EEG Microstates in Early Phase Psychosis: The Effects of Acute Caffeine Consumption

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Abstract

Individuals with schizophrenia use on average twice as much caffeine than the healthy population, but the underlying cortical effects of caffeine in this population are still not well understood. Using resting electroencephalography (EEG) data, we can determine recurrent configurations of the electric field potential over the cortex. These configurations, referred to as microstates, are reported to be altered in schizophrenia and can give us insight into the functional dynamics of large-scale brain networks. In the current study, we use a placebo-controlled, randomized, double-blind, repeated-measures design to examine the effects of a moderate dose of caffeine (200mg) on microstate classes A, B, C, and D in a sample of individuals within the first five years of psychosis onset compared to healthy controls. The results support the reduction of microstate class C and D, as well as the increase of microstate class A and B in schizophrenia. Further, acute caffeine administration appears to exacerbate these group differences by reducing class D, and increasing occurrences of class A and B states in the patient group only. The current results support the hypothesis of a microstate class D reduction as an endophenotypic marker for psychosis and provide the first descriptive account of how caffeine is affecting these microstate classes in an early phase psychosis sample.

Microstates

Using electroencephalography (EEG) to record electrical activity over the surface of the scalp can allow us to view the electric field configuration occurring in the brain with great temporal resolution. Four electrical field configurations have been identified as commonly occurring across the human cortex. In fact, 80% of the variance in changes across time in electrical field configurations can be explained by these four categories.[1] These four configurations are referred to as microstates and are labeled microstate classes A, B, C, and D.[2] Each of these microstate classes are defined by a unique course including duration, frequency, and topographical distribution across the cortex.

Studies comparing the frequency and duration of these microstate classes to functional magnetic resonance imaging (fMRI) data can give us insight into how each microstate class corresponds with the functional state of the brain. Associations between the predefined fMRI resting states and the microstates recorded through resting EEG indicate that microstate classes A, B, C, and D are representative of verbal processing, visual processing, interoceptive autonomic processing, and attention reorientation, respectively.[3] However, relationships between microstate class A and visualization tasks, and microstate B

and verbalization tasks have been reported.[2] This counterintuitive finding is likely in part due to the wide variance of functional correlates that can be attributed to each microstate class (not dissimilar to the spectral alpha band, where the variance in alpha band's functional correlates is large and therefore hard to reduce to a single function[2,4]). Although EEG-derived microstates perform better than EEG spectral band power when predicting fMRI resting states,[5] caution should be used when reducing the functionality of a microstate class to one function or cognitive process. Nonetheless, it is clear that each microstate is closely linked to unique dynamics of large-scale brain networks,[5] and can be used to determine group differences in brain-based illnesses like schizophrenia.

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Microstates in Schizophrenia

Schizophrenia is a psychotic disorder characterized by disturbances in thought, mood, and behavior that directly affects approximately 1.0% of the population worldwide.[6] Studies comparing the duration of microstates over a period of rest find that microstate class D is considerably reduced in those with schizophrenia compared to controls.[1,7-7] This reduction is found regardless of medication status[7], and illness duration.[9] There is also a link between this microstate class alteration and psychosis symptomology. Specifically, increased psychotic symptoms (mainly positive symptoms) are linked to this reduction,[1] and microstate class D is even shorter in duration when patients are actively hallucinating.[8]

Microstate classes A and C have been reported to be longer in duration and more frequent in schizophrenia,[9,11,12] while the reports on microstate class B in this population are varied.[9,13] However, studies examining these microstate classes in schizophrenia are sparse. Ultimately, more research outlining the microstate profile in schizophrenia is merited.

The Effect of Caffeine on Microstates

Caffeine, an adenosine receptor antagonist, indirectly stimulates the widespread release of dopamine, serotonin, and noradrenaline throughout the cortex.[14-14] In a healthy population, previous studies have found benefits of caffeine across multiple cognitive processes like verbal working memory,[17] sustained attention,[18] and executive function.[19] However, no studies to date have examined the effects of acute caffeine consumption on EEG-derived microstates. One study found chronic nicotine smokers displayed a reduced class B microstate compared to non-smokers,[20] which suggests there may be some alteration to these states following the administration of psychostimulants more broadly, however it is unclear whether these effects are limited to nicotine.

