnosed with schizoaffective disorder who were driving the difference between group means for the negative factor. There is no previous study that assesses the impact of caffeine on symptomatology by comparing patients with schizophrenia and schizoaffective disorder.

The final sensitivity analysis compared smokers (n = 8) to non-smokers (n = 11) on symptomatology and no differences in group means were discovered, which appears to suggest smoking on its own does not affect symptomatology. Literature assessing the impact of tobacco on symptomatology in schizophrenia patients in mixed (Iasevoli et al., 2013; Lucatch, Lowe, Clark, Kozak, & George, 2018).

4.4. Summary of The Open-Ended Survey Questions

An additional secondary analysis assessed the role of caffeine for schizophrenia patients from their perspective. To do this, participants were asked open-ended questions about the aspects of caffeine they like/enjoy and dislike/do not enjoy. Participants described liking/enjoying caffeine because it helps with wakefulness (53%), physical energy (37%), cognition (37%), mood (26%), feeling pleasure (hedonicity; 26%), sympathetic arousal (11%), and countering symptoms (5%). On the other hand, participants described disliking/not enjoying caffeine because of its sympathetic arousal (21%), physical distress (21%), sleep disturbance (16%), taste (11%), addictive potential (11%), and cost (5%).

Only one previous study qualitatively assessed the role of caffeine for schizophrenia patients (Thompson et al., 2014). In that study, thematic analysis found participants were using caffeine for its stimulating properties, to satisfy cravings, to help facilitate social interactions,

and to counteract sedative side-effects induced by antipsychotics (Thompson et al., 2014). The current study also found participants were using caffeine for its stimulating properties (e.g., wakefulness, 'the buzz'). Although no participant reported using caffeine to counteract sedation induced by their medication, one participant described liking/enjoying caffeine because it helps with their negative symptoms. Moreover, none of the participants in this current study reported using caffeine to help satisfy cravings or to help facilitate social interactions. The inconsistency between the one previous study (Thompson et al., 2014) and the current study could be due to the fact that the one previous study asked in-depth questions while this current study asked two open-ended questions with no follow-up.

It is also worth mentioning what appears to be a discrepancy between patients' individual beliefs about the role of caffeine and the findings of the current study. Thirty-seven percent of participants described liking/enjoying caffeine because it helped with their cognitive functioning (e.g., concentration). For instance, one participant from the high-caffeine using group is quoted saying *"... I feel like I can concentrate better when I drink coffee"*, while our assessments found high caffeine users actually performed worse on tasks measuring executive function and verbal learning and memory (trending). Moreover, no differences were discovered on measures of processing speed, attention/vigilance, working memory, and verbal learning and memory. Since the survey questions were not detailed, we are unable to determine which aspect of cognition patients believe caffeine benefits the most. For instance, while moderate caffeine users were found to perform better than high caffeine users on a task measuring executive function, it is possible that patients were using caffeine because they believed it helped with attention/vigilance, in which case we would have again concluded that there was a discrepancy

between the participants beliefs versus reality regarding the impact of caffeine on cognition. This notion should be further investigated using a more detailed questionnaire.

4.5. Limitations.

There were several limitations to this study that should be mentioned. This study had a small sample size (N = 19) which may help explain why many of the cognitive tasks, as well as the measure of positive symptoms, were not significant. For instance, using a regression analysis with 34 male schizophrenia patients, Núñez and colleagues (2015) found an association between caffeine intake and better cognitive performance on tasks measuring visual memory, working memory, semantic fluency, and processing speed. Moreover, given the moderate effect sizes for our measures of positive symptoms ($d = 0.5$) and verbal learning and memory ($d = 0.7$), it is possible a larger sample size would have resulted in significant differences between the two caffeine groups.

As this study was hypothesis-driven, less conservative alpha levels ($p < 0.05$, one-tailed) were justified. However, given the large number of analyses that were completed (6 analyses for cognition and 3 analyses for symptomatology), corrections for multiple comparisons might have been employed (e.g., Bonferroni corrections). Had we applied this conservative measure, none of the significant findings would have reached criterion for significance. That is, the GMLT and negative factor would not have been significant and the ISLT would not have been trending towards significant. A balance must be met between the risk of Type I errors (finding an effect when one does not exist) and Type II errors (not finding an effect when it does in fact exist). Larger sample sizes are needed to examine these results in greater detail.

Since the majority of the participants in this study were in an early phase of illness (n = 15), while only a small minority were in a chronic phase of illness (n = 4), it is possible that the

results of this study cannot be appropriately generalized to patients in a chronic phase of illness. For instance, in the sensitivity analysis that excluded patients in a chronic phase of illness (n = 4), our measures of executive function (GMLT) and negative symptoms (negative factor) both became a non-significant trend, which suggests the impact of caffeine may be different for patients in an early versus chronic phase of illness. Additionally, while the one previous study (Núñez et al., 2015) assessed the association between caffeine intake and cognitive functioning in chronic schizophrenia patients, this current study primarily assessed early phase schizophrenia patients (79%; n = 15), and this could help explain the discrepancy between our results. As a result, phase of illness could be an important variable in this line of research and should be considered in future research.

Moreover, since the majority of the participants in this study were diagnosed with schizophrenia (n = 16), while only a small minority were diagnosed with schizoaffective disorder (n = 3), it is possible that the results of this study cannot be appropriately generalized to patients diagnosed with schizoaffective disorder. For instance, in a sensitivity analysis that excluded participants diagnosed with schizoaffective disorder (n = 3), our measure of executive function (GMLT) and negative symptoms (negative factor) were no longer significant. Additionally, the one previous study that assessed the impact of caffeine on cognition used only patients diagnosed with schizophrenia (Núñez et al., 2015), and there is currently no literature assessing the impact of caffeine on cognition for schizoaffective patients. As a result, future research should consider comparing patients diagnosed with schizophrenia and schizoaffective disorder when assessing the impact of caffeine on cognition.

Another limitation is our reliance on the accuracy of patients' self-reported caffeine intake to classify them into groups. However, it is important to note that self-reported caffeine

consumption has been found to be a valid method of predicting actual caffeine intake (Addicott et al., 2009) and this method of recording chronic caffeine intake has a history in previous literature (Kyle et al., 2010; Harvanko et al., 2015). As a result of these findings, and the fact that it is also a practical method to implement, this method is likely the best method to ascertain caffeine usage in this clinical population.

Also, this study design does not lend itself to assigning causation since caffeine was not administered. Although a more stringent design that administers caffeine is sensible for studies assessing acute effects of caffeine (Kelemen & Creeley, 2001; Childs & de Wit, 2006; Ullrich et al., 2015), the goal of this study was to assess chronic (regular) caffeine intake, and hence it was appropriate to conduct a cross-sectional study.

Co-current cannabis, alcohol, and nicotine users were not excluded (or controlled for) and hence may have influenced the outcome of this study. These potential confounders may be important since cannabis has previously been found to affect cognitive functioning- although the direction of impact is mixed (Yücel et al., 2010; Løberg & Hugdahl, 2009). Moreover, this current study also did not measure whether the patients were in withdrawal from any drug (e.g., nicotine or cannabis withdrawal). This is a major limitation that affects drug research in general since the use of multiple drugs can affect the outcome of a study and makes it difficult to attribute or associate any findings to the specific drug of interest (Donoghue & Doody, 2012). However, since approximately 80% of schizophrenia patients use nicotine (Lohr & Flynn, 1992), 40% use cannabis (Rathbone, Variend, & Mehta, 2008), and 32% use alcohol (Uludag & Güleç, 2016), it was decided that it would have a significantly negative impact on recruitment if these participants were excluded. Nevertheless, it may be helpful to control these variables in future

research in order to assess for its potential impact on the association among caffeine intake, cognitive functioning, and symptomatology in schizophrenia patients.

Our statistical analysis also did not allow us to view a curvilinear relationship. In healthy (non-psychiatric) individuals, Kaplan et al. (1997) found that, compared to a placebo and 500 mg of caffeine, participants who consumed 250 mg of caffeine demonstrated better cognitive functioning and had more positive subjective effects. Therefore, it is important to categorize caffeine in a way that allows for the assessment of a curvilinear relationship (i.e., using three different groups rather than two). This approach would have also helped to suggest whether there is an optimal caffeine dose range for schizophrenia patients. Although it was our original intention to compare three different groups (rather than two), we were unable to do so due to a small sample size. It is possible that, as with healthy controls (Kaplan et al., 1997; McLellan et al., 2016), moderate doses of caffeine may have a positive impact on cognition while low doses (or a placebo) and high doses of caffeine do not. However, our sensitivity analyses, excluding participants who were non-caffeine users, suggest that the relationship may be more complicated in patients with psychotic disorders.

The author also could not assess for sex differences due to the small sample of women (n = 3). It has long been established that there are sex differences in schizophrenia patients with respect to illness onset, symptomatology, and treatment outcome (for a detailed review see Abel, Drake, & Goldstein, 2010). However, a sensitivity analysis that excluded females from analyses (n = 3; all of whom were in the moderate dose group) revealed many differences. For instance, the negative factor was no longer significant while the positive factor was trending towards significant when only men were included in the analyses. Additionally, group means were no longer different (or trending) for the GMLT and the ISLT, respectively. Moreover, the one

previous study that assessed the association between caffeine intake and cognition in schizophrenia patients (Núñez et al., 2015) discovered caffeine intake was associated with better cognitive functioning in male but not female schizophrenia patients. However, it should be noted that, when using the same dose of caffeine, women are found to be more affected than men, likely due to their reduced body weight (Carrillo & Benitez, 1996). In any case, it would have been informative to see if in our sample sex differences were apparent in the relationship between caffeine intake and cognitive functioning. Further research should attempt to examine this issue in greater detail.

