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The psychosis-like effects of Δ^9 -THC are associated with increased cortical 'noise' in healthy humans

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Abstract

Background—Drugs that induce psychosis may do so by increasing the level of task-irrelevant *random* neural activity or neural noise. Increased levels of neural noise have been demonstrated in psychotic disorders. We tested the hypothesis that neural noise could also be involved in the psychotomimetic effects of delta-9-tetrahydrocannabinol (Δ^9 -THC), the principal active constituent of cannabis.

Methods—Neural noise was indexed by measuring the level of randomness in the electroencephalogram during the pre-stimulus baseline period of an oddball task using Lempel-Ziv Complexity (LZC), a non-linear measure of signal randomness. The acute, dose-related effects of Δ^9 -THC on LZC and signal power were studied in humans (n=24) who completed three test days during which they received intravenous Δ^9 -THC (placebo, 0.015 and 0.03 mg/kg) in a double-blind, randomized, cross-over, and counterbalanced design.

Results— Δ^9 -THC increased neural noise in a dose-related manner. Furthermore, there was a strong positive relationship between neural noise and the psychosis-like positive and disorganization symptoms induced by Δ^9 -THC, which was independent of total signal power.

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Instead, there was no relationship between noise and negative-like symptoms. In addition, 9 -THC reduced total signal power during both active drug conditions compared to placebo but no relationship was detected between signal power and psychosis-like symptoms.

Conclusions—At doses that produced psychosis-like effects, 9 -THC increased neural noise in humans in a dose-dependent manner. Furthermore, increases in neural noise were related with increases in 9 -THC-induced psychosis-like symptoms but not negative-like symptoms. These findings suggest that increases in neural noise may contribute to the psychotomimetic effects of 9 -THC.

Keywords

electroencephalogram; neural noise; psychosis; cannabinoids; nonlinear analysis; tetrahydrocannabinol

INTRODUCTION

Complex mental processes such as perception, language, emotion, and memory rely on the integrity of long-range functional networks formed by ensembles of brain areas (nodes) processing information in a coordinated manner (1, 2). Alterations in these networks and their information processing capabilities may contribute to the emergence of some core symptoms of psychosis such as hallucinations, delusions, and thought disorganization. Consistent with this view, converging lines of evidence from structural (diffusion tensor imaging: DTI) and functional (functional magnetic resonance imaging: fMRI, electroencephalogram: EEG, and magnetoencephalogram: MEG) studies have shown abnormal neural connectivity in schizophrenia, which has been related to the presence and intensity of psychotic symptoms (3–9).

Concepts used to characterize the functioning of ‘real-world’ complex networks (e.g., the Internet) may provide valuable insights into the abnormalities underlying some psychotic symptoms. A network can be characterized as a set of interconnected nodes that exchange and process information in a coordinated manner. Information is transmitted from one node to another through a medium (e.g., a cable) as part of a signal (e.g., an electromagnetic wave), which is composed by information and *random noise*. The latter is a sum of random activity and interference caused by other signals travelling through the same medium. According to information theory, the *upper limit* of the total amount of undistorted (error-free) information per unit of time that can be carried by a signal is limited by: 1) the *bandwidth* (in Hz), 2) the *total power*, and 3) the amount of *random activity* or *noise* of the signal (10–13). Thus, keeping the bandwidth and the total power of a signal constant, the higher the level of noise, the lower the amount of information that can be carried by the signal without distortion. Increased noise may, therefore, disrupt the coordinated activity between nodes, resulting in the disruption of information processing.

There is growing evidence from EEG, MEG, and neuroimaging studies suggesting increased randomness/noise in the brain activity of schizophrenia patients (14–19). A number of studies have shown increased inter-trial (random) variability in the latency and amplitude of evoked responses measured in the EEG of schizophrenia patients (14, 16–18, 20).

Furthermore, measures developed to characterize the uncertainty (entropy) or randomness of signals have revealed increased levels of *randomness* in the EEG and MEG of schizophrenia patients (21–23), which are higher during periods of exacerbation of psychosis (22). While there may be limitations to the existing EEG and MEG literature, recent *fMRI* data provide further support to the hypothesis that noise is increased in schizophrenia (19).

