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Research paper

Subanesthetic ketamine alters EEG signal complexity: Implications for treatment stratification in depression

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ABSTRACT

Major depressive disorder, particularly its treatment-resistant form (TRD), poses significant treatment challenges. Ketamine, an *N*-methyl-D-aspartate receptor antagonist, has shown promise in rapidly alleviating depressive symptoms by influencing neuroplasticity and glutamatergic modulation, which are thought to influence brain activity complexity. In this placebo-controlled study, we examined the effects of subanesthetic doses of intravenous ketamine on EEG signal complexity in 24 MDD patients, 21 of whom had TRD. Treatment response was defined by a $\geq$ 33 % reduction in Montgomery-Åsberg Depression Rating Scale (MADRS) after ketamine administration. Patients underwent eyes-closed resting state EEG recording pre-, start-, end- and 24 h post-infusion, analyzed for temporospatial and spatiotemporal Lempel-Ziv complexity (LZC_T and LZC_S). Results indicated that ketamine significantly increased whole-brain LZC_T during infusion compared to placebo (sodium chloride 0.9 %) (16.90 % vs. -4.84 %, 95 % CI 4.29 to 39.18, $p = 0.017$). Elevated LZC_T at end-pre was associated with less short-term symptom improvement the following day. Conversely, lower pretreatment occipital LZC_T (0.33 vs. 0.46, 95 % CI 0.007 to 0.26, $p = 0.040$) predicted a favorable response to ketamine, supported by a logistic regression model with an ROC area of 0.75. No significant changes were observed in LZC_S, suggesting limited utility as a biomarker. In conclusion, occipital LZC_T could serve as an effective predictive biomarker for ketamine's therapeutic effects in MDD, with implications for patients with TRD. This underscores the potential of EEG complexity measures in stratifying treatment and enhancing our understanding of the neural impacts of ketamine in depressive disorders.

1. Introduction

Major depressive disorder (MDD) is a pervasive and debilitating mental health condition, with its treatment-resistant form (TRD) posing significant clinical challenges. TRD is defined by a lack of response to at least two distinct antidepressants (McIntyre et al., 2023), such as monoamine reuptake inhibitors, and affects approximately 30 % of patients with depression. TRD underscores the need for more effective therapeutic options (Ionescu et al., 2015; McIntyre et al., 2023). Among emerging treatments, ketamine—a glutamatergic antagonist originally developed as an anesthetic (Gonda et al., 2023; Krystal et al., 2013)—has shown promise for patients unresponsive to standard therapies, demonstrating rapid antidepressant effects through mechanisms distinct from conventional therapies (Marcantoni et al., 2020; McIntyre et al., 2020; Sos et al., 2013; Zhou et al., 2022).

Ketamine's antidepressant effects are thought to be mediated by its ability to enhance neuroplasticity and modulate glutamatergic transmission (Abdallah et al., 2018; Aleksandrova and Phillips, 2021). This process involves the upregulation of brain-derived neurotrophic factor (BDNF) and activation of the mammalian target of rapamycin (mTOR) pathways, which are crucial for improving frontal network connectivity (Deyama and Kaneda, 2023; Zhou et al., 2014). Deficits in balance

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between excitation/inhibition (E/I) in cortical circuits, a hallmark of TRD, can disrupt frontal network function, contributing to cognitive and affective symptoms (Aleksandrova and Phillips, 2021; López-Solà et al., 2020; Xue et al., 2017). Supporting these mechanistic insights, neuroimaging studies provide evidence of ketamine's impact on brain function. For instance, with diffusion tensor imaging (DTI) technique, research has revealed microstructural neuroplasticity in critical brain regions like the prefrontal cortex, left amygdala, and hippocampus within 24 h post-infusion, correlating with better clinical improvements (Kopelman et al., 2023). Similarly, functional Magnetic Resonance Imaging (fMRI) studies have shown increased functional connectivity in prefrontal and limbic regions after ketamine administration, associated with better treatment responses (Rengasamy et al., 2024). Similar Biomarkers studies also support these findings, highlighting changes in functional connectivity (Salvadore et al., 2010), white matter integrity (Vasavada et al., 2016), and gamma power (Nugent et al., 2019), all of which enhance our understanding of ketamine's therapeutic potential.