The Current Study

While the effects of caffeine in a healthy population are well documented,[17-19,21-23], the effects of acute caffeine administration in individuals with schizophrenia are not. This is surprising given the high rates of typical caffeine use in this population,[24,25] and the potential negative effects of that use (i.e. an increase in positive symptoms).[24] More research in this area is certainly needed.[26,27] The current study aims to add to the existing literature on the alteration of microstates in early-phase psychosis, as well as provide a descriptive account of the effects of caffeine on microstates in these individuals. Additionally, we also explore the relationship between psychosis symptom severity, microstate duration, occurrence, and contribution, and the extent of the effect caffeine has on these microstate parameters. We hypothesize that, consistent with previous reports, we will see a reduction of microstate class D parameters,[1,7-7] as well as an increase in microstate class A and C

parameters in the early-phase psychosis sample.[9,11,12] Further, our analysis of caffeine's effects on microstates is exploratory, and not hypothesis driven. This will give us a better understanding of how caffeine is affecting the functional brain states in these individuals and may give us insight into underlying cortical mechanisms that could be driving the high rates of usage in this population.

Methods

Participants

Participants consisted of 13 healthy controls (HC) (4 female, 9 male) between the ages of 19-35 ($M = 23.15$, $SD = 4.18$) as well as 12 individuals within the first five years of a primary diagnosis of schizophrenia (SZ) (3 female, 9 male) between the ages of 23-38 ($M = 28.17$, $SD = 3.59$). HC were recruited from the general public and SZ participants were recruited through the Nova Scotia Early Psychosis Program (NSEPP). For demographic characteristics of each participant group, see table 1. All healthy controls had negative self-reported histories of psychiatric, medical, and neurological illnesses. All SZ patients were judged to be clinically stable by their primary care physician and had no changes in their antipsychotic medication or symptoms in the past two months. Patients were also limited to the use of an atypical antipsychotic (with the exclusion of clozapine due to its known interactions with caffeine).[28] SZ participants were excluded if any of the following criteria were met: co-morbid DSM-V disorder; total PANSS score >65 reflecting an acute psychotic episode; or current history of drug abuse or dependence. Additionally, any participant was excluded if any of the following criteria were met: left-handed; non-normal hearing and/or vision; history of a head injury resulting in a loss of consciousness; diagnosis of a neurological disorder; electro-convulsive therapy within the past year; significant cardiac illness, or extrapyramidal symptoms resulting in movement disorders which could affect EEG recordings.

Caffeine consumption (measured by the Caffeine Consumption Questionnaire or CCQ)[29] was recorded and complete non-users of caffeine were excluded due to the reported differences in behavioral and physiological effects between users and total non-users.[30,31] Beyond this requirement of at least some caffeine use, there were no minimum or maximum amounts of typical caffeine consumption for inclusion in this study.

Design

The study employed a randomized, placebo-controlled, double-blind, repeated measures design. Each participant attended two sessions separated by a minimum of 24 hours. In each session, either placebo or caffeine was administered. The order of drug administration was determined using counterbalancing so that half of the participants received caffeine during the first

Table 1. Participant Characteristics.

	Early Phase Psychosis (SZ) (n = 14)	Healthy Controls (HC) (n = 13)	Significant Group Differences
Age (years)	27.4 (3.9)	23.2 (4.3)	$p = .013*$
Sex (M:F)	11:3	9:4	
CCQ	1490.0 (1201.4)	1250.1 (1398.8)	$p = .638$
CWSC			
Caffeine session	4.4 (3.0)	2.5 (1.9)	$p = .060$
Placebo session	5.1 (2.7)	3.1 (3.2)	$p = .082$
CDRS			
Caffeine session	1.6 (1.0)	1.5 (0.9)	$p = .929$
Placebo session	1.4 (0.6)	1.4 (0.7)	$p = .862$
Medication Status, %	29% medicated		
PANSS			
Total	52.8 (13.2)		
Positive	12.9 (5.8)		
Negative	14.1 (5.1)		
General	25.9 (6.3)		
PSYRATS	13.3 (12.7)		
BNSS	21.6 (12.1)		