A number of drugs including ketamine, delta-9-tetrahydrocannabinol (Δ^9 -THC), psilocybin, and amphetamine have been used in the laboratory to study psychotic states and to understand the contributions of neurotransmitter systems to the pathophysiology of psychosis. The acute administration of Δ^9 -THC, the primary psychoactive constituent in cannabis, and other agonists of brain cannabinoid receptors (CB1R) have been shown to induce transient psychosis-like effects and psychophysiological abnormalities in healthy controls that share some similarities to those observed in schizophrenia (reviewed in 24, 25, 26). Furthermore, Δ^9 -THC has been shown to increase psychotic symptoms transiently in stable schizophrenia patients (27). Studies in rats have shown that CB1R agonists acutely reduce the spectral power of local field potential (LFP) oscillations in a number of frequency bands within the hippocampus and entorhinal cortex (28, 29). Importantly, this effect was not a consequence of a reduction in the individual neurons' activity but was related to an increase in the randomness/noise (decrease in the synchronization) of the neurons' activity (28, 29). Considering that, as mentioned above, neural noise may be involved in the pathophysiology and phenomenology of schizophrenia, these findings raise the intriguing possibility that neural noise could also be involved in the acute psychotomimetic effects of Δ^9 -THC and other CB1R agonists. To our knowledge, no studies in humans have tested this hypothesis.

Lempel-Ziv Complexity (LZC) is a non-linear measure first developed to characterize the level of randomness (30) or *noise* of signals. It is a measure of the minimum number of different terms (e.g., 'words') necessary to fully reconstruct a signal (e.g., 'sentence') without losing information. Applying this to EEG, LZC measures the minimum number of distinct patterns of activity that are necessary to characterize the behavior of a signal (see supplementary figure S1). The higher the randomness of a signal (e.g., the volume of the background babble of a crowded room), the larger is the minimum number of different terms ('word fragments') necessary to reconstruct the signal and, hence, the higher is LZC. For infinite random signals, which lack regular recurrent terms (e.g., white noise), the normalized value of LZC approaches 1, while for infinite regular (periodic) signals it approaches 0 (31, 32). LZC has been increasingly theoretically and empirically validated in the study of electrophysiological signals (reviewed in 21, 33, 34–38).

Traditional measures of neural noise used to study the EEG and MEG of schizophrenia patients (14–18, 39), have characterized noise as brain responses that are not time-locked to the stimuli in the context of time-locked paradigms (e.g. ERP). In this sense, neural noise refers to the random variation of the brain's response *across the different trials* of a task (i.e., inter-trial variability). Thus, this conceptualization of noise provides information about the capacity of the brain to produce consistent patterns of activity in response to repeated presentations of a stimulus. In contrast to these measures, LZC provides direct information about the level of randomness *of EEG signals* (30), which makes it especially suited for

detecting cannabinoid-induced changes in the randomness (noise) of the brain's electrical activity (28, 29).

Until recently, brain activity during the baseline or pre-stimulation period received little attention. However, evidence from both animal and humans suggests that this period plays a key role in the brain's response to tasks. The characteristics (e.g., phase, randomness) of pre-stimulation brain activity are known to modulate the electrical and behavioral responses to tasks (40, 41). More importantly, evidence for an interaction between *aberrant* (increased) baseline brain activity and a reduction of task-related post-stimulus activity measured by both EEG (14) and fMRI (42), has been observed in schizophrenia patients. Furthermore, schizophrenia patients show increased baseline activity, especially in the gamma (γ)-band, and an inverse relationship between pre- and post-stimulation γ activity (43). These findings suggest that at least part of the task-related abnormalities observed in schizophrenia may be associated to the presence of aberrant brain activity during the pre-stimulation period.

This study was part of a larger project that aimed to assess the dose-related effects of 9 -THC on several electrophysiological indices of information processing relevant to schizophrenia (e.g., P300 (44), oscillations, and neural noise) and to determine the relationship between the electrophysiological and behavioral effects of 9 -THC. 9 -THC was hypothesized to increase neural noise (LZC) during the pre-stimulation period of an oddball task, and psychosis-like effects. Furthermore, we hypothesized that there would be a positive relationship between neural noise and the psychosis-like effects induced by 9 -THC, and that this relationship would be independent of changes in signal power.

