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Influence of low-dose ketamine on periodic and aperiodic components of resting-state EEG dynamics

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Abstract

Ketamine, an NMDA receptor antagonist, has garnered interest for scientific use due to its unique effects on brain dynamics. Previous research has demonstrated that ketamine reduces the alpha peak power and shifts the excitation inhibition balance (E:I balance) toward excitation when administered in anaesthetic dosages. This study investigates the effects of low-dose ketamine on resting-state EEG dynamics, focusing on these two findings. Using a crossover design, participants received ketamine, propofol, or a placebo. The 1/f-like aperiodic component of the spectrum was analyzed to assess changes in the E:I balance. Results showed a significant decrease in alpha peak power and a reduction in the exponents of the 1/f spectrum in the ketamine condition, indicating a shift toward excitation in the E:I balance. These findings are consistent with the previous research on narcotic dosages and suggest that even at low doses, ketamine induces measurable alterations in brain activity. It should be noted that the current data collection is still ongoing, but these preliminary results already underscore the potential of ketamine in probing NMDA receptor hypofunction and E:I balance in cognitive and behavioral contexts.

I. Introduction

The electroencephalogram (EEG) is a widely utilized methodology for the assessment of human brain function. An EEG allows for the measurement of electric, rhythmic activity that reflects neural oscillations in the brain. These oscillations can be described in terms of their frequency in Hertz (Hz), their power, and their phase. Over decades of EEG research, a categorization has been established for different brain frequency bands. The alpha band for example, occurring at approximately 8-12 Hz, is particularly prominent. To identify these different frequency bands, one can compute the Fourier transformation, which converts oscillations from the time domain into the frequency domain and calculates the power spectral density (PSD).

The objective of this study is to analyze the influence of ketamine on resting-state EEG dynamics, especially the impact of ketamine on the alpha peak power and the excitatory and inhibitory balance in the brain (E:I balance). The participants were injected with either ketamine, propofol, or a placebo. Here, we focus on the ketamine-related data. Ketamine is primarily used for anaesthesia and pain medication, but it is becoming increasingly relevant in other fields as well, such as for treating depression. Additionally, there is growing interest in ketamine for scientific purposes, because of its inhibitory effect on N-Methyl-D-Aspartate (NMDA) re-

ceptors [1]. This results in NMDA hypofunction, which is also the case in schizophrenia [2]. Consequently, ketamine serves as a valuable investigative tool for examining schizophrenia-like behavior and/or physiological and psychological symptoms in healthy subjects. In our study design we used low dosages of ketamine.

The present analysis utilizes EEG data collected during periods of rest and unstimulated activity, also known as the "resting-state". The analysis focused on the alpha peak power. The alpha peak is generally situated within the frequency band of 8 to 12 Hz, and its power varies across different states. A higher alpha peak power is associated with a state of wakeful relaxation. The impact of ketamine on alpha peak power is characterized by a reduction in power after injection [3].

Additionally, we examined the aperiodic component of resting-state EEG data, which exhibited a 1/f-like spectrum. The 1/f pattern, a prevalent phenomenon in natural systems, is defined by an exponential decline in power with increasing frequency. In this context, the term "aperiodic" is used to describe a distribution of EEG data that lacks periodic components, e.g. the alpha peak. From this spectrum, the exponent can be extracted, which serves as an indicator for the steepness of the spectrum. This exponent varies with cognitive and perceptual states, aging, and diseases [4].

To quantify the E:I balance, the exponent of the 1/f-like spectrum can be a used as a proxy. The E:I balance is imperative for maintaining homeostasis and effective information processing. This balance exerts a significant influence on neuronal activity by for example modulating the interplay of rapid glutamatergic and slower gamma-aminobutyric acid (GABA) inputs. Imbalance in this regulatory system has been associated with various psychiatric disorders, including schizophrenia [5]. NMDA hypofunction has been shown to result in a shift of the E:I balance toward excitation [6]. In general, the following can be stated: A shift in the E:I balance toward excitation results in a flatter spectrum, leading to a lower exponent for the 1/f spectrum. Conversely, when the E:I balance shifts toward inhibition, the spectrum will be steeper and the exponent will be higher [4].

Ketamine has been demonstrated to induce hypofunction of the NMDA receptor. This, in turn, has been shown to result in a shift toward excitation in the E:I balance. This shift is predicted to result in lower exponents in the 1/f spectra. Consequently, the exponents of an 1/f-like spectra under ketamine should be lower compared to the absence of ketamine. This has been demonstrated in real data from anaesthetized patients. The researcher observed lower exponents in ketamine-anaesthetized patients compared to those in awake condition, while propofol showed opposite effects [7].