4.6. Potential Strengths

Unlike the one previous study that assessed the association between caffeine intake and cognition in schizophrenia patients (Núñez et al., 2015), this current study used a neuropsychological battery that was tailored for the measurement of cognition in schizophrenia patients (Cogstate battery; Pietrzak et al., 2009). Moreover, unlike the previous study, the current study employed a more precise measurement of self-reported daily caffeine intake by estimating this information in milligrams rather than cups. Finally, unlike the one previous study, this study assessed for differences in symptomatology between the two caffeine groups using the PANSS. In order to gather the most accurate representation of symptomatology in schizophrenia patients, this current study used a specific factor structure (Wallwork et al., 2012).

The survey questions included in the caffeine questionnaire helps us better understand the potential motivations behind caffeine use. Given the high rate of caffeine intake in this population (Strassnig et al., 2006), this line of research is necessary. Only one previous study assessed the role of caffeine for schizophrenia patients (Thompson et al., 2014). Although this current study used only two survey questions, the information collected can be informative for

clinicians by helping them better understand the motivations behind the high rate of caffeine use in schizophrenia patients.

4.7. Future Directions

Future directions mentioned in this section are based primarily from the current study (for an analysis of future directions in general, please see Appendix A: Supplementary Table 3). First, researchers who intend to work with schizophrenia participants should plan accordingly (e.g., plan ahead of time). In this current study, 19 schizophrenia participants were recruited in 13 months (females = 3). Patients with schizophrenia are a challenging group to recruit. For instance, many patients do not have a cell phone and, as such, it can be difficult to contact them, while other patients may be prevented from participating due to their symptomatology, and in particular, paranoia. Despite having access to multiple resources, such as the NSEPP (QEII Hospital), recruitment remained a challenge.

Researchers should make an effort to assess the impact of caffeine on both male and female schizophrenia participants. The one previous study found a positive association between caffeine intake and cognitive functioning in male, but not female, schizophrenia patients (Núñez et al., 2015). In our study, we had only three female participants, all of whom were in the moderate caffeine dose group (0-250 mg/day), which meant we were unable to conduct this analysis. Future research should attempt to recruit as many females as possible to allow for the assessment of sex differences in cognitive functioning.

Qualitative research would be extremely helpful in this line of research. Only one previous study qualitatively assessed the role of caffeine for schizophrenia patients from their perspective (Thompson et al., 2014). Patients in that study reported using caffeine for positive reasons, such as to help facilitate social interactions and to counteract antipsychotic-induced

side-effects such as sedation (Thompson et al., 2014). In the current study, the survey component should have been more detailed. Future qualitative caffeine research should ask several in-depth questions concerning the role of caffeine from their perspective, including the opportunity for elaboration and explanation. Additional qualitative research needs to be conducted so that we can better understand the motivations behind the high rates of caffeine consumption in schizophrenia patients. More importantly, qualitative research can then be compared to experimental research to see if there is a discrepancy between their beliefs about caffeine and the actual impact.

Future caffeine research should focus on the impact of both chronic and acute caffeine intake on schizophrenia patients. Only one previous study assessed the association between caffeine intake and cognition in schizophrenia patients, and that study assessed chronic (regular) caffeine intake (Núñez et al., 2015). This current study also assessed the impact of regular caffeine intake on cognitive functioning. There are currently no published research articles that assess the impact of acute caffeine intake on cognitive functioning in schizophrenia patients. While assessing chronic caffeine intake informs clinicians about the potential impact of regular caffeine intake, it does not help clinicians understand the potential impact of caffeine intake for caffeine-naïve patients or the dose/response effects of acute caffeine administration.

It is also important for researchers to assess the impact of more than one caffeine dose. This current study divided participants into two caffeine groups (Group 1: 0-250 mg/day and Group 2: > 250 mg/day) based on findings from healthy (non-psychiatric) controls that suggest doses of up to ~250 mg can benefit cognition (McLellan et al., 2016; Kaplan et al., 1997) and that doses of up to ~200 mg can help with mood (Brice & Smith, 2001; Lara, 2010). However, future research should also consider assessing three caffeine groups. In healthy (non-psychiatric)

controls, Kaplan et al. (1997) found that while administering 250 mg of caffeine had positive effects on cognition and mood, a placebo and 500 mg of caffeine did not. Hence, it is possible there is an inverted-U relationship among caffeine intake, cognition, and mood (Kaplan et al., 1997). Moreover, the assessment of multiple doses will help determine if there is an optimal dosage for schizophrenia patients.

Caffeine titration is self-regulated and participants in this study may be attempting to regulate their negative symptoms with this substance. With our current study design, causation cannot be directly inferred. However, future research should continue to assess the impact of both chronic and acute caffeine intake on negative symptoms. As mentioned previously, current antipsychotic treatments are poor at targeting the enduring negative symptoms in psychotic disorders. It is possible that caffeine may be one way to reduce the burden of these symptoms.

Also, researchers should consider using imaging technologies when assessing the impact of caffeine on cognition in schizophrenia patients. It would be ideal to use imaging technology in conjunction with assessments of cognition and symptomatology. This way, after acute or chronic caffeine consumption, researchers can associate functional or neuroanatomical changes in the brain with changes in cognitive performance and symptomatology.

4.8. Conclusions

The present study assessed the potential impact of moderate versus high caffeine intake on cognitive functioning and symptomatology in schizophrenia outpatients. There was a statistical difference between group means for a task measuring executive function (GMLT), such that moderate caffeine users performed better than high caffeine users. Moreover, there was a trending difference between group means for a task measuring verbal learning and memory (ISLT), such that moderate caffeine users performed better than high caffeine users.

These discoveries partially support our first hypothesis (H_1) that moderate caffeine users would perform better on cognitive tasks than high caffeine users. No other differences in cognition were observed.

Assessing for differences in symptomatology between the two caffeine groups discovered a difference between group means for the negative factor. High caffeine-using participants had fewer negative symptoms than moderate caffeine-using participants, supporting our second hypothesis (H_2). There were no differences in the positive factor and cognitive factor. The third hypothesis (H_3) was not supported, in which we hypothesized that high caffeine-using participants would demonstrate more positive symptoms than moderate caffeine-using participants.

The open-ended survey questions were intended to assess the role of caffeine for schizophrenia patients from their perspective. Our results showed that participants liked/enjoyed caffeine because it helped with wakefulness, physical energy, cognition, mood, feeling pleasure (hedonicity), sympathetic arousal (highness), and to counter negative symptoms. Moreover, participants described disliking/not enjoying caffeine because of its sympathetic arousal (highness), physical distress, sleep disturbance, taste, addictive potential, cost, and because they do not feel anything.

Overall, schizophrenia patients should be transparent with the clinicians about any drugs they may be using, including caffeine, so as to avoid metabolic interactions that could negatively affect treatment outcome. By being forthcoming, medication dosages can be adjusted to maintain normal concentrations in the blood and to ensure the patient is receiving the most effective care. Moreover, results from this study suggest that schizophrenia patients who are experiencing difficulties with their cognitive functioning should be encouraged to drink little or

no caffeine. That is, while high caffeine-using patients appear to believe caffeine benefits their cognitive functioning, it was discovered that high-caffeine using patients performed worse than moderate-caffeine using patients on measures of executive function and verbal learning and memory (trending). The discrepancy between a patients' individual beliefs and the reality of how caffeine impacts them is something clinicians should bring to their attention. On the other hand, this study found that high caffeine users demonstrated fewer negative symptoms than moderate caffeine users. Therefore, it may be appropriate to encourage patients with enduring negative symptoms to drink higher doses of caffeine. As a result, it appears caffeine intake could be tailored differently for each patient, depending on their presenting symptoms.

Given that nearly all schizophrenia patients consume caffeine, it is important to conduct additional research on the impact of acute and chronic caffeine consumption for schizophrenia patients. This way, clinicians can be provided with the information necessary to decide when to encourage caffeine intake where it may be beneficial and when to discourage (or to limit) caffeine intake where it may be harmful to the patient.

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Table 1

Demographic and Illness-Related Data for All Participants.

	Patient
N	19
Age (years)	28.8 (8.4)
Sex (m/f)	16/3
Education (years)	13.9 (2.1)
Caffeine Intake (mg)*	315.5 (426.7)
FTND**	2.1 (2.9)
Antipsychotic Dose in mg (CPZE)***	283.8 (260.1)

Note: *mg: milligrams. **FTND**:** Fagerstrom Test for Nicotine Dependence. ***CPZE: Chlorpromazine Equivalence.

Table 2

Demographic and Illness-Related Data by Caffeine Group

	Moderate Dose (0-250 mg/day	High Dose (251 mg or more/day)	*P* value	Effect Size
# of Participants (m/f)*	10 (7/3)	9 (9/0)	.07	0.4
Age (years)	28.5 (9.5)	29.2 (7.5)	.86	0.1
Education (years)	13.6 (2.1)	14.2 (2.1)	.53	0.3
Caffeine Intake (mg**)	65.5 (68.3)	593.2 (489.3)	**.01**	1.5
FTND***	0.7 (1.5)	3.6 (3.4)	**.04**	1.1
Antipsychotic Dose (mg; CPZE****)	167.1 (178.3)	413.4 (283.7)	**.04**	1.0

Note: **Bold** means significant ($p \leq .05$). *Chi-squared analysis was used to analyze this data **mg: milligrams. ***FTND: Fagerstrom Test for Nicotine Dependence. **** CPZE: Chlorpromazine Equivalence.

