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Regular Caffeine Intake in Patients with Schizophrenia: Cognition and Symptomatology

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Abstract

Individuals with schizophrenia use more caffeine than the general population. This study investigated the impact of caffeine on cognition and symptomatology in individuals with schizophrenia. A cross-sectional study was undertaken with 27 outpatients diagnosed with either schizophrenia or schizoaffective disorder. Participants were divided into two caffeine groups: moderate caffeine users (≤ 250 mg/day; N=13) and high caffeine users (>250 mg/day; N=14). Participants were then compared on measures of cognitive functioning, including processing speed, executive function, working memory, sustained attention, visual learning and memory, and verbal learning and memory. Symptomatology was also compared between the two caffeine groups, including positive, negative, and cognitive symptoms. The results showed that moderate caffeine users, compared to high caffeine users, demonstrated better performance on a task measuring executive function. While high caffeine users had fewer negative symptoms, they had more positive symptoms than moderate caffeine users. Nicotine dependence did not alter these findings. No other differences were discovered. In conclusion, our data suggests that moderate caffeine doses, rather than high caffeine doses, may be beneficial to executive function performance in patients with schizophrenia. Our results also suggest that while high caffeine users may be experiencing fewer negative symptoms compared to moderate caffeine users, they should also be aware of the potential increase in positive symptoms. Future research should continue to investigate the impact of caffeine on individuals with schizophrenia, including its possible therapeutic effects.

Keywords: Schizophrenia• Schizoaffective disorder• Symptomatology

Introduction

Approximately 85% of the population consumes at least one caffeinated beverage per day (M=165 mg/day), making caffeine the most widely used psychoactive substance in the world [1]. Fortunately, most healthy adults do not experience adverse effects from this level of caffeine intake [2]. While Caffeine Intoxication and Caffeine Withdrawal are listed as disorders in the DSM-5, Caffeine Use Disorder is not. It is argued that by not including caffeine as an addictive drug, it allows for more research and discussion related to its potentially beneficial effects [3].

In healthy individuals, chronic caffeine consumption has been associated with better verbal memory [4], as well as processing speed and executive function [5], while acute caffeine intake has been associated with better sustained attention [6], and working memory [7]. Conversely, Kaplan et al. [8] reported that while 250 mg of caffeine increased performance on a working memory task and had positive subjective effects (e.g., elation), 500 mg decreased working memory performance and had negative subjective effects (e.g., tension). Additionally, while lower doses of caffeine have been reported to improve mood and energy (~200 mg/day) [9,10], excessive caffeine consumption may be associated with a depressive mood [11,12]. Hence, it appears that only moderate doses of caffeine (i.e., ~250 mg/day) have potential beneficial effects on both mood and cognition while higher doses have more negative outcomes.

It has long been documented that individuals with schizophrenia consume a significant amount of caffeine [13], with consumption estimates including on average 500 mg of caffeine per day (3X more than the general population). One report approximates one-third of patients with schizophrenia consume more than 550 mg per day [14]. However, despite consuming large doses of caffeine, the reasons for their enhanced consumption and effects on symptoms and cognition have not yet been adequately investigated [15,16].

Only one previous study assessed the impact of caffeine on cognition in patients with schizophrenia [16]. In that study, the impact of chronic caffeine consumption on cognition was assessed using neuropsychological testing in 52 individuals with long-term schizophrenia (M age=47). A regression analysis found that chronic caffeine consumption was associated with better performance on tasks measuring semantic fluency, processing speed, working memory, and visual memory, however only for male and not female individuals with schizophrenia [16]. These results suggest that patients may be using large doses of caffeine because they are gaining some cognitive benefit.

It has also been suggested that patients with schizophrenia may be using caffeine to counteract negative symptoms [17]. In one previous

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study, a high caffeine dose (10 mg/kg) was administered to 13 patients with schizophrenia [18]. A decrease in negative symptoms (i.e., improved mood and decreased withdrawal) was observed along with an increase in positive symptoms (i.e., BPRS total score increase of 33%) [18]. In contrast, a cross-sectional study examining 250 outpatients with schizophrenia was conducted and found no association between caffeine intake and 6 PANSS factors (i.e., positive, negative, disorganized, excited, anxious, and depressive factors) [19].

It is also possible that patients with schizophrenia use caffeine to offset antipsychotic induced side effects such as sedation [20,21], with some physicians recommending using caffeine to help reduce sedation in patients with schizophrenia [22]. However, contrary to this notion, a study found that patients with schizophrenia who were prescribed more sedating medications were not consuming more caffeine, even after adjusting for chlorpromazine equivalents [23].