METHODS AND MATERIALS

A complete description of subjects, regulatory approvals, and general study procedures is included in the supplement (see text and table S1). In brief, in this 3 test-day randomized, double-blind, placebo-controlled, cross-over study, subjects received 9 -THC (vehicle (ethanol), 0.015mg/kg, or 0.03mg/kg) over 10 min by IV route. The sample included subjects with and without recent cannabis exposure (within the last 30 days), and excluded cannabis naïve and cannabis dependent subjects.

EEG paradigm and data acquisition—A detailed account of the EEG paradigm and data acquisition procedure is provided in the supplement. Briefly, 22-electrode EEG data were recorded (sampling rate 1000Hz) while subjects performed an auditory oddball task described elsewhere (44).

General EEG preprocessing—A detailed description of the EEG preprocessing is provided in the supplement. Briefly, EEG data were band-pass filtered (0.5–100Hz; bandwidth=99.5Hz), and power line, muscle, eye movement, and blink artifacts were removed using multi-tapering (45), blind source separation (46), and adaptive filtering techniques (47), respectively. The data were segmented in 1150ms epochs time-locked to stimulus onset with a 250ms pre-stimulus segment. To minimize the confounding effect that muscle activity could have on measuring neural noise, only midline electrodes were used for

statistical analyses, given that they tend to be less contaminated by muscle activity than the rest (48).

EEG measures

Lempel-Ziv complexity—A detailed description of the calculation of LZC is provided in the supplement. For each subject and electrode, LZC was calculated on the pre-stimulation segment (–250 to –1ms) of each trial and then averaged across trials. Finally, a single LZC value was calculated for each subject by averaging LZC across electrodes.

Signal power—For each subject, the signal power of each electrode was obtained by calculating the root-mean-square power (average of the squared amplitudes) of each trial's pre-stimulation interval (–250 to –1ms) and then averaging across trials. Finally, for each subject, a single signal power measure was obtained by averaging across electrodes.

Behavioral measures

The positive, disorganization and negative symptom subscales from a 5-factor model of the Positive and Negative Syndrome Scale (PANSS) (49) were used to measure psychosis- and negative-like symptoms. This model was selected for its stability and for not excluding items from the final solution (50). By characterizing positive and disorganization symptoms, this 5-factor model was hypothesized to more completely capture the range of psychosis-like effects induced by Δ^9 -THC than the usual 3-factor model of the PANSS.

Statistical analysis

Data were examined descriptively using means, standard deviations and distribution plots. In addition, each outcome was assessed for normality using the Kolmogorov-Smirnov test in each drug condition separately. Unless specified, statistical analyses were conducted using SPSS 21 (IBM Corporation, Armonk, NY, USA).

Effect of drug condition on EEG measures—The effect of drug condition (placebo, 0.015mg/kg, and 0.03mg/kg) on EEG measures was assessed using generalized estimating equations (GEEs) (51, 52) with an unstructured working correlation matrix. GEE modeling is a robust method that corrects for correlated samples, handles missing data, and has been shown to be more powerful than typical repeated measures analysis of variance for small/medium-size samples (51–53). Independent GEE models were fitted for LZC with and without signal power as a covariate and *p*-values were adjusted for 2 comparisons with the Holm-Bonferroni (HB) method. Pairwise comparisons (3 per model) were conducted and *p*-values were HB-adjusted for 6 comparisons. In addition, independent GEE models were fitted for signal power with and without LZC as a covariate and *p*-values were HB-adjusted for 2 comparisons; pairwise comparisons were performed and *p*-values were HB-adjusted.

To examine the relationship between LZC and signal power, the standardized regression coefficient was obtained for the longitudinal regression of LZC on signal power. The regression was done by fitting a GEE model with an unstructured working correlation matrix to the data of the three drug conditions transformed into composite *z* scores.