Table 3

Performance on Cognitive Tasks per Caffeine Group

Cognitive Task[a]		Moderate Caffeine Intake (≤250 mg/day)	High Caffeine Intake (>250 mg/day)	*t*-value	*p*-value	Effect Size	Range of Scores
Detection Test	M (SD)	2.5 (0.1)[b]	2.5 (0.1)	0.8	.23	0.4	2.3 – 2.7 *
GMLT	M (SD)	47.6 (16.8)	68.7 (27.5)	2.0	.03[c]	0.9	32 – 114 *
Identification Test	M (SD)	2.7 (0.1)	2.7 (0.1)	0.9	.18	0.4	2.6 – 2.8 *
International Shopping List Test	M (SD)	24.6 (3.2)	21.6 (5.0)	1.6	.06[d]	0.7	15 – 33 **
One Back Test	M (SD)	1.4 (0.1)	1.3 (0.2)	1.0	.16	0.5	1.0 – 1.6 **
One Card Learning Test	M (SD)	0.9 (0.1)	0.9 (0.1)	0.2	.42	0.1	0.8 – 1.2 **

Note. * lower score means better performance ** higher score means better performance. [a]Detection Test measures processing speed, Groton Maze Learning Test (GMLT) measures executive function, Identification Test measures attention/vigilance, International Shopping List Test measures verbal learning and memory, One Back Test measures working memory, and the One Card Learning Test measures visual learning and memory. [b]Numbers are reported as raw scores. [c]$p \leq 0.05$, one-tailed. [d]Non-significant trend, one-tailed.

Table 4

Symptomatology per Caffeine Group

Factor		Moderate Caffeine Intake (≤250 mg/day)	High Caffeine Intake (>250 mg/day	*t*-value	*p*- value	Effect Size
Positive	M (SD)	6.7 (3.1)	8.3 (3.6)	1.1	.15	0.5
Negative	M (SD)	12.6 (4.7)	8.9 (4.4)	1.8	.05*	0.8
Cognitive	M (SD)	4.6 (2.5)	4.3 (1.8)	0.3	.40	0.1

Note. *$p \leq 0.05$, one-tailed.

Table 5

The Aspects of Caffeine That Participants Like/Enjoy

Respondent #	Responses	Codes	Code names	Statistics (frequency)	Percent (rounded)
1	I like the jitteriness, I like that it makes me wired. I also like the cognitive benefits- I feel more awake and alert, and it helps me concentrate.	6, 3, 1	Wakefulness = 1	10	53%
2	It makes me feel refreshed, alert, so it's like positive cognitive aspects. I have the negative symptom of not being able to get out of bed and so caffeine helps me get out of bed and helps me function.	4, 3, 8	Physical energy = 2	7	37%
3	Nothing.	9	Cognition = 3	7	37%
4	Makes me powerful- makes me stay awake, keeps me concentrated. If I don't drink it, I feel weak and tired- I can't concentrate on my job.	2, 1, 3	Mood = 4	5	26%
5	The taste, and it gives me energy- it wakes me up from my deep slumber.	5, 2, 1	Hedonicity = 5	5	26%
6	It gives me energy- it helps me mentally, physically, I feel motivated. I drink a cup of coffee and I feel ready to approach the day.	2, 3, 4	Sympathetic arousal = 6	2	11%
7	I like the warm drink, and it makes me feel more alert. I feel like I can concentrate better when I drink coffee. Makes me feel good.	5, 1, 3	No Caffeine = 7	2	11%
8	Drinks that have caffeine taste good. It may have good effects on my brain, but I can't really tell.	5	Counter Symptoms = 8	1	5%

Respondent #	Responses	Codes	Code names	Statistics (frequency)	Percent (rounded)
9	Increased energy and wakefulness. Also I feel it helps with creativity.	2, 1, 4	Nothing = 9	1	5%
10	No caffeine	7			
11	The buzz, the energy.	6, 2			
12	Wakes me up, helps me concentrate, helps my focus, keeps me sharp, and sometimes helps my mood.	1, 3, 4			
13	It gives me an energy boost.	2			
14	It makes me feel awake- especially if I feel sedated.	1			
15	I like the taste.	5			
16	It soothes my throat, nothing to do with caffeine. I guess it does help wake me up too.	5, 1			
17	It helps me with my workouts, it helps me function because I am addicted to it, and it helps me feel better and awake.	2, 4, 1			
18	I like that it helps with wakefulness and my focusing.	1, 3			
19	No caffeine	7			

Table 6

The Aspects of Caffeine That Participants Dislike/Do Not Enjoy.

Respondent #	Responses	Codes	Code names	Statistics (frequency)	Percent (rounded)
1	I do not like the taste of coffee.	5	Sympathetic arousal = 1	4	21%
2	If I have too much it makes me jittery- don't like that.	1	Physical distress = 2	4	21%
3	I don't feel anything, even after drinking a vente	7	Sleep disturbance = 3	3	16%
4	Too much of it is not good (and I drink a lot).	5	No caffeine = 4	2	11%
5	Drinking too much makes me feel sick	2	Taste = 5	2	11%
6	The fact that it is addicting	6	Addictive = 6	2	11%
7	If I drink too much it will keep me up at night. And it costs money, I rather get it for free.	3, 8	Feel nothing = 7	1	5%
8	Makes me jittery if I have too much.	1	Cost = 8	1	5%
9	Bothers my stomach.	2	Nothing = 9	2	11%
10	No caffeine	4			
11	Nothing	9			
12	Heart burn if I have too much and it sometimes makes me anxious	2			
13	It affects digestion, addiction.	2, 6			
14	When the buzz goes away and I feel more tired than I was before.	3			

Respondent #	Responses	Codes	Code names	Statistics (frequency)	Percent (rounded)
15	If I consume it too close to bed time, I can't sleep.	3			
16	Sometimes I get agitated	1			
17	None	9			
18	The jittery and shakiness of caffeine	1			
19	No caffeine	4			

Appendix A
Letter to The Editor, Submitted to Schizophrenia Research

Caffeine Effects and Schizophrenia: Is There a Need for More Research?

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Caffeine (1,3,7–trimethylxanthine) is the most widely used psychoactive substance in the world. Approximately 85% of the general population consumes caffeine, in one form or another, with an average daily intake of 165 mg (Mitchell et al., 2014). Most physically healthy individuals do not experience any significant distress nor any significant decrease in functioning from this level of caffeine intake (Mohanty et al., 2014). However, both Caffeine Intoxication and Caffeine Withdrawal are listed as disorders in the DSM-5 as there are specific criteria for each that can be identified (American Psychiatric Association, 2013).

Interestingly, Caffeine Use Disorder (CUD) is no longer a specified diagnosis as there was a lack of research that would support caffeine causing a use disorder as defined by DSM-5. CUD is now in the category of "Conditions for Further Study" in DSM-5 (Addicott, 2014). It has been argued that by not including caffeine as an addictive drug, there may be research opportunities to examine its potential beneficial effects (Addicott, 2014).

Caffeine consumption is significantly higher in individuals with schizophrenia compared to the general population (Strassnig et al., 2006), estimated at approximately 500 mg per day (3X that of the general population). Additionally, approximately one-third of the patients with schizophrenia have been reported to consume more than 550 mg per day (Mayo et al., 1993). Despite the high rates of caffeine use in schizophrenia, the reasons for this enhanced consumption have not been adequately investigated (Núñez et al., 2015).

The psychostimulant effects of caffeine are thought to underlie its widespread use. Several studies have assessed the impact of acute caffeine administration on the cognitive functioning of healthy individuals and the results are mixed (Supplementary Table 1). Research on the cognitive effects of regular caffeine consumption in healthy individuals is sparse, but also mixed (Supplementary Table 2). Methodology differences may explain these controversial results.

Strikingly, there are no studies assessing the effects of acute administration of caffeine on cognition of patients with schizophrenia; however, there is a single study reporting the cognitive effects of regular consumption of caffeine in these patients (Núñez et al., 2015). The dearth of studies is even more surprising considering that 1) there is a sizeable literature in the healthy population; 2) most, if not all, of the cognitive domains shown to be enhanced by acute or regular intake of caffeine in healthy people are impaired in patients with schizophrenia (Green et al., 2004); and 3) as stated above, patients with schizophrenia consume large doses of caffeine.

In the study by Núñez et al. (2015), the effects of regular caffeine consumption were assessed in 52 individuals with long term schizophrenia (M age = 47 years) using standardized neuropsychological testing. A regression analysis found that caffeine use was associated with better cognitive performance on tasks measuring semantic fluency, cognitive speed, working memory, and visual memory, however only for male and not female schizophrenia patients. No associations were found in healthy controls. Given there are currently no approved medications for cognitive symptoms in schizophrenia, do these findings warrant a closer look at caffeine as a pharmacological adjunctive therapy option?

A recent qualitative study assessed the role of caffeine for individuals with schizophrenia from their perspective (Thompson et al., 2014). Thematic analysis based on in-depth interviews with 20 patients found that, among other reasons, patients consumed caffeine as a countermeasure to medication-induced side-effects such as sedation. Other reasons included using caffeine for its stimulating properties, satisfying cravings, and helping to facilitate social interactions. The suggestion that caffeine can be used as an avenue to counter sedation is shared among some physicians (Miller, 2004).

In fact, the high rates of caffeine use in schizophrenia supports the self-medication hypothesis of Khantzian (1997); patients use substances because they are gaining some benefit from their use. However, it has also been previously suggested that schizophrenia patients overvalue the positive effects of drug use and devalue its negative effects (Krystal et al., 2006). To date, very little in-depth knowledge has been obtained regarding the positive and negative effects of caffeine in individuals with schizophrenia.