It has been shown that ketamine exerts a variety of effects on EEG dynamics. These changes were observed in subjects undergoing anaesthesia. The objective of this study is to ascertain whether analogous alterations in the EEG occur in participants who receive a low dosage, thereby maintaining the capacity to perform a task. In long term this has the potential to investigate decision-making during a state of NMDA hypofunction.

II. Materials and Methods

As this study is still in progress, we have used preliminary data. The analysis encompassed a total of 18 participants, ranging in age from 20 to 41 years (12 female). Four of these participants engaged in three sessions, thereby undergoing all conditions. Eight participants engaged in two instances, while six participants participated on a single occasion. This results in a total of 14 data sets in the propofol condition, 9 in the placebo condition, and 11 in the ketamine condition.

The study employs a crossover design with healthy, young participants who are asked to perform an auditory decision making task. The goal is that every participant engages in all three conditions carried out on three different days. The study utilized three distinct pharmacological agents applied intravenously via target controlled infusion (TCI): ketamine (target plasma concentration of 150 ng/ml), propofol (target plasma concentration of 500 ng/ml), and a placebo (NaCl). The order was randomized. The EEG recording started with a four-minute recording of the eyes closed resting-state (pre). Following the training period, the infusion was initiated, and a 30-minute waiting period was observed to allow for the uniform distribution of the substance. Subsequently, the participant completed the task, the specifics of which are not relevant here. Immediately following the completion of the task, which lasted approximately an hour and ten minutes, the infusion was stopped, and a second eyes closed resting-state EEG was recorded (post).

Ethical approval for the study was obtained, and the subjects of the study received a compensation of 20 euros per hour for their participation.

II.I. Analysis

The raw EEG data (64 channels) were subjected to preprocessing in MATLAB 2023b, employing the Fieldtrip and EEGlab toolboxes. An independent components analysis (ICA) was conducted, and a plugin was utilized to classify components associated with muscle, eye, heart, line noise, channel noise, and other sources. The threshold of rejection for each component was set at a probability greater than 90%. The ICA was conducted on the entire experiment, and the resting-state segments were subsequently extracted for further analysis. The EEG data were downsampled to 250 Hz, and a high-pass filter with a cutoff frequency of 0.3 Hz and a low-pass filter with a cutoff frequency of 180 Hz were applied. Subsequently, the data

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were re-referenced to the average of all electrodes.

The power spectrum of each electrode was estimated using Welch method (pwelch function) and subsequently averaged across all electrodes. The alpha peak power was determined between 7 and 13 Hz by extracting the maximum power value within this range. The EEG data were further analyzed in Python using the package "fooof" (version 1.1.0; for further details see [4]) for calculating the aperiodic 1/f distribution. The settings for this analysis were based on previous research (peak width limits=[1, 8], max n peaks=8, min peak height=0.05, peak threshold=2.0, aperiodic mode='fixed') [7]. Power spectra were parameterized in the frequency range of 1 to 50 Hz.

III. Results

The results of the alpha peak power analysis are shown in Fig. 1. Due to our focus on the ketamine-related data,

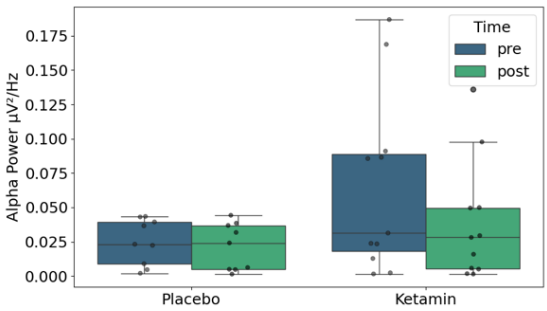

Figure 1: Alpha peak power in μV^2/Hz comparing the placebo and ketamine condition, before (pre) and after (post) the injection. Black horizontal line is the median.

only the ketamine and placebo alpha peak power were analysed. As illustrated in Fig. 1, the alpha peak power is reduced in both conditions, though this decrease is not statistically significant. Nevertheless, the relative difference in the ketamine condition exceeds that of the placebo condition. This difference in differences, or the interaction, is significant in the mixed model, as demonstrated in Table. 1.

Table 1: Statistical results from the linear mixed model Formula: Alpha peak power~condition:time. C stands for ketamine condition.