The higher proportion of smokers among individuals with schizophrenia compared to healthy controls (60% vs. 24%, respectively) may also help explain higher caffeine consumption rates [24]. Since nicotine is an inducer of CYP1A2 and caffeine is a substrate of that same enzyme [25], nicotine intake leads to a quicker clearance of caffeine. As a result, smokers require two to three times more caffeine to reach the same plasma concentration as a non-smoker [19]. In further support for this idea, Strassnig et al. [24] found that caffeine consumption was correlated to the number of cigarettes smoked per day in individuals with schizophrenia.

The purpose of this study is to help us better understand the impact of caffeine on cognition and symptomatology in patients with schizophrenia and to expand the current small literature base on caffeine consumption in schizophrenia [15]. The primary objective of this study was to compare moderate (≤ 250 mg/day) and high (>250 mg/day) caffeine-using individuals with schizophrenia on measures of sustained attention, working memory, processing speed, executive function, verbal learning and memory, and visual learning and memory. It was hypothesized that moderate caffeine users would demonstrate better cognitive performance than high caffeine users and that high caffeine users would demonstrate fewer negative symptoms and more positive symptoms than moderate caffeine users.

Methods

Participants

This study was conducted in Halifax (NS, Canada) and approved by the Nova Scotia Health Authority Research Ethics Board (File #1023131). Participants were recruited through the Nova Scotia Early Psychosis Program (NSEPP), as well as through advertisements in the QEII Health Sciences Centre, community note boards, and Kijiji.com. Inclusion criteria was a DSM-5 diagnosis of schizophrenia or schizoaffective disorder [26], 18 to 55 years of age, stable medication regime for at least 4 weeks, an outpatient, fluent in English, and (corrected to-) normal vision. Participants were excluded if they had recent illicit substance use (3+ months; caffeine, nicotine, cannabis, and alcohol were permitted). Verbal consent was obtained to contact their primary health care providers to confirm eligibility.

Data collection

Demographics and health-related questionnaire: Participants responded to nine questions that queried for age, sex, diagnosis, medication, education, ethnicity, employment status, marital status, and smoking status. Antipsychotic dose was reported using chlorpromazine equivalents [27].

Nicotine questionnaire: The Fagerstrom Test for Nicotine Dependence (FTND) includes six questions that were used to assess nicotine dependence [28]. The FTND is a valid [29] and among the most commonly used measures of nicotine dependence [30]. The highest score is 10 while a score of 0 was applied to non-smokers, and higher scores indicate higher levels of dependence.

Neuropsychological assessment: The Cogstate Schizophrenia Battery (CSB) is a reliable and valid measure of cognitive domains typically impaired in patients with schizophrenia [31]. The following six cognitive domains were assessed using the CSB: 1) Detection Test, measuring processing speed (the average speed of correct responses) using a simple reaction time paradigm; 2) Identification Test, measuring sustained attention (the average speed of correct responses) using a choice reaction time paradigm; 3) One Back Test, measuring working memory (proportion of correct responses) using an n-back paradigm; 4) One Card Learning Test, measuring visual learning and memory (the proportion of correct responses) using a pattern separation paradigm; 5) International Shopping List Test, measuring verbal learning and memory (the total number of correct responses made in remembering the items on the list over three consecutive trials) using a word list learning paradigm; and 6) Groton Maze Learning Test, measuring executive function (the total number of errors made while attempting the same hidden pathway over five consecutive trials) using a maze learning paradigm.

Symptom assessment: The Positive and Negative Syndrome Scale (PANSS) is a 30-item clinical scale that was used to measure the severity of symptoms associated with schizophrenia [32]. Data for the PANSS was collected using the Structured Clinical Interview-Positive and Negative Syndrome Scale [33]. Data from the PANSS was then analyzed using a specific factor structure [34]. The factor structure included the positive factor (P1, P3, P5, G9), negative factor (N1-N4, N6, G7), and cognitive factor (P2, N5, G11).

Caffeine questionnaire: Participants were asked eight detailed questions about their average daily caffeine intake. For example, participants were asked about the brand, size, and type of roast their coffee was as well as quantity. Participants were also asked about other items known to include caffeine, such as tea, medication, chocolate, and energy drinks with on-line searches allowing for accurate caffeine content (in milligrams) of identified products used.

Design and procedure: This cross-sectional study compared two caffeine groups: Group 1 was a moderate dose group (≤ 250 mg/day) and Group 2 was a high dose group (>250 mg/day). This was based on literature that suggested doses up to ~250 mg per day had the most beneficial effects on cognition and mood [8,10,11,35]. The study materials were administered in the same order that they were outlined above.