There are currently no approved medications for cognitive and negative symptoms in schizophrenia. Assessing the varying degrees of caffeine intake on cognition and negative symptoms, as well as antipsychotic induced side effects such as sedation, could lead to novel lines of research. That is, is it possible caffeine can function as an adjunct treatment for some schizophrenia patients? If this is possible, can we identify which patients are more likely to benefit from caffeine? Or which patients should avoid caffeine intake? There is a void in the literature which has left several questions unanswered. We propose several effective ways to conduct this line of research (Supplementary Table 3). The inability to homogenize results derived from previous research is a barrier in caffeine and cognitive research. These suggestions may be the first step to construct standardized guidelines that will facilitate and encourage research on the effects of caffeine.

Research investigating caffeine and schizophrenia have constructed a particular narrative: caffeine induces negative effects in schizophrenia patients – primarily by increasing psychotic-like symptoms (Wang, Woo, & Bahk, 2015; Lucas et al., 1990). However, literature assessing the effects of various caffeine doses on sedation as well as cognitive and negative symptoms has been minimal. Clinicians may not be fully cognizant of the effects that caffeine has on schizophrenia patients. It is possible for caffeine to exert positive effects on some patients and may potentially serve as an adjunct treatment for sedative side-effects as well as cognitive and negative symptoms. It is important for clinicians to be well-informed of these effects so as to not discourage caffeine use where it may be effective and/or so as to not encourage caffeine use where it may be ineffective. In conclusion, we need a better understanding of the role that caffeine serves in patients with schizophrenia.

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Conflict of interest
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Supplementary Material

Table 1: The impact of acute caffeine administration on the cognitive functioning of healthy individuals.

Author(s)	Country	Type of Study	Conditions	Total N	Cognitive Domains Assessed & Outcome
Kelemen et al. (2001)	U.S.A	Double-blind, placebo-controlled, between-subjects design	Experimental: 4 mg caffeine per kilogram of body weight mixed into an orange drink Placebo: orange drink mixed with flat tonic water	142	**Sustained Attention ↑ *** Learning and Memory - Free Recall ↔ - Cued Recall ↔ - Recognition ↔
Childs et al. (2006)	U.S.A	Double-blind, placebo-controlled, within-subjects design	Experimental: 50, 150, and 250 mg caffeine capsules Placebo: 0 mg caffeine capsule	102	**Sustained Attention ↑** Processing Speed ↔ **Working Memory ↓** Behavioural Inhibition ↔
Mackay et al. (2002)	U.K	Double-blind, placebo-controlled, between-subjects design	Experimental: 110-120 mg caffeine, 0.66 g/kg alcohol, or both. Placebo: Neither caffeine nor alcohol	64	Choice Reaction Time↔ **Processing Speed ↑**
Smit et al. (2000)	U.K	Double-blind, placebo-controlled, within-subjects design	Experimental: 12.5, 25, 50, and 100 mg caffeine Placebo: 0 mg caffeine	23	**Reaction Time ↑** **Working Memory ↑**
Smillie et al. (2010)	U.K	Double-blind, placebo-controlled, within-subjects design	Experimental: 200 mg caffeine tablet Placebo: 100 mg vitamin supplement tablet	59	**Working Memory ↑**
Liguori et al. (1999)	U.S.A	Double-blind, placebo-controlled, within-subjects design	Experimental: 2 and 4 mg/kg caffeine Placebo: 0 mg/kg caffeine	36	Processing Speed ↔

Haskell et al. (2005)	U.K	Double-blind, placebo-controlled, crossover design	Experimental: 75 and 150 mg caffeine Placebo: 0 mg caffeine	48	**Reaction Time ↑** Sustained Attention ↔ Processing Speed ↔
Kuhman et al. (2015)	U.S.A	Double-blind, placebo-controlled, crossover design	Experimental: 150 mg caffeine only, and both theacrine and 150 mg caffeine Placebo: 0 mg caffeine	20	Reaction Time ↔ Processing Speed ↔ Executive Function ↔
Ullrich et al. (2015)	Germany	Double-blind, placebo-controlled, within-subjects design	Experimental: 200 mg caffeine, and glucose Placebo: 2g of decaffeinated instance coffee powder	17	Logical Reasoning↔ Working Memory↔ Processing Speed↔ Verbal Memory↔ Sustained Attention↔
Klaassen et al. (2013)	Netherlands	Double-blind, placebo-controlled, crossover design	Experimental: 100 mg caffeine Placebo: < 3 mg decaffeinated caffeine	21	**Working Memory ↓**

Note: See Nehlig (2010) for a review.
*****Bold means significant ($p < .05$), ↑ means caffeine improved performance, ↓ means caffeine worsened performance, ↔ means caffeine had no effect on performance

Table 2: The impact of regular caffeine consumption on the cognitive functioning of healthy individuals.

Author(s)	Country	Type of Study	Caffeine Measurement	Total N	Cognitive Domains Assessed & Outcome
Jarvis (1993)	U.K	Cross-sectional	Self-reported (cups)	7414	**Reaction Time ↑ *** **Choice Reaction Time ↑** **Verbal Memory ↑** **Reasoning ↑**
Hameleers et al. (2000)	Netherlands	Longitudinal	Self-reported (cups)	1875	**Long-term memory ↑** **Reaction Time ↑** Short-term memory ↔ Processing speed ↔ Executive Function ↔ Attention ↔
Araújo et al. (2016)	Netherlands	Cross-sectional**	Self-reported (cups)	2914	**Processing Speed ↑** **Executive Function ↑** **Word Fluency ↑** Verbal Learning ↔ **Verbal Memory ↓**
Kyle et al. (2010)	U.K	Cross-sectional	Self-reported (mg)	351	Reasoning ↔ Processing Speed ↔ Constructional ability ↔ Verbal Memory ↔
Harvanko et al. (2015)	U.S.A	Cross-sectional	Self-reported (cups)	140	Decision-making ↔ Sustained Attention ↔ Response Inhibition ↔ Reaction Time ↔

Núñez et al. (2015)	Spain	Cross-sectional	Self-reported (cups)	61	Semantic Fluency ↔ Phonemic Fluency ↔ Processing Speed ↔ Motor Speed ↔ Working Memory ↔ Short-term Memory ↔ Visual Memory ↔ Verbal Memory ↔

Note: See Zhou et al. (2018) for a detailed analysis.

*****Bold means significant ($p < .05$), ↑ means better performance, ↓ means worse performance, ↔ means no difference was discovered

******Cross-sectional and longitudinal. No associations were discovered when cognition was analyzed longitudinally.

Table 3: Methodology Suggestions

Type of Research	Why is this important?
Randomized, Double-blind, Placebo-controlled	The effects of acute caffeine consumption on cognition and symptomatology should be studied under controlled designs – e.g., designs should be randomized, double-blind, placebo-controlled, and should account for confounding variables that are particularly relevant to schizophrenia, such as other substances intake (mainly tobacco and cannabis), body mass index, antipsychotic medication, age, sex, personality traits, and complexity of the tasks.
Cross-sectional or longitudinal	The effects of regular (chronic) caffeine consumption on schizophrenia patients should also be assessed. For instance, is it possible for schizophrenia patients with regular caffeine consumption to develop tolerance to the adverse effects of caffeine while continuing to benefit from its positive effects?
Qualitative	Assessing the role of caffeine in schizophrenia is warranted given this could generate knowledge about the reasons for their enhanced caffeine consumption. This can involve in-depth questions regarding their caffeine intake.
Neuroimaging	Neuroimaging should also be utilized to help better understand the brain effects of caffeine. Structural neuroimaging would allow us to explore the long-term neuroanatomical effects of regular caffeine intake and how these potential neuroanatomical changes are associated with clinical and cognitive variations, while functional neuroimaging would be suitable for looking at the effects of caffeine administration and relate them to the cognitive performance shown by the participants.
What to include	
Reliable and Validated Measures of Cognition and Symptomatology	This body of caffeine research should include reliable and validated measures of cognition (outlined by MATRICS; Green et al., 2004) and symptomatology (e.g., PANSS; Kay et al., 1987) for schizophrenia patients
More than one dose of caffeine	Comparing different doses of caffeine will generate an understanding about whether there is an inverted-U relationship between caffeine dose and symptomatology as well as cognitive performance in schizophrenia patients, and whether an 'optimal' caffeine dose can be defined based on patient variables. For example, some cognitive studies have reported different effects of caffeine intake as a function of age (Núñez et al., 2015), sex (Johnson-Kozlow et al., 2002; Núñez et al., 2015), personality traits (Smith, 2002; Smillie & Gökçen, 2010; Smith, 2013), and the complexity of the task (Smith, 2002; Smillie & Gökcen, 2010; Núñez et al., 2015).

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Appendix B
Demographics Questionnaire

1. Date of Birth (month / year) _____

How old are you? _____

2. What is your biological sex?
Female
Male
Other/Prefer not to say

3. What has your doctor told you that you are diagnosed with? _____

When did you receive this diagnosis? _____ (year); or age you were then _____

4. What medications are you on? How long have you been on these medications? Have there been any changes to these medications in the past 4 weeks?

_____

_____

_____

5. What is the highest level of education you have completed?
Elementary School _____ (grade)
Middle School _____ (grade)
High School _____ (grade)
Post-Secondary (e.g., College, University, Trade School)
Post-Graduate (Master's)
Doctoral degree
Other _____

6. What is your current employment status?
Part-time
Full-time
Unemployed
Casual (typical # hours per week in past month) _____
Self-Employed (typical # hours per week in past month) _____
Freelance (typical # hours per week in past week) _____
Other _____

7. What is your marital status?
Married / Common Law
Separated
Divorced
Never married
Other _____

8. What is your ethnicity? Select all that apply

Arab
Black
Chinese
Filipino
First Nations
Inuk
Japanese
Korean
Latin American
Metis
South Asian
Southeast Asian
West Asian
White
Unknown
Other _____

9. Are you or were you ever a smoker? Yes No
If "No" → Skip this question
If "Yes" → Fill out below
- How much do you smoke? _____ (# of cigarettes per day)
- Former smoker; when did you quit? _____ (year); _____ (cigarettes per day when smoking heaviest)
- Occasional smoker. How many cigarettes do you smoke a week, typically? _____
- In the process of quitting smoking. _____ (cigarettes per day or week)

RA name _____

Appendix C

Nicotine Questionnaire (Fagerstrom Test for Nicotine Dependence; Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991).