Name	coeff	StdError	p-value
Intercept	0.028	0.015	0.073
time [T.post]	-0.004	0.007	0.605
cond.[T.C]	0.037	0.020	0.067
cond.[T.C]:time[T.post]	-0.023	0.010	0.017*

From the fooof analysis we obtained the full model fit, the aperiodic fit and the exponents from the pre and post resting-state EEG. The placebo and ketamine condition are visualized in Fig. 2. The descriptive trend indicates a

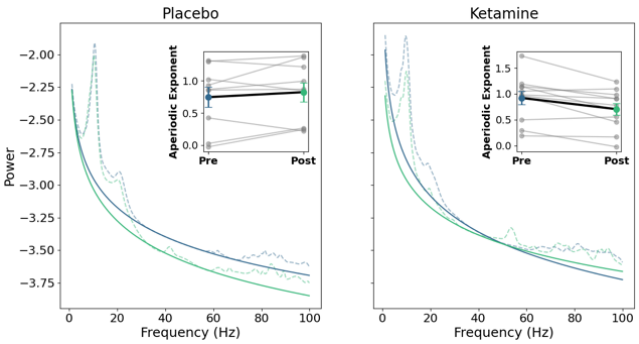

Figure 2: Spectra and exponents (with mean and SD) comparing placebo and ketamine condition. Dashed line full model fit, solid line aperiodic fit. Blue before (pre) and green after (post) injection.

decrease of the exponents from pre to post drug in the ketamine group, which is consistent with the anticipated outcome. In contrast, the exponents in the placebo condition exhibited a comparatively small change.

Changes in the exponents were analyzed with mixed-effects model (Table. 2). The contrast were simple effect coded with the placebo condition as reference. The Interaction condition ketamine/placebo with time pre to post is significant, whereas all the other main effect and interaction do not show significant effects.

Table 2: Statistical results from the linear mixed model formula: Exponents ~condition:time. The letters A, B, and C are used to denote the drugs propofol, placebo, and ketamine, respectively.

Name	coeff	StdError	p-value
Intercept	1.038	0.071	0.000***
time [T.post]	-0.078	0.054	0.147
cond. AB	0.099	0.117	0.105
cond. AB:time [T.post]	-0.221	0.131	0.093
cond. CB	0.198	0.108	0.067
cond. CB:time [T.post]	-0.293	0.138	0.034*

IV. Discussion

Two significant findings were identified that support our hypotheses. First, the reduction of the alpha peak power under ketamine, second, the decline of the exponents in the ketamine condition. In both instances, such a decline was not observed in the placebo condition, thereby validating our hypotheses. Those results demonstrate that even at low-dose ketamine dosages, similar changes in the EEG dynamics, especially increased excitation in

the E:I balance, can be observed as under anaesthetic dosages.

This analysis employed preliminary data, which resulted in a limited number of data points. This limitation is particularly evident in Fig. 1, where the medians are considerably closer to each other than the means, whereas the median is more stable against outliers. When data sets are limited, a small number of outliers can exert a significant influence on the analysis of averages. When the data acquisition is completed, we expect the pre alpha peak power to have comparable means and standard deviations across the conditions. However, this expectation is not supported in the preliminary data, seen in Fig. 1, in which the blue boxes are not the same. This difference may be due to some subjects participated in only one condition yet, while others have participated already in both. But the significance of our findings is preserved through the implementation of a mixed effect model analysis, which equalizes the mix of within and between subject comparisons.

A potential cause of the decrease of the exponents from the 1/f distribution is the time constant of NMDA receptors. It is acknowledged that different synapses possess distinct temporal domains, with glutamate receptors being classified as slow-acting [8]. Consequently, NMDA receptor blockade exerts a suppressive effect on slow frequencies in the EEG signal. This effect leads to a flattened spectrum, a reduced exponent, and potentially a shift of the E:I balance toward excitation.

Another issue concerns the relationship between the steepness of the 1/f distribution and the E:I balance. It is necessary to determine whether this steepness is indicative of the E:I balance or if it is primarily influenced by the alpha peak. It is possible that the increase in alpha peak power creates greater dynamical range for decline, potentially leading to steeper spectra and higher exponents. Conversely, a diminished alpha peak power can result in flatter spectra and lower exponents, owing to the reduced capacity for decline. Based on this consideration, we have used fooof to calculate the exponents. The exclusion of the alpha peak makes the exponents independent of its height. Additionally, the observation that the exponents in the pre-resting state are approximately equivalent to those in the placebo condition appears to contradict this hypothesis.

V. Conclusion

Taken together, this study demonstrates that low-dose ketamine induces measurable alterations in EEG signals, namely a reduction in alpha peak power and a flattening of the 1/f-like aperiodic spectrum. These changes suggest a shift in the E:I balance toward excitation, consistent with NMDA receptor hypofunction. While preliminary findings align with prior research on anaesthetized subjects, further investigation with a larger sample is needed to validate the results. However, these insights underscore ketamine's potential even at a low dosage, to investigate behavioral tasks.

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Author's statement

Authors state no conflict of interest. Informed consent has been obtained from all individuals included in this study. The research related to human use complies with all the relevant national regulations, institutional policies and was performed in accordance with the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee.

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