Statistical analysis: Our initial analysis was with ANCOVA, covarying for the degree of nicotine dependence using FTND, but the covariate was not significant in any of our analyses, so it was dropped from the model. One-way ANOVAs were carried out to compare the two caffeine groups on measures of cognitive functioning, symptomatology, as well as demographic and health-related variables. Alpha was set at $p \leq 0.05$ and two-tailed tests were employed for all analyses. Effect size was calculated using Eta squared.

Results

Subjects

Twenty-seven participants were recruited for this study (21 males; 21 with less than 5 years of illness (early phase psychosis)). General demographic and health related information are in Table 1 for the whole group and by caffeine intake (moderate caffeine intake N=13; high caffeine intake N=14). As a reliability check, a difference between group means was discovered for caffeine intake ($F(1,25)=16.5$, $p<0.05$, $\eta^2=0.4$); those in the high dose group consumed more caffeine than those in the moderate dose group. A difference between group means was also discovered for FTND ($F(1, 25)=17.5$, $p<0.05$, $\eta^2=0.4$ and the average number of cigarettes

smoked per day (F(1, 25)=18.9, p<0.05, η^2=0.4); high caffeine users were more dependent on nicotine and smoked more cigarettes per day, respectively. No other differences were discovered.

Table 1. Demographic and health-related data.

	All participants	Moderate caffeine (≤ 250 mg/day)	High caffeine (>250 mg/day)	P value	Effect size
# of Participants	27	13	14		
Age (years)	27.3 (7.8)	27.1 (8.8)	27.5 (7.0)	0.89	0.0
Education (years)	13.5 (1.9)	13.2 (1.9)	13.7 (2.1)	0.53	0.0
Caffeine Intake (mg*)	304.9 (371.4)	66.6 (62.1)	526.2 (403.5)	**0**	0.4
FTND**	2.4 (2.9)	0.5 (1.3)	4.1 (2.8)	**0**	0.4
Cigarettes per day	6.2 (8.7)	0.4 (1.4)	11.5 (9.1)	**0**	0.4
Antipsychotic Dose (mg; CPZE***)	264.5 (249.0)	201.6 (221.4)	322.9 (266.8)	0.21	0.1

Note: Bold means significant (p ≤ 0.05, two-tailed); p value of .00 indicates p < 0.01. *mg: milligrams. **FTND: Fagerstrom Test for Nicotine Dependence. *** CPZE: Chlorpromazine Equivalence.

Cognitive functioning

A difference was discovered between group means for the task that measured executive function (F(1, 25)=7.5, p<0.05, η^2=0.2); moderate caffeine users made fewer errors on the Groton Maze Learning Test than high caffeine users. No other differences were discovered (Table 2).

Table 2. Performance on cognitive tasks per caffeine group.

Cognitive task[a]		Moderate caffeine (≤ 250 mg/day)	High caffeine (>250 mg/day)	F-value	p-value	Effect size	Range of scores
Detection test	M (SD)	2.5 (0.1)b	2.5 (0.1)	0.0	0.87	0.0	2.3–2.7*
Groton maze learning task	M (SD)	49.8 (15.3)	70.9 (23.7)	7.5	**0.01**	0.2	32–114*
Identification test	M (SD)	2.7 (0.1)	2.7 (0.1)	0.0	0.51	0.0	2.6–2.9*
International shopping list test	M (SD)	24.5 (3.8)	22.6 (4.9)	1.3	0.26	0.1	15–33**
One back test	M (SD)	1.4 (0.1)	1.3 (0.2)	0.1	0.79	0.0	1.0– 1.6**
One card learning test	M (SD)	0.9 (0.1)	0.9 (0.1)	0.2	0.68	0.0	0.8–1.2**

Note: Bold means significant (p ≤ 0.05, two-tailed).*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.

bNumbers are reported as raw scores.

Symptomatology

A difference was discovered between group means for the negative factor (F(1,25)=7.7, p<0.05, η^2=0.2); high caffeine users had fewer negative symptoms than moderate caffeine users. A difference was also discovered between group means for the positive factor (F(1,25)=5.3, p<0.05, η^2=0.2); high caffeine users had more positive symptoms than moderate caffeine users. No other differences were discovered (Table 3).

Table 3. Symptomatology per caffeine group.

Factor		Moderate caffeine (≤ 250 mg/day)	High caffeine (>250 mg/day)	F-value	p-value	Effect size
Negative	M (SD)	12.5 (4.6)	8.0 (3.7)	7.7	**.01**	0.2
Positive	M (SD)	6.1 (2.9)	8.8 (3.1)	5.3	**.03**	0.2
Cognitive	M (SD)	4.2 (2.3)	4.3 (1.8)	0.0	.94	0.0

Note: Bold means significant (p ≤ 0.05, two-tailed).