Notes: The above table displays the average age, sex, caffeine consumption (CCQ), caffeine withdrawal (CWSC), and caffeine-related symptoms (CDRS) of each participant group as well as the clinical symptom scale scores of the SZ group.
Statistically significant differences in group means were analyzed using independent-samples two-tailed T-tests where equal variances were assumed.
*Indicates a statistically significant ($p < .05$) difference between groups in the specified demographic variable.

session and placebo during the second, while the remaining participants received the reverse order. Blinding was accomplished by having the principle investigator prepare the pills for the research sessions, and another member of the research team run the sessions and interact with the participants. Blinds were broken to all other members of the research team after data collection was complete and data analysis began.

Caffeine pills contained 200mg of caffeine and were physically identical to the pills used for the placebo. This dose approximates the dose that would be consumed in an average 500mL cup of drip coffee and was selected in accordance with previous studies that showed a moderate dose of caffeine can exert widespread cerebral effects.[32,33] Caffeine and placebo pills were consumed with water.

Procedure

Sessions were booked in the morning to ensure uniformity across sessions and to control for time-of-day effects[34]. Participants were required to abstain from illicit substances, alcohol, and cannabis from midnight the night before the session. They were also asked to abstain from any form of caffeine (coffee, tea, cola) from midnight until the testing session to ensure adequate clearing of caffeine given the typical elimination half-life of 4.5 hours.[35] Verbal confirmation of abstinence was obtained before the start of each session.

Upon arriving at the lab, relevant questionnaires were given and drug treatment was administered at the same time as EEG set up. Directly following drug administration, withdrawal

symptoms were measured using the Caffeine Withdrawal Symptom Checklist (CWSC).[36] Thirty minutes after administration, EEG was recorded in a sound-attenuated chamber. Recordings included a 3-minute eyes-open resting task (where the participant focused on a spot in front of them and relaxed with their eyes open) immediately followed by a 3-minute eyes-closed resting task (where participants relaxed for three minutes with their eyes closed). At the end of the session, side effects of caffeine were assessed using the Checklist of Drug-Related Symptoms (CDRS).[37] Informed consent was obtained from all participants and the study was cleared by the Nova Scotia Health Authority Research Ethics Board as well as the Mount Saint Vincent University Research Ethics Board.

Questionnaires

Additional information on the CCQ, CWSC, and CDRS is included in supplemental materials.

Psychotic Symptom Rating Scale (PSYRATS). The PSYRATS can be further divided into the two subscales of auditory hallucinations and delusions.[38] The auditory hallucinations subscale of the PSYRATS was given to the SZ group to assess the presence and severity of positive symptoms.

Brief Negative Symptom Scale (BNSS). The BNSS was given to the SZ group to assess the presence and severity of negative symptoms. The BNSS quantifies the following six specific

domains of negative symptoms: distress, blunted affect, alogia, asociality, anhedonia, and avolition.[39]

Positive and Negative Symptom Scale (PANSS). The PANSS is a 30-item scale to assess the presence and severity of clinical psychotic symptoms.[40] The PANSS includes 3 subscales of positive, general, and negative symptoms, and scores can be derived for each subscale separately. A higher score indicates increased symptomology.

EEG Data Acquisition

EEG recordings were digitally sampled at 500 Hz with an ActiCHamp amplifier and obtained from an ActiCAP electrode cap with Ag + /Ag + -Cl- active electrodes at sixty-four scalp sites (Brain Products GmbH, Gilching, Germany). Scalp sites were chosen according to the 10-10 system of electrode placement.[41] Electrodes were also placed bilaterally on each mastoid, on the mid-forehead, and nose. Mastoid was used as an online reference during recording. Bipolar recordings of horizontal (HEOG) and vertical (VEOG) electrooculogram activity were taken from supra-/sub orbital and external canthi sites, respectively. Electrode impendence were kept under 10 kΩ and all electrical signals were amplified with a bandpass of DC-250 Hz. Preprocessing included applying filters from 2-20 Hz with a notch filter at 60 Hz, segmentation into 2-second epochs (with no overlap), and artifact rejection of any epochs with electrical activity exceeding ± 50μV.