Effect of drug condition on behavioral measures—PANSS factors' scores exhibited floor effects and positive skewness in the placebo condition. Thus, a nonparametric method was used (54) and the resulting p -values were HB-adjusted for 3 comparisons (1 per PANSS factor). For this method, the data were ranked and fitted with a mixed effects model using dose as within-subject factor and an unstructured variance-covariance matrix; p -values were adjusted for ANOVA-type statistics. Pairwise comparisons (3 per measure) were performed and p -values were HB-adjusted for 9 comparisons. These analyses were performed with the nparLD package (55) for R 2.14.2 (56).

Relationship between EEG and behavioral measures—To characterize the relationship between 9 -THC-induced changes in EEG measures (LZC and signal power) and PANSS factors, standardized regression coefficient (β s) were obtained for the longitudinal regression across both 9 -THC-active conditions of each PANSS factor score on each EEG measure (controlling and not-controlling for the other EEG measure) with a significant main effect of drug (3 coefficients per EEG measure). The p -values of the regression coefficients were HB-adjusted for 9 comparisons (see supplement).

RESULTS

Demographic information is reported in table 1. Of the 56 subjects who were consented, 10 failed the screening process, 8 never initiated, 8 dropped out prior to completing, and 30 completed all 3 test days. Due to technical difficulties during EEG acquisition, 6 completers were excluded from the analyses; in addition, 1 subject from the 0.015mg/kg condition and 1 from the 0.03mg/kg condition were excluded from analysis due to artifactual contamination in the preprocessed EEG data. Thus, a total of 24 subjects in the placebo condition and 23 in both the 0.015mg/kg and 0.03mg/kg conditions were included in the analyses. As reported elsewhere, 5 non-serious and no serious adverse events occurred on test days (44). For parsimony, statistics are reported either in the text or tables, but not both.

Effect of drug condition on EEG measures

Lempel-Ziv Complexity—There was a significant effect of drug condition on LZC (Wald $\chi^2(2)=42.696$, $p_{Adj}<0.001$) that remained significant (Wald $\chi^2(2)=36.319$, $p_{Adj}<0.001$) after controlling for signal power. These findings persisted despite HB-adjustment for 2 comparisons. The 6 HB-adjusted pairwise comparisons performed before and after controlling for signal power (3 comparisons each) revealed significantly higher LZC for the 0.03mg/kg (both $p_{sAdj}<0.001$) and 0.015mg/kg ($p_{Adj}<0.001$ and $p_{Adj}=0.002$, respectively) doses compared to placebo, and for the 0.03mg/kg dose compared to the 0.015mg/kg dose (both $p_{sAdj}<0.001$) (figure 1 and table 2).

Signal power—There was a significant effect of drug condition on signal power (Wald $\chi^2(2)=8.004$, $p_{Adj}=0.036$) which disappeared after controlling for LZC (Wald $\chi^2(2)=2.236$, $p_{Adj}>0.1$). Three HB-adjusted pairwise comparisons performed on the data before controlling for LZC revealed significantly lower power for the 0.03mg/kg and 0.015mg/kg doses compared to placebo (both $p_{Adj}=0.029$) but no difference between the 0.03mg/kg and 0.015mg/kg doses ($p_{Adj}>0.1$) (figure 2 and table 2).

Relationship between LZC and signal power—The regression of LZC on signal power revealed a significant inverse relationship between both variables ($\beta=-0.544$, Wald $\chi^2(1)=42.229$, $p<0.001$).

Effect of drug condition on behavioral measures

The nonparametric analyses HB-adjusted for 3 comparisons revealed a significant effect of drug condition for the PANSS positive (ANOVA-type statistic (ATS)(1.864)=28.147, $p_{Adj}<0.001$), disorganization (ATS(1.660)=26.555, $p_{Adj}<0.001$), and negative (ATS(1.914)=12.608, $p_{Adj}<0.001$) symptoms factors. The 9 HB -adjusted pairwise comparisons showed significantly higher scores for the 0.03mg/kg and 0.015mg/kg doses compared to placebo (all $p_{sAdj}<0.001$ excepting $p_{sAdj}=0.031$ for the 0.015mg/kg dose versus placebo comparison of the negative factor) and for the 0.03mg/kg dose compared to the 0.015mg/kg dose (all $p_{sAdj}<0.02$) (table 2).