Discussion

This is the second study to assess the impact of caffeine on cognition in patients with schizophrenia [16]. However, in addition to the previous study, the current study also assessed caffeine's impact on symptomatology, administered a cognitive battery that is specifically tailored for patients with schizophrenia, and recorded caffeine intake in milligrams rather than cups. Our results found moderate caffeine users demonstrated better performance on a task measuring executive function and that high caffeine users demonstrated fewer negative psychotic symptoms but higher positive symptoms.

Results for the cognitive tests between the current and previous study appear to be in conflict. While the previous study found that higher caffeine intake was associated with better cognitive functioning, the current study found moderate caffeine users, rather than high caffeine users, demonstrated better cognitive functioning. Specifically, the current study found moderate caffeine users performed better than high caffeine users on a task that measured executive function. The difference in the results could be a result of caffeine consumption measures (milligrams vs cups) and cognitive tests used.

Symptoms were also different between the two caffeine groups. Participants with high caffeine intake had fewer negative symptoms and more positive symptoms than those with moderate caffeine intake. These findings are consistent with a previous study that found an increase in positive symptoms and a decrease in negative symptoms after administering a high dose of caffeine to individuals with schizophrenia [18]. However, our findings are inconsistent with a previous cross-sectional study that found no relationship between caffeine intake and symptoms in individuals with schizophrenia [19]. Since it is possible that patients with schizophrenia are using caffeine to counteract negative symptoms [17], patients should be educated to understand that high caffeine intake may simultaneously be increasing their positive symptoms. In other words, patients with schizophrenia might be overvaluing the positive effects of caffeine while devaluing its negative effects [36], and so it is important that they are made aware of the potential consequences of having too much caffeine.

Demographic and health-related data also yielded useful information. For instance, it was previously suggested that patients with schizophrenia use caffeine to offset sedation induced by their antipsychotics [20,21]. However, using chlorpromazine equivalents [27], the current study found that high caffeine users were not prescribed higher antipsychotic doses than moderate caffeine users. Our finding is consistent with a previous study that found more sedating medications were not associated with increased caffeine intake in patients with schizophrenia [23]. Our study also found that high caffeine users were more dependent on nicotine and smoked more cigarettes than moderate caffeine users. This is consistent with a previous study that found a correlation between cigarette use and caffeine intake in patients with schizophrenia [24]. This correlation is likely due to a metabolic interaction between nicotine and caffeine that results in smokers requiring more caffeine in order to reach the same plasma concentration as a nonsmoker [19,25]. In other words, it is entirely possible that a sub group of patients with schizophrenia consume significantly more caffeine for the simple reason that they also smoke more cigarettes than healthy controls.

However, the level of nicotine dependence did not affect the results of these analyses which suggests that it is the consumption of caffeine that is driving the group differences.

There were several limitations in this study that should be mentioned. First, the sample size was small (N=27) and could explain why many cognitive tasks were not significant. For instance, Núñez et al. [16] found significant results when using a regression analysis with 34 male patients with schizophrenia. Secondly, the female subgroup in the current study was small (n=6) and hence we were unable to assess for sex differences. Núñez and colleagues had previously found an association between cognitive performance and caffeine intake, but only in males and not females. Third, caffeine was not administered and hence causation cannot be inferred. Rather, participants self-reported their caffeine intake. However, it is important to note that self-reported caffeine intake has been found to be a valid method of predicting actual caffeine intake [37]. Fourth, since a majority of participants were diagnosed with schizophrenia (n=22), and only a few were diagnosed with schizoaffective disorder (n=5), it is possible these results cannot be generalized to individuals with schizoaffective disorder. Moreover, since a majority of participants were in an early phase of illness (n=21), and only a few were in a chronic phase of illness (n=6), it is possible these results cannot be generalized to individuals in a chronic phase of illness. Additionally, this study did not include a control group. Only moderate and high caffeine users were compared. Finally, there was no premorbid IQ measurement in this study.

Conclusions

The results of this study suggest that, when comparing moderate and high caffeine intake, patients with schizophrenia consuming moderate doses of caffeine demonstrate better executive function while patients with high caffeine intake have fewer negative symptoms and more positive symptoms. Given the high intake of caffeine in patients with psychotic disorders, it is important to continue researching caffeine intake in these patients. Additionally, there are currently no approved or widely accepted treatments for cognitive deficits and negative symptoms associated with schizophrenia, and antipsychotic induced sedation continues to be a problem for many patients. We must better understand the effects of caffeine in psychotic patients so that clinicians can encourage caffeine use where it might be effective and to discourage caffeine use where it might be detrimental.

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