Microstate data was then analyzed using the microstates plug-in created for EEGlab by Thomas König (https://www.thomaskoenig.ch/index.php/software/microstates-in-eeglab).[42] First, individual microstate maps were identified by k-means spatial cluster analysis. Individual microstate maps were then sorted according to distributions of scalp potentials from previously established maps,[43] and class labeled according to the Norms NI202 published template. Finally, the resulting class-labeled individual model maps were exported for statistical analysis. Within each participant, each microstate class yielded the following parameters:

  (a) Duration: the mean duration of that microstate class in seconds (s).
  (b) Occurrence: the mean amount of observations of that specific microstate class each second.
  (c) Contribution: the proportion (%) of total time spent in that specific microstate class while recording.

Statistical Analysis

All statistical analyses were done using the Statistical Packages for Social Sciences (SPSS; IBM Corp. Armonk NY). Duration, occurrence, and contribution values for each microstate class were separately analyzed using a repeated-measures general linear model (GLM) where drug (caffeine vs. placebo),

served as a within-subject factor and group (SZ vs. HC) served as a between-subject factor. In the case that the GLM indicated significant effects ($p < .05$), simple effects analyses within interactions were done to determine main effects using Fisher correction for multiple comparisons.

To examine the relationship between psychosis symptoms and microstate parameters independent of the effects of caffeine, Spearman's bivariate correlations were completed between duration, occurrence, and contribution of each microstate class during the placebo session and total scores on the PSYRATS, PANSS and BNSS in the SZ group. Additionally, to examine the relationship between psychosis symptoms and the effect of caffeine on the microstate parameters, correlations between total scores on the PSYRATS, PANSS, and BNSS and difference in duration, occurrence, and contribution values between sessions for each microstate class were done for the SZ group.

Results

Topographic distribution maps of each microstate class separated by group and drug condition are displayed in Figure 1.

Microstate Parameters

Duration. There was a main effect of group on class A microstates ($p = .047$, *Hedges' g = 0.60*), where the HC group had shorter class A microstates ($M = 0.041s$, $SD = 0.011s$) than the SZ group ($M = 0.065s$, $SD = 0.057s$). Conversely, there was a main effect of group on class D microstates ($p = .020$, *Hedges' g = 0.67*), where the HC group had longer class D microstates ($M = 0.069s$, $SD = 0.020s$) than the SZ group ($M = 0.055s$, $SD = 0.022s$). There was no significant main effects of drug for any of the microstate classes. However, there was a significant drug-by-group interaction ($p = .014$, *Hedges' g = 1.00*), in which microstate class D was shorter following caffeine administration ($M = 0.045s$, $SD = 0.014s$) than placebo ($M = 0.064s$, $SD = 0.023s$) in the SZ group only.

Occurrence. There was a main effect of group ($p = .044$, *Hedges' g = 0.65*) for occurrences of class C microstates where the HC group displayed more class C microstates per second ($M = 4.80$, $SD = 1.38$) than the SZ group ($M = 4.08$, $SD = 0.70$). Similarly, there was also a main effect of group ($p = .001$, *Hedges' g = 1.17*) for microstate class D where the HC group displayed more class D microstates per second ($M = 7.09$, $SD = 2.25$) than the SZ group ($M = 4.61$, $SD = 1.95$). There were no significant main effects of group found for microstate classes A and B. However, there was a main effect of drug ($p = .029$, *Hedges' g = 0.55*) in which caffeine administration resulted in more occurrences of class B microstates per second ($M = 4.55$, $SD = 1.77$) than placebo ($M = 3.67$, $SD = 1.44$) across both groups.