Relationship between EEG and behavioral measures

The regressions of the PANSS factor scores on LZC revealed significant HB-corrected (9 comparisons) coefficients for the positive symptoms factor before ($\beta=0.442$, Wald $\chi^2(1)=9.114$, $p_{Adj}=0.015$) (supplementary figure S2A) and after ($\beta=0.685$, Wald $\chi^2(1)=39.419$, $p_{Adj}<0.001$) (figure 3A) controlling for signal power; and for the disorganization symptoms factor before ($\beta=0.646$, Wald $\chi^2(1)=15.819$, $p_{Adj}<0.001$) (supplementary figure S2B) and after ($\beta=0.754$, Wald $\chi^2(1)=25.861$, $p_{Adj}<0.001$) (figure 3B) controlling for signal power. No significant coefficients were found for the regression of the negative symptoms factor on LZC (all $p_{sAdj}>0.1$). In contrast to LZC, no coefficient reached significance for signal power after HB-correction ($p_{Adj}>0.1$).

Exploratory analysis to determine whether recent (30 day) cannabis exposure influenced the effects of 9 -THC on LZC revealed no significant effects of cannabis exposure (see supplement). Finally, plasma levels of 9 -THC and its metabolite 9 -THC-COOH were sampled periodically (see supplement), showing a dose-dependent increase as reported previously (44).

DISCUSSION

To our knowledge, this is the first study to demonstrate an increase in neural noise, defined as the randomness of EEG signals, induced by a psychotomimetic drug in humans. More specifically, this study showed for the first time that 9 -THC increased neural noise indexed by LZC in a dose-related manner. As expected (reviewed in 24, 25, 26), 9 -THC increased positive, disorganization and negative symptoms. Furthermore, there was a strong positive relationship between neural noise and the psychosis-like effects induced by 9 -THC, which was independent of the changes in total signal power. In contrast, there was no relationship between noise and negative-like symptoms. This suggests a specific relationship between neural noise and 9 -THC induced psychosis-like effects, raising the intriguing possibility that neural noise may be involved in other forms of psychosis as well. In addition, 9 -THC reduced total signal power during both active drug conditions compared to placebo but this effect disappeared after controlling for LZC. No relationship was detected between signal

power and psychosis-like symptoms. Finally, an inverse relationship between LZC and signal power was observed.

Noise and signal power

As described above, LZC is a nonlinear measure of the randomness (noise) of time series (30). While Δ^9 -THC increased noise in a dose-dependent manner, the signal did not become completely random, a state which would be associated with an LZC value of 1. Note that the LZC value associated with a perfectly regular (periodic) or predictable signal would approach 0 (31, 32). What the associated LZC value is for optimal brain function remains unknown, and is likely an intermediate value between 0 and 1.

Animal studies have revealed that cannabinoids acutely reduce the spectral power of LFP oscillations by increasing the randomness (reducing the synchronization) of the activity of populations of neurons rather than reducing the activity of individual neurons (28, 29). The increased randomness would reduce the neurons' capacity to form temporally coordinated ensembles, leading to a reduction of LFP spectral power (28). Consistent with these findings, our results showed that Δ^9 -THC reduced signal power and increased randomness, and that there was an inverse relationship between signal power and randomness.

Relationship between noise, connectivity and behavior

As discussed in the introduction, keeping the bandwidth and total power of a signal constant, the higher the level of random noise, the lower the amount of information that can be carried by a signal without distortion. Considering that our findings were independent of total signal power and that the bandwidth of the signals was kept constant (99.5Hz) across conditions by filtering, we speculate that our findings could reflect a negative relationship between the amount of error-free information capable of being carried by the brain signals and the psychosis-like effect induced by Δ^9 -THC. Furthermore, we hypothesize this may affect the capacity of different brain areas (nodes) to process information coordinately. This would of course apply only to the brain sources captured by the midline electrodes used in our analyses. However, if the activity captured by these electrodes is representative of the activity within larger brain areas, then one might speculate that the results of this study may be informative about brain function in general. If so, these results would be aligned with some theoretical models proposing an aberrant connectivity (*dysconnection*) between brain areas as the underlying mechanism of psychotic symptoms in schizophrenia (57–59). Furthermore, we speculate that LZC will be inversely correlated to electrophysiological indices of connectivity such as Phase lag index (60) and Inter-electrode coherence (61).