Electroencephalography (EEG) has emerged as a crucial tool in capturing these dynamic brain changes induced by ketamine. Ketamine has also been shown to reduce EEG vigilance, marked by an increase in stage B1 during infusion. This reflects decreased wakefulness and enhanced fast oscillations (Ip et al., 2024). Beyond these biomarkers, EEG neural complexity, particularly Lempel-Ziv complexity (LZC), offers a promising biomarker closely linked with the integrity of interneuronal connectivity (Lempel and Ziv, 1976; Murphy et al., 2023; Zhang et al., 2015). LZC, an algorithmic measure of neural signal complexity, is particularly well-suited for capturing ketamine-induced changes in brain activity due to its sensitivity to dynamic oscillatory systems (Aboy et al., 2006; Lempel and Ziv, 1976; Zhang et al., 2013). Research has shown that LZC is altered in conditions like unipolar depression are associated with increased LZC, particularly in the frontal region due to impaired cortical inhibition and reduced network efficiency (Bachmann et al., 2015; Hernández et al., 2023; Mohammadi and Moradi, 2021). Ketamine, by enhancing excitatory activity and promoting neuroplasticity, has been shown to elevate LZC shortly after administration in healthy individuals, correlating with subjective psychedelic experiences such as sensory alteration and dissociation (Farnes et al., 2020; Schartner et al., 2017). In late-life TRD, a recent study found that LZC significantly increased after ketamine infusion, but this enhancement did not persist in the following days (Murphy et al., 2023). These findings suggest that LZC could serve as a potential biomarker for assessing the therapeutic effects of ketamine and investigating the neural mechanisms underlying treatment response.

Despite its promise, the specific relationship between LZC and the regional network's functional dynamics, particularly the frontal network, remains underexplored. Frontal circuits are central to cognitive and emotional regulation, and their dysfunction in MDD is well-documented (Arns et al., 2017; Fitzgerald et al., 2008; Ip et al., 2021b). However, whether LZC changes in the frontal region specifically correlate with symptom improvement or treatment resistance remains unclear. Furthermore, the utility of LZC in predicting treatment response to ketamine, particularly in TRD, has not been systematically validated. By leveraging a placebo-controlled design (Sos et al., 2013), this study provided a robust framework for isolating ketamine-specific effects on LZC, enabling a more precise evaluation of its therapeutic potential. In this secondary analysis of our previously reported clinical trial (Meyer et al., 2021), we aimed to investigate the rapid and residual effects of ketamine on both temporospatial and spatiotemporal measures of LZC, which refer to time dynamics and global changes among electrodes respectively (Li and Mashour, 2019; Murphy et al., 2023). We hypothesized that ketamine increases LZC during infusion, reflecting enhanced cortical dynamics and that regional variations may serve as predictive biomarkers for treatment response. Additionally, we explored whether LZC correlates with symptom severity, offering further insights into its potential role in stratifying patients for ketamine therapy.

2. Materials and methods

2.1. Patients

Detailed methodologies and participant recruitment processes were described elsewhere (Ip et al., 2024; Meyer et al., 2021). Twenty-four patients aged 18 to 65, were diagnosed with MDD according to DSM-IV criteria and confirmed through the Mini-International Neuropsychiatric Interview. Recruitment occurred between 2010 and 2015 (EudraCT Number: 2013–000952-17). Key inclusion criteria included a Montgomery-Åsberg Depression Rating Scale (MADRS) score of 20 or higher and a history of non-response to at least one adequate antidepressant treatment, with 21 classified as having TRD. All participants were required to maintain stable antidepressant dosages for at least four weeks prior to enrollment, with no treatment augmentation permitted. Exclusion criteria included suicide risk, current psychiatric comorbidities, and serious unstable medical or neurological conditions. See supplementary materials S.1 for the study flow diagram.

2.2. Study design and procedures

The study employed a controlled single-blind, one-arm, fixed-sequence design without randomization. Participants first received a placebo infusion, followed by ketamine infusion after a 7-day washout period. Care providers and evaluators were aware of the infusion sequence. All participants provided informed consent. All data were anonymized. The study protocol was approved by the Ethical Committee of the Prague Psychiatric Centre/National Institute of Mental Health and followed the Declaration of Helsinki's ethical standards.

2.3. Ketamine and placebo infusion

Infusions were administered via a unilateral intravenous catheter placed in the participants' forearms, using an infusion pump (ID 20/50, Polymed Medical CZ Ltd). For the ketamine infusion, participants received a total dose of 0.54 mg/kg racemic ketamine hydrochloride (Calypsol, Gedeon Richter Plc., Czech Republic) over 30 min, consisting of a loading dose of 0.27 mg/kg followed by a maintenance infusion of 0.27 mg/kg over 20 min. In the placebo infusion, participants received an equivalent volume of saline solution (0.9 % sodium chloride), administered in the same manner.