There were significant drug-by-group interactions for microstate class A ($p = .017$, *Hedges' g = 0.78*) and B ($p = .001$,
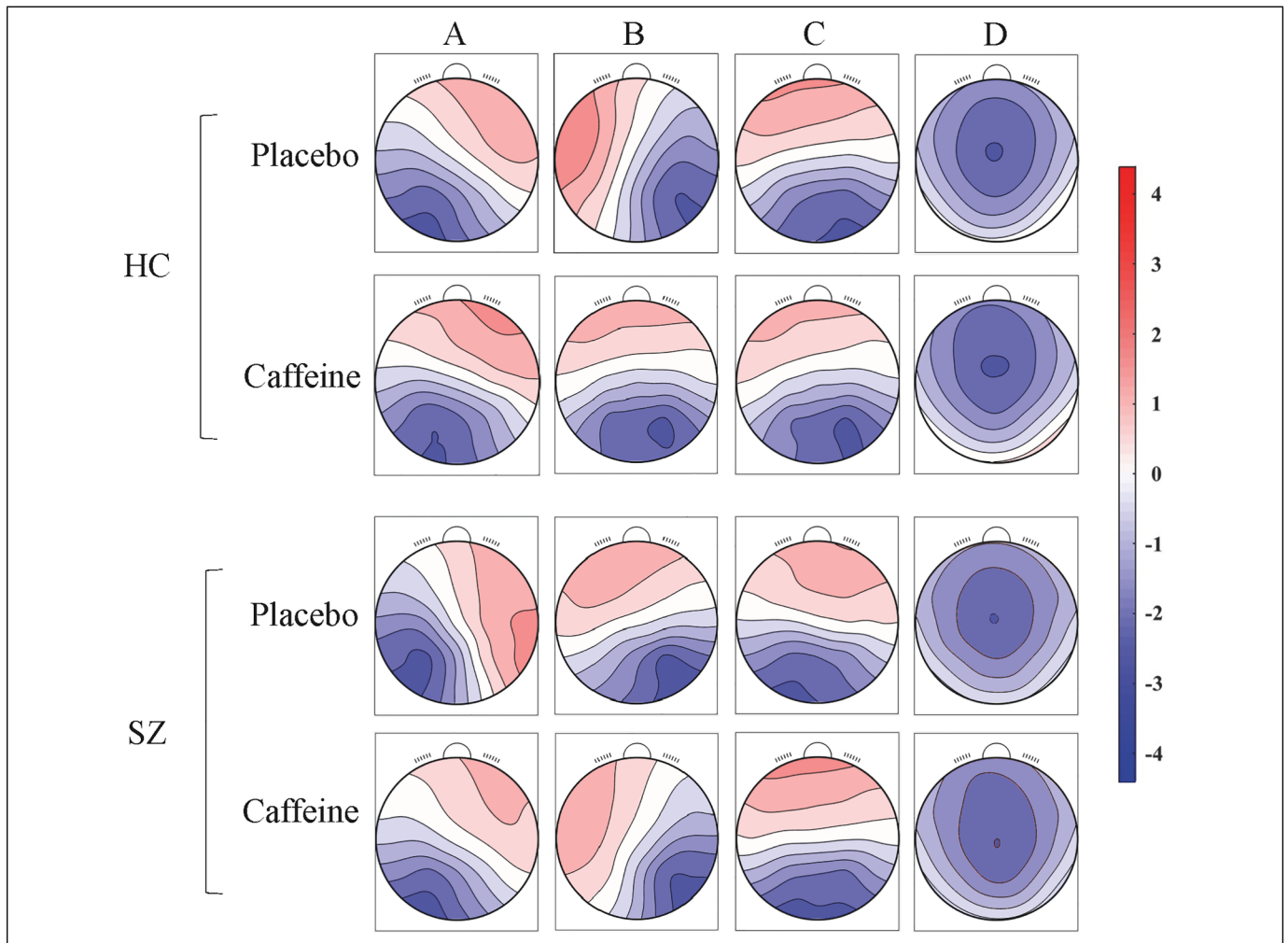
Figure 1. Topographic distributions of each microstate class. *Note*: The above figure displays the average topographical distribution of each microstate class following placebo and caffeine administration in both healthy control (HC) and early phase psychosis (SZ) groups.