	PLEASE TICK (✓) ONE BOX FOR EACH QUESTION	
How soon after waking do you smoke your first cigarette?	Within 5 minutes 5-30 minutes 31-60 minutes	☐ 3 ☐ 2 ☐ 1
Do you find it difficult to refrain from smoking in places where it is forbidden? e.g. Church, Library, etc.	Yes No	☐ 1 ☐ 0
Which cigarette would you hate to give up?	The first in the morning Any other	☐ 1 ☐ 0
How many cigarettes a day do you smoke?	10 or less 11 – 20 21 – 30 31 or more	☐ 0 ☐ 1 ☐ 2 ☐ 3
Do you smoke more frequently in the morning?	Yes No	☐ 1 ☐ 0
Do you smoke even if you are sick in bed most of the day?	Yes No	☐ 1 ☐ 0
	Total Score	

SCORE		
	1- 2 = low dependence 3-4 = low to mod dependence	5 - 7= moderate dependence 8 + = high dependence

Appendix D
Cogstate Battery (Version 5: 2008)

Test	**Description**	**Domain**	**Outcome Measure**
Detection Test	As soon as the card flips over the participant must press "yes"	Processing Speed	Speed of performance (mean of the log10 transformed reaction times for correct responses)
Identification Test	As soon as the card flips over the participant must decide whether the card is red or not. If it is red the participant should press "yes".	Attention/ Vigilance	Speed of performance (mean of the log10 transformed reaction times for correct responses)
International Shopping List Test	The participant is read a shopping list and must remember and recall as many items from the list as possible	Verbal Learning and Memory	Total number of correct responses made in remembering the list on three consecutive trials at a single session
Groton Maze Learning Test	Find the hidden pathway	Executive Function	Total number of errors made in attempting to learn the same hidden pathway on five consecutive trials during a single session
One Back Test	The participant must decide whether the card is the same as the previous card. If so, press "yes"	Working Memory	Accuracy of performance (arcsine transformation of the square root of the proportion of correct responses
One Card Learning Test	A playing card is presented face up in the center of the screen and the participant must decide whether they have seen the card before in this test. If so, press "yes"	Visual Learning and Memory	Accuracy of performance (arcsine transformation of the square root of the proportion of correct responses

Appendix E
PANSS (Kay, Fiszbein, & Opler, 1987)

PANSS RATING FORM

		absent	minimal	mild	moderate	moderate severe	severe	extreme
P1	Delusions	1	2	3	4	5	6	7
P2	Conceptual disorganisation	1	2	3	4	5	6	7
P3	Hallucinatory behaviour	1	2	3	4	5	6	7
P4	Excitement	1	2	3	4	5	6	7
P5	Grandiosity	1	2	3	4	5	6	7
P6	Suspiciousness/persecution	1	2	3	4	5	6	7
P7	Hostility	1	2	3	4	5	6	7
N1	Blunted affect	1	2	3	4	5	6	7
N2	Emotional withdrawal	1	2	3	4	5	6	7
N3	Poor rapport	1	2	3	4	5	6	7
N4	Passive/apathetic social withdrawal	1	2	3	4	5	6	7
N5	Difficulty in abstract thinking	1	2	3	4	5	6	7
N6	Lack of spontaneity & flow of conversation	1	2	3	4	5	6	7
N7	Stereotyped thinking	1	2	3	4	5	6	7
G1	Somatic concern	1	2	3	4	5	6	7
G2	Anxiety	1	2	3	4	5	6	7
G3	Guilt feelings	1	2	3	4	5	6	7
G4	Tension	1	2	3	4	5	6	7
G5	Mannerisms & posturing	1	2	3	4	5	6	7
G6	Depression	1	2	3	4	5	6	7
G7	Motor retardation	1	2	3	4	5	6	7
G8	Uncooperativeness	1	2	3	4	5	6	7
G9	Unusual thought content	1	2	3	4	5	6	7
G10	Disorientation	1	2	3	4	5	6	7
G11	Poor attention	1	2	3	4	5	6	7
G12	Lack of judgement & insight	1	2	3	4	5	6	7
G13	Disturbance of volition	1	2	3	4	5	6	7
G14	Poor impulse control	1	2	3	4	5	6	7
G15	Preoccupation	1	2	3	4	5	6	7
G16	Active social avoidance	1	2	3	4	5	6	7

Red = Positive Factor, Blue = Negative Factor, Green = Cognitive Factor

Appendix F
Caffeine Questionnaire

<u>Question 1:</u> How much caffeine do you have per day, on average?
Please respond in milliliters, cups, or ounces.

_____ milliliters (ML) **OR** _____ Cups **OR** _____ Ounces (OZ)

Please list the **brand and size**: _____

<u>Question 2:</u> Over the Counter Medication Consumption

Please fill-in the following chart if you consume **over the counter medications that contain caffeine** on a regular basis; or within the past week. These can include Anacin, One-A-Day Energy, Excedrin, Excedrin Migraine, or others that are not listed.

Name of Medication	**Dosage Amount (**milligrams, milliliters, etc.)	**Consumption Frequency Per Week** (number of times)	**How Much Caffeine Does It Contain?** (Write "not sure" if you do not know this information)
1.			
2.			

<u>Question 3:</u> During which times of the day do you consume the <u>most</u> caffeine?
Please circle **<u>one</u>** of the following:

Morning *Afternoon* *Evening* *Equal Amounts*

<u>Question 4:</u> What are the aspects of caffeine that you like/enjoy and those you dislike/do not enjoy?

Likes / enjoy: _____

_____

Dislikes / do not enjoy: _____

_____

<u>Question 5:</u> During which times of the day do you typically wake up from sleep?
Please circle **<u>one</u>** of the following:

Morning *Afternoon* *Evening* *It is random*

<u>Question 6:</u> How many days can you go <u>without</u> having any caffeine?
Please circle **<u>one</u>** of the following:

0 Days 1 Day 2 Days 3 Days 4 Days 5 days >5 days

<u>Question 7:</u> Has your caffeine consumption changed <u>in any way</u> in the past 3 months? (Example: Have you increased or decreased your caffeine use in the past three months?) If YES, please explain how it has changed.

<u>Question 8:</u> Can you think of a reason why your caffeine consumption has changed in the past 3 months? Please mention any possible reasons here.

Appendix G
Screening Criteria

Screen date _____ **Phone / email: 1/ _____**

Name _____ **Phone / email: 2/ _____**

How old are you? _____ (must be aged 18-55 years old inclusive)

Are you diagnosed with schizophrenia? Yes No If 'no' → REJECT

Do you have any other diagnosis? Yes No

Has your medication or medication dose changed in the past one month? Yes No If "yes" → REJECT

Do you consume caffeine? Yes No

Have you used any drug in the past three months Yes No If "yes" → REJECT (caffeine, nicotine, alcohol, and cannabis are permitted)

Do you have any vision impairments? Yes No If 'yes' → REJECT; if corrective lenses not worn

Are you fluent in the English language? Yes No If 'No' → REJECT

Can we contact your physician? Yes No

What is the name & phone number of your physician? _____

Notes (if any)

Interviewer's initials _____

Date overall screening status was determined _____ (dd/mm/yyyy)

Appendix H
Informed Consent

Informed Consent Form Non-Interventional Study

STUDY TITLE:	The Effects of Caffeine on Schizophrenia: Symptom Assessment and Neuropsychological Testing
PRINCIPAL INVESTIGATOR:	Mehmet Topyurek Department of Psychiatry 5909 Veterans' Memorial Lane Halifax, Nova Scotia, B3H 2E2 mehmet@dal.ca (902) 473-1062
FUNDER:	**Dr. Kimberley Good**

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1. Introduction

You have been invited to take part in a research study. A research study is a way of gathering information on a treatment, procedure or medical device or to answer a question about something that is not well understood. Taking part in this study is voluntary. It is up to you to decide whether to be in the study or not. Before you decide, you need to understand what the study is for, what risks you might take and what benefits you might receive. This consent form explains the study.

The research team will tell you if there are any study timelines for making your decision.

Please ask the research team to clarify anything you do not understand or would like to know more about. Make sure all your questions are answered to your satisfaction before deciding whether to participate in this research study.

The researchers will:

- Discuss the study with you
- Answer your questions
- Be available during the study to deal with problems and answer questions

You are being asked to consider participating in this study because you are diagnosed with schizophrenia or schizoaffective and consume caffeinated products.

If you decide not to take part or if you leave the study early, your usual health care will not be affected.

2. Why Is This Study Being Conducted?

The aim of this study is to investigate whether differences in symptoms and thinking processes exist between schizophrenia patients who consume low, moderate, or high doses of caffeine. Schizophrenia patients currently use caffeine at high rates, yet there is currently little research on the effects of caffeine on symptoms and thinking processes in schizophrenia. Only one previous study has investigated the effects of caffeine on schizophrenia patients using thinking processes testing. This research will help better inform professionals on the effects of caffeine. Currently, the literature is divided: caffeine has been associated with the onset of psychosis, but recent literature suggests that caffeine may improve thinking processes for some patients. The data from the current study will help to examine these effects and inform health professionals who treat schizophrenia and/or schizoaffective patients.