Mechanism of Noise

While it is beyond the scope of this study to determine the mechanism by which Δ^9 -THC increased noise, it is tempting to speculate on some explanations. In the cerebral cortex and hippocampus, CB1Rs are located on the axon terminals of cholecystokinin (CCK)-expressing GABAergic interneurons (62). While parvalbumin (PV)-expressing GABAergic interneurons seem to have the main role in the generation of regular oscillatory activity (non-random recurrent patterns), it has been proposed that CCK cells enhance the signal-to-noise ratio of neural oscillations (like a 'noise filter') through a CB1R-mediated mechanism

(63–65). Thus, it may be the case that the observation that 9 -THC increased LZC resulted from a disruption of this “noise filter” mechanism by the non-physiologic activation of CB1Rs by 9 -THC. While the manner in which this abnormality would affect neural computations is far from being clear, it is interesting to note that increased levels of LZC and similar measures have been reported in schizophrenia and have been related to periods of symptomatic exacerbation (21–23).

LZC complements traditional measures of brain activity

Event-related potentials (ERPs) are one of the EEG measures most widely used in current studies of psychoses. ERPs provide valuable information about the consistency and strength of the brain’s time-locked response to different presentations of a stimulus. Using this approach we showed that 9 -THC reduced the amplitude of the P300 (44). LZC complements these measures by capturing a different aspect (randomness) of the neural dysfunction underlying 9 -THC-induced psychosis-like symptoms. Interestingly, exploratory analyses revealed medium-sized ($\beta -0.4$) negative relationships between LZC and the amplitudes of P3a and P3b. Of note, while P3a or P3b amplitudes were not related to symptoms measured either by the 3 (44) or 5-factor (current) solution of the PANSS, LZC was (see supplement). Furthermore, we explored the relationship between baseline power (an index of brain activity not evoked by a task) in the traditional frequency bands and psychosis-like symptoms. Similar to Spencer’s study on schizophrenia patients (43), we found no relationship between baseline power and psychosis-like symptoms in any frequency band (see supplement). Taken together, these findings suggest that LZC may be more sensitive to the pathophysiology underlying positive symptoms than some traditional EEG measures. Thus, LZC may be able to provide information about the pathophysiology of positive symptoms that has been overlooked by studies using these measures.

Strengths and Limitations

Unlike other measures of noise (e.g., inter-trial variability, increased task-unrelated activity) (14–18, 39, 43), LZC provides direct information about the level of randomness of the EEG signals (30), which makes it more suitable for quantifying the noise of brain activity. The obvious differences between these measures limit any direct comparisons between the results of this study and those previously obtained in schizophrenia.

In contrast to previous evoked-response studies (14–18, 39), in this study data captured immediately prior to the onset of the stimulation period were analyzed. Despite the fact that the pre-stimulation period doesn’t capture evoked activity, it is not true resting state activity due to the anticipation elicited by recurring events (i.e., auditory click trains) and the expectation associated with task-related stimuli (i.e., P3b). Thus, whether our findings apply to resting state activity or to activity associated with expectancy during the pre-stimulation, will need to be determined in future studies.

In this study, continuous EEG data were transformed into binary symbolic sequences using the threshold-crossing approach (see Methods), prior to calculating LZC. While this approach is associated with some loss of information (66, 67) about the fine-grained dynamics of the system generating the signals (e.g., the brain), it is capable of providing an

accurate representation of the macroscopic-level dynamics of the system (67). Furthermore, a consequence of using the median as the threshold is that low-range frequencies are preferentially represented in the resulting binary data (see supplement). Even though the median-crossing approach is widely used, alternate approaches (e.g. 68) that better represent the entire frequency spectrum should be explored. The loss of some information notwithstanding, LZC based on this approach has been informative about the brain in health and disease (34, 35, 37, 38).