Hedges' g = 1.07) where in the SZ group only, caffeine resulted in more occurrences of microstate class A per second (*M* = 4.83, *SD* = 2.44) than placebo (*M* = 3.28, *SD* = 1.38), as well as more occurrences of microstate class B per second (*M* = 5.47, *SD* = 2.39) than placebo (*M* = 3.34, *SD* = 1.48). Conversely, a significant drug-by-group interaction for microstate class D (*p* = .049, *Hedges' g* = 0.82) revealed the opposite effect in which caffeine administration decreased the occurrences of microstate class D each second (*M* = 3.85, *SD* = 1.08) compared to placebo (*M* = 5.36, *SD* = 2.38) in the SZ group only.

Contribution. There were significant main effects of group for both microstate class A (*p* = .013, *Hedges' g* = 0.78) and B (*p* = .002, *Hedges' g* = 0.88) in which the HC group spent less time in microstate class A (*M* = 14.6%, *SD* = 5.2%) than the SZ group (*M* = 23.3%, *SD* = 15.2%), and less time in microstate class B (*M* = 16.1%, *SD* = 8.5%) than the SZ group as well (*M* = 29.5%, *SD* = 20.1%). Additionally, there were trends with

moderate effect sizes for drug-by-group interactions for microstate classes A (*p* = .054, *Hedges' g* = 0.59) and B (*p* = .079, *Hedges' g* = 0.61), where for the SZ group only, caffeine administration resulted in more time being spent in microstate class A (*M* = 27.6%, *SD* = 17.9%) than placebo (*M* = 18.9%, *SD* = 10.9%), and more time being spent in microstate class B (*M* = 35.5%, *SD* = 17.6%) than placebo as well (*M* = 23.5%, *SD* = 21.4%).

For microstate class D, there was a main effect of group (*p* < .000, *Hedges' g* = 1.34) where the SZ group spent less time in microstate class D (*M* = 27.4%, *SD* = 17.6%) compared to the HC group (*M* = 47.5%, *SD* = 12.1%). There was also a main effect of drug (*p* = .022, *Hedges' g* = 0.62) where caffeine resulted in less time being spent in microstate class D (*M* = 33.0%, *SD* = 18.2%) than placebo (*M* = 42.0%, *SD* = 16.7%). Finally, there was a drug-by-group interaction (*p* = .001, *Hedges' g* = 1.40) where caffeine resulted in in less time spent in microstate class D (*M* = 17.3%, *SD* = 7.8%) than placebo (*M* = 37.6%, *SD* = 18.9%) in the SZ group only.

Correlations

When examining correlations between SZ group microstate parameters during the placebo session only, there was a significant correlation between the contribution of microstate class C and negative symptoms indexed by the PANSS negative subscale ($r = -0.596$, $p = .041$). There were no significant correlations found between PSYRATS, BNSS, or PANSS symptom scale scores and the difference in duration, occurrence, or contribution values between the caffeine and placebo sessions (representing the effect of caffeine on microstate classes) for any microstate class.

Discussion

The duration, occurrence, and contribution of microstate class D was reduced in patients compared to controls. This is consistent with previous findings of reduced microstate class D duration,[1,7-7,44] and further supports the hypothesis that this reduction is independent of illness duration[9] considering the current sample was in the first five years post psychosis onset. However, unlike previous studies that report an association between positive psychosis symptoms and a microstate class D reduction,[1,8] the current study found no relationship between symptom severity and microstate class D parameters. Alternatively, our results suggest that this reduction of microstate class D is independent of illness duration as well as symptom severity. This reinforces the idea of a class D microstate reduction being used as an endophenotypic marker for the illness.[44]

When conceptualizing microstate class D as being related to processes of contextual information integration,[45] a reduction of this microstate class is well aligned with the symptomology of schizophrenia. Specifically, deficits in contextual updating and executive function skills. Although no significant correlation was found between symptom scales and this class D reduction, this reduction may be underlying poor function in cognitive processes that have not been captured by our symptom scales or that we had insufficient variance within our sample. Future research on this phenomenon should consider incorporating scales that measure general functioning, like the Global Assessment of Functioning scale (GAFs), to confirm this. Interestingly, our results suggest that caffeine further reduces the duration, occurrence, and contribution of class D microstates in patients. This may point to a potential adverse effect of caffeine in schizophrenia, where caffeine is exacerbating the reduction of class D microstates that may be underlying deficits in contextual information integration. A qualitative study examining reasons for caffeine use in people with schizophrenia highlighted that individuals are using caffeine for reasons other than pursuing cognitive benefits (ie enjoying the taste, or having a break throughout their day) and that many individuals perceive caffeine as harmless and do not realize the potential negative effects of their use.[46] These results provide more evidence for the potential negative effects of excessive caffeine use and highlight the need for those effects to be understood in this population.