3. How Long Will I Be In The Study?

Participants are expected to visit once for a maximum duration of 1.5 hours (90 minutes). At the end of their participation, patients will be asked to record their caffeine consumption on a daily basis for 7-days and return the document through mail once it is completed. The entire study is expected to take about 12 months and the results should be known in 16 months.

4. How Many People Will Take Part In This Study?

It is anticipated that 90 schizophrenic patients will participate in this study at the Abbie J. Lane Memorial Hospital in Halifax, Nova Scotia.

5. How Is The Study Being Done?

This study will include three different caffeine dosage groups; minimal caffeine (20-100 mg/day), moderate caffeine (101-250 mg/day), high caffeine (251 mg or more/day). Each participant will undergo screening and, if approved, will be asked to visit Abbie J. Lane Building once for approximately 1.5 hours (90 minutes). Participants will be instructed to consume their regular level of caffeinated beverages prior to visiting.

During the visit, you will undergo several questionnaires and assessments. These include, a questionnaire asking information about you (e.g., age, gender, etc.; 5 minutes), a caffeine questionnaire (5 minutes), a nicotine questionnaire (5 minutes), memory and thinking tests (using the Cogstate battery; 30 minutes), and psychiatric symptoms using the Positive and Negative Syndrome Scale (PANSS; 40 minutes). Following this aspect of the study, you will be asked to self-report your daily caffeine consumption for 7-days and to return the caffeine questionnaire by mail, once it is completed. You will be supplied with a pre-addressed and stamped envelope.

6. What Will Happen If I Take Part In This Study?

In order to participate in this study, you must fit the inclusionary criteria outlined in the screening procedure. You must be aged 18-55 years old (inclusive), diagnosed with schizophrenia or schizoaffective, must not have any other major psychiatric illness, must be on stable medication for four or more weeks, and must not have vision impairments (corrected to normal eyesight is fine), and must be fluent in the English language. In order to confirm your health status, or verify certain of your responses, we require your consent so we can contact your physician.

Next you will be expected to respond to a demographic questionnaire, asking about your background. These questions may ask your age, biological sex, psychiatric diagnosis, the medications you consume, level of education, employment status, marital status, ethnicity, and smoking status.

After this, you are required to undergo a caffeine questionnaire. There are two parts to the caffeine questionnaire. The first part requires you to respond to questions regarding your caffeine consumption, such as your likes and dislikes about caffeine. The second part requires you to record your caffeine consumption on a daily basis for 7-days and to return this recording by mail (envelope and postage will be provided).

You will also be asked to fill out a nicotine questionnaire, which investigates your level of nicotine consumption and dependence. The researcher will skip this section if you do not use nicotine.

Next the Cogstate Battery will be administered as a way to assess your thinking and memory function. The Cogstate battery is a well validated set of tests and has been extensively used in psychosis patients.

Finally, you will be asked to undergo the Positive and Negative Syndrome Scale (PANSS) interview. This scale assesses the level of psychotic symptoms.

Please notify the researcher if there are any changes in your health status or changes in your medication and/or medication dosage as this could affect the study data.

It is important that you tell the research team about any drugs or medicines you are taking or have been newly prescribed. You must also tell the research team about anything unusual that is happening with your health. This includes any medical problems that seem to be getting worse. If you have to see another doctor or have to go to a hospital, you should let the doctors know that you are in a research study. You should also tell your own doctor as quickly as possible that you are participating in a non-interventional study.

7. Are There Risks To The Study?

You may experience the following inconveniences;

- The time it takes to complete the study can take up to 1.5 hours (90-minutes) to do; but you may take breaks in between tasks if you want to.
- You may be required to to sit for up to 1.5 hours (90-minutes) as a result of the study.

Questionnaires: You may find the questions you receive during the course of the study upsetting or distressing. You may not like all of the questions that you will be asked. You do not have to answer those questions you find too distressing.

Breach of confidentiality: As with all research, there is a chance that confidentiality could be compromised; however, we are taking precautions to minimize this risk. Only the members of the research team, the Nova Scotia Health Authority (NSHA) or Health Canada, and their auditors have the right to see your study data. Your data will be kept under constant security, while it is being used, and while it is being stored, as per NSHA protocols. To minimize the risk of a privacy breach, you will be given a study specific code that masks your identity.

8. Are There Benefits Of Participating In This Study?

We cannot guarantee or promise that you will receive any benefits from this research. However, possible benefits include a better understanding of the effects of caffeine on the symptoms and thinking processes of schizophrenia or schizoaffective patients. This in turn may help clinicians properly address caffeine use by schizophrenia and schizoaffective patients. Your participation may or may not help other people with schizophrenia and schizoaffective in the future.

9. What Happens at the End of the Study?

It is anticipated that the results of this study will be published and or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that you cannot be identified.

You will have access to the results and will be provided a link once publication occurs. In order to provide you with a link, the researcher will ask you for an email as a way to communicate the results to you. It is your choice whether or not you would like to view the results of the research.

10. What Are My Responsibilities?

As a study participant you will be expected to:

- Follow the directions of the research team;
- Report all medications being taken or that you plan on taking;
- Report any changes in your health to the research team;
- Report any problems that you experience that you think might be related to participating in the study;
- Visit Abbie J. Lane Building once for an approximate 1.5-hour duration;
- Consume your regular level of caffeinated beverages prior to visiting;
- Respond to questionnaires and undergo thinking processes testing;
- Record your caffeine consumption for one-week and return the document by mail;

11. Can My Participation in this Study End Early?

Yes. If you chose to participate and later change your mind, you can say no and stop the research at any time. If you wish to withdraw your consent please inform the research team. If you choose to withdraw from this study, your decision will have no effect on your current or future medical treatment and healthcare.

Withdrawal of study participation cannot include withdrawal of personal data collected up until that point. Data collected up until the point of your withdrawal may be used in the study analysis. We will maintain confidentiality and all standards of care and ethics as they apply to your personal information.

Also, the NSHA Research Ethics Board and the principal investigator have the right to stop patient recruitment or cancel the study at any time.

Lastly, the principal investigator may decide to remove you from this study without your consent for any of the following reasons:

- You do not follow the directions of the research team;
- There is new information that shows that being in this study is not in your best interests;
- There is new information that renders you ineligible to participate in this study.

If you are withdrawn from this study, a member of the research team will discuss the reasons with you and plans, if needed, will be made for your continued care outside of the study.

There are no study procedures or tests that you will be asked to undergo after you withdraw from the research.

12. What About New Information?

You will be told about any other new information that might affect your health, welfare, or willingness to stay in the study and will be asked whether you wish to continue taking part in the study or not.

13. Will It Cost Me Anything?

<u>Compensation</u>

Participating in this study may result in added costs to you such as costs for parking, transportation, and lunch. You will receive a payment of $15.00 for your participation at the end of the study session. If you decide to leave the study, you will receive a prorated payment for participating in the study.

<u>Research Related Injury</u>

If you become ill or injured as a direct result of participating in this study, necessary medical treatment will be available at no additional cost to you. Your signature on this form only indicates that you have understood to your satisfaction the information regarding your participation in the study and agree to participate as a subject. In no way does this waive your legal rights nor release the principal investigator, the research staff, the study sponsor or involved institutions from their legal and professional responsibilities.

14. What About My Privacy and Confidentiality?

Every effort to protect your privacy will be made. However, complete privacy cannot be guaranteed. For example, the principal investigator may be required by law to allow access to research records.

If you decide to participate in this study, the research team will look at your personal health information and collect only the information they need for this study. "Personal health information" is health information about you that could identify you because it includes information such as your;

- Name,
- Address,
- Telephone number,
- Age or month/year of birth (MM/YY),
- Information from the study interviews and questionnaires;
- New and existing medical records, or
- The types, dates and results of various tests and procedures. >>

Access to Records

Other people may need to look at your personal health information to check that the information collected for the study is correct and to make sure the study followed the required laws and guidelines. These people might include:

- The Nova Scotia Health Authority Research Ethics Board (NSHA REB) and people working for or with the NSHA REB who oversee the ethical conduct of research studies within the Nova Scotia Health Authority.

Use of Your Study Information

Participant information will not be transferred to parties outside the Nova Scotia Health Authority.

The research team and the other people listed above will keep the information they see or receive about you confidential, to the extent permitted by applicable laws. Even though the risk of identifying you from the study data is very small, it can never be completely eliminated.

The research team will keep any personal health information about you in a secure and confidential location for 7 of years and then destroy it according to NSHA policy. Your personal health information will not be shared with others without your permission.

After your part in the study ends, we may continue to review your health records for safety and data accuracy until the study is finished or you withdraw your consent.

You have the right to be informed of the results of this study once the entire study is complete.

The REB and people working for or with the REB may also contact you personally for quality assurance purposes.

Your access to records

You have the right to access, review, and request changes to your study data.

15. Declaration of Financial Interest

Dr. Kimberley Good's General Research Account will fund this study and pay for expenses. The amount of payment is sufficient to cover only the costs of conducting the study.

The Principal Investigator has no vested financial interest in conducting the study.

16. What About Questions or Problems?

For further information about the study you may call the principal investigator, who is the person in charge of this study and/or the supervisory investigator listed below.

The principal investigator is Mehmet Topyurek
Telephone: (902) 473-1062.

The supervisor investigator is Dr. Kimberley Good
Telephone: (902) 473-4250

17. What Are My Rights?

You have the right to all information that could help you make a decision about participating in this study. You also have the right to ask questions about this study and your rights as a research participant, and to have them answered to your satisfaction before you make any decision. You also have the right to ask questions and to receive answers throughout this study.

If you have any questions about your rights as a research participant, contact Patient Relations at (902) 473-2133 or healthcareexperience@nshealth.ca

In the next part you will be asked if you agree (consent) to join this study. If the answer is “yes”, please sign the form.