Conclusions

At doses that produced increases in psychosis-like effects, 9 -THC increased neural noise (LZC) measured in the EEG of humans in a dose-dependent manner. Furthermore, increases in neural noise were positively related with 9 -THC-induced psychosis-like, but not negative-like, effects. These findings suggest that neural noise may contribute to the psychotomimetic effects of 9 -THC. Further replication of these findings is warranted as are studies into the mechanisms underlying the increases in neural noise (e.g., studying the intracortical correlates of these surface recordings in animals). It would be interesting to determine whether these findings are exclusive to 9 -THC or whether other drugs known to produce psychosis-like effects (e.g., ketamine [NMDA receptor antagonist] and psilocybin [5-HT_{2a} agonist]) increase LZC and whether the drug-induced increases in LZC correlate with psychosis-like effects. While LZC is increased during decompensation (22), to our knowledge, whether LZC is correlated with psychotic symptoms in schizophrenia patients has not been studied. If confirmed, LZC may have significant utility as a novel biomarker for the functional deficits underlying psychotic symptoms. Finally, while admittedly speculative, if psychotic symptoms are a result of brain dysconnectivity related to an abnormal increase of neural noise, interventions directed towards reducing noise may have therapeutic potential.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Lempel-Ziv complexity per drug condition

The graph shows the mean and standard error bars of Lempel-Ziv complexity (raw values, not corrected for signal power) per drug condition. Significant differences ($p < 0.001$) between conditions are indicated with **.

Figure 2. Baseline signal power per drug condition

The graph shows the mean and standard error bars of baseline signal power (raw values, not corrected for LZC) per drug condition. Significant differences ($p < 0.05$) between conditions are indicated with *.

Figure 3. ⁹-THC-induced positive and disorganization symptoms versus Lempel-Ziv complexity corrected for signal power

The figure shows the regression lines and standardized coefficients of the regressions of positive (A) and disorganization (B) symptoms factors of the PANSS on Lempel-Ziv complexity (LZC) corrected for signal power. PANSS scores and LZC values are presented in z scores.

Table 1

Sample demographics

<i>General Characteristics</i>	
No. Male (Female)	17 (7)
Age [Mean (SD)]	26.208 (8.108)
Handedness	1 left handed
Years of Education [Mean (SD)]	15.167 (2.014)
Estimated IQ [Mean (SD)]	115.750 (4.416)
<i>Cannabis Exposure</i>	
Age of First Cannabis Use	17.000 (2.523)
Days Since Last Use/Last exposure [Mean (SD), Range]	445.688 (846.645), 1–3650
Total Years of Use [Mean (SD), Range]	7.094 (4.486), 1–15
<i>Frequency of Cannabis Use Within Past 30 Days</i>	<i>No. of Subjects</i>
0 days	12
1–3 days	4
4–8 days	3
9–15 days	3
16–29 days	2
<i>Lifetime Cannabis Use (Total No. of Exposures)</i>	<i>No. of Subjects</i>
1–10	4
11–50	8
51–200	3
201–500	3
501–1000	3
>1000	3
<i>Cannabis Exposure During Heaviest Use (No. of Exposures)</i>	<i>No. of Subjects</i>
<1 to 1 per year	6
1 per 3–6 months	4
1–3 per month	3
1–2 per week	2
3–6 per week	5
7 per week	4
<i>Other Drug Exposure</i>	
Daily Cigarette Smokers (# of subjects)	2
Average No. of Alcoholic Drinks Per Week [Mean (SD)]	6.01 (6.06)
<i>Previous Recreational Exposure to Illicit Drugs Other Than Cannabis</i>	<i>No. of Subjects</i>
None	11
Hallucinogens	12
Stimulants	10
Opiates	3

<i>General Characteristics</i>	
Inhalants	2
<i>(None of the subjects met criteria for abuse or dependence of the above illicit substances)</i>	

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Table 2⁹-THC effects on electroencephalographic and behavioral measures

Measure	Placebo Mean (SD)	0.015 mg/kg Mean (SD)	0.03 mg/kg Mean (SD)
Lempel-Ziv complexity	0.395 (0.021)	0.408 (0.023)	0.420 (0.025)
Total signal power	64.391 (32.448)	55.088 (23.082)	54.507 (21.643)
PANSS Positive factor	6.833 (2.334)	9.435 (2.936)	11.217 (2.999)
PANSS Disorganization factor	11.667 (2.353)	14.304 (3.183)	16.739 (4.223)
PANSS Negative factor	7.208 (2.395)	8.870 (3.348)	11.826 (4.579)