Microstate class C had fewer occurrences per second in the SZ group compared to the controls. There was also an association between increased negative symptoms and reduced occurrences of microstate class C. This is against the findings from a recent meta-analysis that reported a moderate effect for an increased occurrence of microstate class C in this population.[44] Caffeine did not affect this microstate class in patients or controls. The finding of reduced class C occurrences in the patients could be due to the effects of antipsychotic mediation on this microstate. Kikuchi and colleagues hypothesized antipsychotic medications may "normalize" this microstate class by reducing its occurrence in individuals who respond well to antipsychotic medications.[7] Considering the current sample was primarily medicated, this may explain the reduction in this microstate class observed. Alternatively, the difference in our findings and the reported meta-analysis may represent differences between early and chronic schizophrenia samples; more research is needed in this area.

Our data showed a longer duration and larger contribution of microstate class A in the SZ group. Previous reports on the alteration of microstate class A in schizophrenia have been varied.[9,12] Although Giordano and colleagues (2018), did not find an increase in microstate class A in their sample of chronic schizophrenia, they did report a significant relationship between the contribution of microstate class A and negative symptoms (specifically, avolition-apathy).[12] The authors hypothesized that the discrepancy in reports on microstate class A in this population could be representative of the heterogeneity of symptoms, and only some presentations of the illness may be linked to an increase in microstate class A.[12] Additionally, high levels of avolition-apathy are related to worse clinical outcomes in patients.[47] Therefore, an increase of microstate A may be present in a sub-group of patients who experience avolition-apathy and may be representative of more severe psychopathology.

Microstate class B also had a larger contribution in patients compared to controls. This contributes to the varied reports of microstate class B alterations in this population. The inconsistencies in reports of microstate class B could be attributable to the heterogeneity of the illness. Additionally, two studies found that the contribution of class B microstates was altered in patients, but this alteration was not present in unaffected siblings or a high-risk group,[13,44] suggesting the alteration of microstate class B is not as promising of an endophenotypic marker for the illness as a microstate class D reduction.

Caffeine increased the occurrence of microstate classes A and B in the patient group but not in the controls. While the exact functional correlates of these two microstate classes are still being discovered, the assumption that they are associated with sensory processing is prevalent.[2,4] These findings as well as early reports on an altered alpha and beta power following caffeine administration in patients[48] solidifies the fact that

this psychostimulant is affecting individuals with schizophrenia differently than controls, and that difference in experience may be driving the high usage rates in this population.

Limitations & Future Directions

The clear major limitation of this study was the relatively small sample size. This may have resulted in underpowered correlation effects between psychosis symptoms and microstate parameters. In future studies, a larger sample should be achieved to determine if our findings are replicated with greater power.

Conclusion

Ultimately, parameters of microstate class A and B were increased in patients with early-phase psychosis while classes D and C were decreased. Further, it appears as though caffeine is exacerbating these group differences by increasing class A and B microstate parameters, and decreasing class D microstate parameters in individuals with schizophrenia but not in controls. There were no relationships found between the effect caffeine had on any microstate parameters and psychosis symptoms, signifying that the observed effect of caffeine (notably the reduction of microstate class D) is independent of illness duration or severity, and may allude to an underlying biomarker for the illness. Future research examining the effect of caffeine on microstates in unaffected relatives and high-risk individuals is needed to confirm this. These findings contribute to our understanding of microstates in early phase psychosis and provide the first descriptive account of how these states are affected by acute caffeine administration.

Author Contributions

DF and PT were responsible for the study design and overall investigation. TA and KM participated in data collection. JB was responsible for statistical analysis and the original draft of the manuscript. Each author had participated sufficiently in the work to take public responsibility for appropriate portions of the content. All authors read and approved the final manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

This project was approved by Nova Scotia Health Authority and Mount Saint Vincent University research ethics boards.

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