18. Consent Form Signature Page

I have reviewed all of the information in this consent form related to the study called:

The Effects of Caffeine on Schizophrenia: Symptom Assessment and Neuropsychological Testing

I have been given the opportunity to discuss this study. All of my questions have been answered to my satisfaction.

I authorize access to my personal health information, and research study data as explained in this form.

This signature on this consent form means that I agree to take part in this study. I understand that I am free to withdraw at any time without affecting my future care.

_____	_____	_____ /	_____ /	____
Signature of Participant	Name (Printed)	Year	Month	Day*
_____	_____	_____ /	_____ /	____
Signature of Person Conducting Consent Discussion	Name (Printed)	Year	Month	Day*
_____	_____	_____ /	_____ /	____
Signature of Investigator	Name (Printed)	Year	Month	Day*

I will be given a signed copy of this consent form.

Appendix I
Sensitivity Analysis Excluding Patients in a Chronic Phase of Illness: Demographic and Illness-Related Data

Sensitivity Analysis Excluding Patients in a Chronic Phase of Illness: Demographic and Illness-Related Data

	Moderate Dose (0-250 mg/day	High Dose (251 mg or more/day)	*P* value	Effect Size
# of Participants (m/f)*	8 (6/2)	7 (7/0)	.16	0.1
Age (years)	27.9 (10.3)	27.7 (7.5)	.97	0.2
Education (years)	13.0 (1.9)	13.7 (2.1)	.50	0.3
Caffeine Intake (mg**)	53.7 (53.1)	456.7 (164.9)	**.00**	3.3
FTND***	0.9 (1.6)	4.4 (3.3)	**.02**	1.3
Antipsychotic Dose (mg; CPZE****)	121.1 (93.0)	371.3 (251.6)	**.04**	1.3

Note: **Bold** means significant ($p \leq .05$). *Chi-squared analysis was used to analyze this data **mg: milligrams. ***FTND: Fagerstrom Test for Nicotine Dependence. **** CPZE: Chlorpromazine Equivalence.

Appendix J

Sensitivity Analysis Excluding Non-Caffeine Users: Demographic and Illness-Related Data

Sensitivity Analysis Excluding Non-Caffeine Users: Demographic and Illness-Related Data

	Moderate Dose (0-250 mg/day	High Dose (251 mg or more/day)	*P* value	Effect Size
# of Participants (m/f)*	8 (6/2)	9 (9/0)	.11	0.1
Age (years)	26.4 (5.9)	29.2 (7.5)	.40	0.4
Education (years)	13.5 (2.1)	14.2 (2.1)	.49	0.3
Caffeine Intake (mg**)	81.8 (66.8)	593.2 (489.3)	**.01**	1.5
FTND***	0.4 (1.1)	3.6 (3.4)	**.02**	1.3
Antipsychotic Dose (mg; CPZE****)	208.9 (175.81)	413.4 (283.7)	.09[a]	0.9

Note: **Bold** means significant ($p \leq .05$). [a]Non-significant trend. *Chi-squared analysis was used to analyze this data **mg: milligrams. ***FTND: Fagerstrom Test for Nicotine Dependence. **** CPZE: Chlorpromazine Equivalence.

Appendix K

Sensitivity Analysis Excluding Females: Demographic and Illness-Related Data

Sensitivity Analysis Excluding Females: Demographic and Illness-Related Data

	Moderate Dose (0-250 mg/day	High Dose (251 mg or more/day)	*P* value	Effect Size
# of Participants (m/f)	7 (7/0)	9 (9/0)		
Age (years)	24.7 (5.2)	29.2 (7.5)	.19	0.7
Education (years)	13.1 (1.9)	14.2 (2.1)	.31	0.5
Caffeine Intake (mg**)	88.4 (70.1)	593.2 (489.3)	**.02**	1.4
FTND***	1.0 (1.7)	3.6 (3.4)	.07*	0.9
Antipsychotic Dose (mg; CPZE****)	212.2 (197.0)	413.4 (283.7)	.13	0.8

Note: **Bold** means significant ($p \leq .05$). *Non-significant trend **mg: milligrams. ***FTND: Fagerstrom Test for Nicotine Dependence. **** CPZE: Chlorpromazine Equivalence.

Appendix L

Sensitivity Analysis Excluding Participants Diagnosed with Schizoaffective Disorder: Demographic and Illness-Related Data

Sensitivity Analysis Excluding Participants Diagnosed with Schizoaffective Disorder: Demographic and Illness-Related Data

	Moderate Dose (0-250 mg/day	High Dose (251 mg or more/day)	*P* value	Effect Size
# of Participants (m/f)*	9 (7/2)	7 (7/0)	.18	0.1
Age (years)	26.0 (5.6)	28.0 (7.5)	.55	0.3
Education (years)	13.3 (2.0)	13.7 (2.1)	.72	0.2
Caffeine Intake (mg**)	72.7 (68.2)	448.4 (171.6)	**.00**	2.9
FTND***	0.8 (1.6)	4.6 (3.1)	**.01**	1.5
Antipsychotic Dose (mg; CPZE****)	185.7 (178.6)	384.9 (239.5)	.08[a]	0.9

Note: **Bold** means significant ($p \leq .05$). [a]Non-significant trend. *Chi-squared analysis was used to analyze this data **mg: milligrams. ***FTND: Fagerstrom Test for Nicotine Dependence. **** CPZE: Chlorpromazine Equivalence.

Appendix M

Sensitivity Analysis Comparing Smokers to Non-Smokers: Demographic and Illness-Related Data

Sensitivity Analysis Comparing Smokers to Non-Smokers: Demographic and Illness-Related Data

	Smoker	Non-Smoker	*P* value	Effect Size
# of Participants (m/f)*	8 8/0)	11 (8/3)	.11	0.1
Age (years)	27.4 (7.2)	29.9 (9.3)	.53	0.3
Education (years)	13.5 (2.1)	14.2 (2.1)	.49	0.3
Caffeine Intake (mg**)	355.4 (258.1)	286.4 (528.1)	.74	0.2
FTND***	4.9 (2.4)	0.0 (0.0)	**.00**[a]	2.9
Antipsychotic Dose (mg; CPZE****)	270.4 (235.4)	293.5 (287.6)	.86	0.1

Note: **Bold** means significant ($p \leq .05$). [a]Significant at $p < .001$. *Chi-squared analysis was used to analyze this data **mg: milligrams. ***FTND: Fagerstrom Test for Nicotine Dependence. **** CPZE: Chlorpromazine Equivalence

Appendix N
Correlations Among FTND and Demographic and Illness-Related Variables.

Correlations Among FTND and Demographic and Illness-Related Variables

	Sex	Age (years)	Education (years)	Caffeine Intake (mg**)	Antipsychotic Dose (mg; CPZE***)
FTND*	-.32	-.02	-.24	.12	.03
# of Cigarettes Per Day	-.26	.06	-.07	.14	.07

Note: **Bold** means significant ($p \leq .05$). *FTND: Fagerstrom Test for Nicotine Dependence. ** mg: milligrams. *** CPZE: Chlorpromazine Equivalence

Appendix O

Sensitivity Analysis Excluding Patients in a Chronic Phase of Illness: Performance on Cognitive Tasks

Sensitivity Analysis Excluding Patients in a Chronic Phase of Illness: Performance on Cognitive Tasks

Cognitive Task[a]		Moderate Caffeine Intake (≤250 mg/day)	High Caffeine Intake (>250 mg/day)	*t*-value	*p*-value	Effect Size	Range of Scores
Detection Test	M (SD)	2.5 (0.1)[b]	2.5 (0.1)	0.6	.30	0.4	2.3 – 2.6 *
GMLT	M (SD)	49.9 (18.1)	68.7 (28.4)	1.6	.07[c]	0.8	32 – 114 *
Identification Test	M (SD)	2.7 (0.1)	2.7 (0.1)	0.7	.26	0.4	2.6 – 2.8 *
International Shopping List Test	M (SD)	25.0 (3.3)	20.0 (3.0)	3.1	.01[d]	1.6	15 – 30 **
One Back Test	M (SD)	1.4 (0.1)	1.3 (0.2)	1.3	.10	0.7	1.0 – 1.6 **
One Card Learning Test	M (SD)	0.9 (0.1)	0.9 (0.1)	0.1	.45	0.1	0.8 – 1.2 **

Note. * lower score means better performance ** higher score means better performance. [a]Detection Test measures processing speed, Groton Maze Learning Test (GMLT) measures executive function, Identification Test measures attention/vigilance, International Shopping List Test measures verbal learning and memory, One Back Test measures working memory, and the One Card Learning Test measures visual learning and memory. [b]Numbers are reported as raw scores. [c]Non-significant trend, one-tailed. [d]$p < 0.05$, one-tailed.

Appendix P
Sensitivity Analysis Excluding Non-Caffeine Users: Performance on Cognitive Tasks

Sensitivity Analysis Excluding Non-Caffeine Users: Performance on Cognitive Tasks

Cognitive Task[a]		Moderate Caffeine Intake (≤250 mg/day)	High Caffeine Intake (>250 mg/day)	*t*-value	*p*-value	Effect Size	Range of Scores
Detection Test	M (SD)	2.5 (0.1)[b]	2.5 (0.1)	0.5	.32	0.2	2.3 – 2.7 *
GMLT	M (SD)	50.0 (17.9)	68.7 (27.5)	1.6	.06[c]	0.8	32 – 114 *
Identification Test	M (SD)	2.7 (0.1)	2.7 (0.1)	0.9	.19	0.4	2.6 – 2.8 *
International Shopping List Test	M (SD)	24.1 (3.3)	21.6 (5.0)	1.2	.12	0.6	15 – 33 **
One Back Test	M (SD)	1.4 (0.1)	1.3 (0.2)	1.3	.11	0.6	1.0 – 1.6 **
One Card Learning Test	M (SD)	0.9 (0.1)	0.9 (0.1)	0.0	.49	0.0	0.8 – 1.2 **

Note. * lower score means better performance ** higher score means better performance. [a]Detection Test measures processing speed, Groton Maze Learning Test (GMLT) measures executive function, Identification Test measures attention/vigilance, International Shopping List Test measures verbal learning and memory, One Back Test measures working memory, and the One Card Learning Test measures visual learning and memory. [b]Numbers are reported as raw scores. [c]Non-significant trend, one-tailed.

Appendix Q
Sensitivity Analysis Excluding Females: Performance on Cognitive Tasks

Sensitivity Analysis Excluding Females: Performance on Cognitive Tasks

Cognitive Task[a]		Moderate Caffeine Intake (≤250 mg/day)	High Caffeine Intake (>250 mg/day)	*t*-value	*p*-value	Effect Size	Range of Scores
Detection Test	M (SD)	2.5 (0.1)[b]	2.5 (0.1)	0.2	.41	0.1	2.3 – 2.7 *
GMLT	M (SD)	52.4 (17.9)	68.7 (27.5)	1.4	.10	0.7	32 – 114 *
Identification Test	M (SD)	2.7 (0.1)	2.7 (0.1)	0.4	.36	0.2	2.6 – 2.8 *
International Shopping List Test	M (SD)	24.1 (3.6)	21.6 (5.0)	1.2	.13	0.6	15 – 33 **
One Back Test	M (SD)	1.4 (0.1)	1.3 (0.2)	0.8	.23	0.4	1.0 – 1.6 **
One Card Learning Test	M (SD)	1.0 (0.1)	0.9 (0.1)	0.2	.34	0.2	0.8 – 1.2 **

Note. * lower score means better performance ** higher score means better performance. [a]Detection Test measures processing speed, Groton Maze Learning Test (GMLT) measures executive function, Identification Test measures attention/vigilance, International Shopping List Test measures verbal learning and memory, One Back Test measures working memory, and the One Card Learning Test measures visual learning and memory. [b]Numbers are reported as raw scores.

Appendix R
Sensitivity Analysis Excluding Participants Diagnosed with Schizoaffective Disorder: Performance on Cognitive Tasks

Sensitivity Analysis Excluding Participants Diagnosed with Schizoaffective Disorder: Performance on Cognitive Tasks

Cognitive Task[a]		Moderate Caffeine Intake (≤250 mg/day)	High Caffeine Intake (>250 mg/day)	*t*-value	*p*-value	Effect Size	Range of Scores
Detection Test	M (SD)	2.5 (0.1)[b]	2.5 (0.1)	0.7	.24	0.4	2.3 – 2.7 *
GMLT	M (SD)	48.1 (17.7)	67.0 (29.6)	1.6	.07[c]	0.8	32 – 114 *
Identification Test	M (SD)	2.7 (0.1)	2.7 (0.1)	0.9	.19	0.4	2.6 – 2.8 *
International Shopping List Test	M (SD)	24.2 (3.1)	21.6 (5.8)	1.2	.13	0.6	15 – 33 **
One Back Test	M (SD)	1.4 (0.1)	1.3 (0.2)	0.8	.21	0.4	1.0 – 1.6 **
One Card Learning Test	M (SD)	1.0 (0.1)	1.0 (0.1)	0.2	.44	0.1	0.8 – 1.2 **

Note. * lower score means better performance ** higher score means better performance. [a]Detection Test measures processing speed, Groton Maze Learning Test (GMLT) measures executive function, Identification Test measures attention/vigilance, International Shopping List Test measures verbal learning and memory, One Back Test measures working memory, and the One Card Learning Test measures visual learning and memory. [b]Numbers are reported as raw scores. [c]Non-significant trend, one-tailed.

Appendix S
Sensitivity Analysis Comparing Smokers to Non-Smokers: Performance on Cognitive Tasks

Sensitivity Analysis Comparing Smokers to Non-Smokers: Performance on Cognitive Tasks

Cognitive Task[a]		Smokers	Non-Smokers	*t*-value	*p*-value	Effect Size	Range of Scores
Detection Test	M (SD)	2.5 (0.1)[b]	2.5 (0.1)	1.15	.13	0.5	2.3 – 2.7 *
GMLT	M (SD)	63.4 (29.6)	53.4 (20.2)	0.9	.19	0.4	32 – 114 *
Identification Test	M (SD)	2.7 (0.1)	2.7 (0.1)	1.1	.15	0.5	2.6 – 2.8 *
International Shopping List Test	M (SD)	22.8 (6.2)	23.5 (2.6)	0.3	.38	0.1	15 – 33 **
One Back Test	M (SD)	1.3 (0.2)	1.4 (0.1)	0.9	.17	0.4	1.0 – 1.6 **
One Card Learning Test	M (SD)	1.0 (0.1)	0.9 (0.1)	0.8	.22	0.4	0.8 – 1.2 **

Note. * lower score means better performance ** higher score means better performance.
[a]Detection Test measures processing speed, Groton Maze Learning Test (GMLT) measures executive function, Identification Test measures attention/vigilance, International Shopping List Test measures verbal learning and memory, One Back Test measures working memory, and the One Card Learning Test measures visual learning and memory. [b]Numbers are reported as raw scores.

Appendix T
Correlations Between FTND and Number of Cigarettes Per Day and Performance on Cognitive Tasks

Correlations Between FTND and Number of Cigarettes Per Day and Performance on Cognitive Tasks

	Detection Test	Identification Test	One Card Learning Test	One Back Test	ISLT**	GMLT***
FTND*	-.14	-.20	.04	-.34	.19	.16
# of Cigarettes Per Day	-.11	-.28	-.01	-.17	-.32	.33

Note: **Bold** means significant ($p \leq .05$). *FTND: Fagerstrom Test for Nicotine Dependence. **International Shopping List Test. *** Groton Maze Learning Test.

Appendix U

Sensitivity Analysis Excluding Patients in a Chronic Phase of Illness: Symptomatology

Sensitivity Analysis Excluding Patients in a Chronic Phase of Illness: Symptomatology

Factor		Moderate Caffeine Intake (≤250 mg/day)	High Caffeine Intake (>250 mg/day	*t*-value	*p*- value	Effect Size
Positive	M (SD)	6.5 (3.4)	7.7 (2.9)	0.5	.24	0.4
Negative	M (SD)	13.5 (4.7)	9.7 (4.7)	1.6	.07*	0.8
Cognitive	M (SD)	5.0 (2.7)	4.4 (1.9)	0.7	.33	0.3

Note. *non-significant trend, one-tailed.

Appendix V
Sensitivity Analysis Excluding Non-Caffeine Users: Symptomatology

Sensitivity Analysis Excluding Non-Caffeine Users: Symptomatology

Factor		Moderate Caffeine Intake (≤250 mg/day)	High Caffeine Intake (>250 mg/day	*t*-value	*p*- value	Effect Size
Positive	M (SD)	7.3 (3.2)	8.3 (3.6)	0.6	.26	0.3
Negative	M (SD)	11.4 (4.4)	8.8 (4.4)	1.2	.13	0.6
Cognitive	M (SD)	4.1 (1.8)	4.3 (1.8)	0.2	.41	0.1

Appendix W
Sensitivity Analysis Excluding Females: Symptomatology

Sensitivity Analysis Excluding Females: Symptomatology

Factor		Moderate Caffeine Intake (≤250 mg/day)	High Caffeine Intake (>250 mg/day	*t*-value	*p*- value	Effect Size
Positive	M (SD)	6.1 (1.9)	8.3 (3.6)	1.4	.09 *	0.7
Negative	M (SD)	11.9 (5.1)	8.9 (4.4)	1.3	.12	0.6
Cognitive	M (SD)	5.0 (2.9)	4.3 (1.8)	0.6	.29	0.3

Note. * non-significant trend, one-tailed.

Appendix X
Sensitivity Analysis Excluding Participants Diagnosed with Schizoaffective Disorder: Symptomatology

Sensitivity Analysis Excluding Participants Diagnosed with Schizoaffective Disorder: Symptomatology

Factor		Moderate Caffeine Intake (≤250 mg/day)	High Caffeine Intake (>250 mg/day	*t*-value	*p*- value	Effect Size
Positive	M (SD)	7.0 (3.1)	7.0 (2.6)	0.0	.50	0.0
Negative	M (SD)	11.9 (4.4)	9.4 (4.9)	1.1	.15	0.5
Cognitive	M (SD)	4.8 (2.6)	4.4 (1.9)	.30	.39	0.2

Appendix Y
Sensitivity Analysis Comparing Smokers to Non-Smokers: Symptomatology

Sensitivity Analysis Comparing Smokers to Non-Smokers: Symptomatology

Factor		Smokers	Non-Smokers	*t*-value	*p*- value	Effect Size
Positive	M (SD)	6.8 (2.5)	8.0 (3.9)	0.8	.22	0.4
Negative	M (SD)	10.6 (5.2)	11 (4.8)	0.2	.44	0.1
Cognitive	M (SD)	5.1 (2.7)	4.0 (1.6)	1.1	.14	0.5

Appendix Z

Correlations Between FTND and Number of Cigarettes Per Day and Symptomatology

Correlations Between FTND and Number of Cigarettes Per Day and Symptomatology

	Cognitive Factor	Negative Factor	Positive Factor
FTND*	.23	-.03	-.09
# of Cigarettes Per Day	.04	-.06	-.04

Note: **Bold** means significant ($p \leq .05$). *FTND: Fagerstrom Test for Nicotine Dependence.