2.4. Clinical measures and treatment response

Serum samples for ketamine and norketamine levels were collected at 10 and 30 min following the first loading dose of ketamine. Depressive symptom severity was assessed using the MADRS at pretreatment (pre-infusion) and 24 h after both the placebo and ketamine infusions. For the ketamine infusion, MADRS scores were also collected at three additional time points: 4 days, 7 days and 14 days post-infusion. Since only a small proportion of patients typically achieve the conventional $\geq$50 % reduction in MADRS scores at 24 h post-infusion, we applied a lower cut-off of $\geq$33 % reduction to define treatment response. This threshold was chosen to better capture patients exhibiting early antidepressant effects, even if they did not meet the conventional criteria, and to preserve sufficient statistical power for subgroup comparisons. While previous literature has reported 24-hour response rates of up to 41 % at the $\geq$50 % threshold (Marcantoni et al., 2020), variability is expected across studies and patient populations, particularly in treatment-resistant cohorts. The $\geq$33 % threshold was selected a priori and is consistent with prior analyses conducted on the same patient cohort (Ip et al., 2024; Meyer et al., 2021).

2.5. EEG recordings and processing

EEG recordings were conducted using a 22-channel BrainScope

digital amplifier (M&I, Prague, Czech Republic), following the extended international 10–20 system. Participants were seated semi-recumbently with eyes closed in a sound-attenuated room. EEG data were sampled at 1000 Hz, with impedances maintained below 5 kΩ. EEG recordings were taken at baseline (pre-infusion), 10 min after the first infusion (start-infusion), and 20 min after the second infusion (end-infusion) to capture rapid effects. An additional 10-min recording was conducted 24 h post-infusion to evaluate any residual effects. Data preprocessing involved re-referencing to an average reference, and manual removal of artifacts such as sudden movements and impedance-related issues using DeepPsy software. Independent component analysis (ICA) was employed to correct eye movement, cardioballistic effects, and technical disturbances. No significant differences were observed in the exclusion of epochs and ICA components across conditions; further details can be found in Ip et al. (2024). A bandpass filter (0.5–70 Hz) and a 50 Hz notch filter were applied, with bad channels reconstructed using spherical spline interpolation (Perrin et al., 1987).

2.6. Lempel-Ziv complexity of EEG signal

Lempel-Ziv complexity (LZC) analysis was performed to evaluate the EEG signal's complexity, indicating the richness of neuronal connectivity (Lempel and Ziv, 1976). LZC was computed from the first 10 min of the end-infusion recordings for consistency across all treatment conditions. Following the calculation described in a previous study (Aamodt et al., 2023), preprocessed EEG signals were downsampled to 250 Hz. A Hilbert transform was then applied to extract the instantaneous amplitude, which was subsequently binarized based on each channel's median value (see supplementary materials S.2 for the schematic of the LZC calculation). The algorithm quantified randomness by counting unique binary patterns, expressed as "0"s and "1"s. Two distinct LZC metrics were derived: temporospatial (LZC_T) and spatiotemporal (LZC_S) complexity indices (Li and Mashour, 2019, also refer to supplementary materials S.2). LZC_T assessed distinct temporal patterns across channels, normalized against a randomly shuffled baseline to provide values ranging from 0 (uniform) to 1 (max randomness) (Casali et al., 2013). This measure reflects the evolving temporal complexity of each signal and the degree of differentiation across electrode sites. The LZC_T was analyzed at whole-brain and regional levels, averaging values across all electrodes or specific regions: frontal (Fp1, Fp2, AFz, F3, F4, F7, F8, Fz), parietal (P3, P4, Pz, C3, C4, Cz), temporal (T3, T4, T5, T6), and occipital (O1, O2). In contrast, LZC_S focused on the variability of spatial pattern across the scalp at each time point, focusing on how the distribution of activity across electrodes changes over time (Casali et al., 2013). LZC_S was computed within 1-min blocks and over the entire 10-min window to assess both short- and broader dynamics in topographic complexity. This dual-index approach allowed us to separately examine the temporal evolution of complexity across the scalp (LZC_T) and the diversity of spatial signal topographies over time (LZC_S), aligning with recent frameworks emphasizing multiscale and multidimensional signal dynamics (Li and Mashour, 2019; Murphy et al., 2023).

2.7. Statistical analyses

Statistical analysis was conducted using SPSS 27.0 (SPSS Inc., Chicago, Illinois, USA) and RStudio 2024.4.1.748 (R Foundation for Statistical Computing, Vienna, Austria). Age and gender were included as covariates in all models, following previous analyses (Ip et al., 2024; Lord and Allen, 2023; Méndez et al., 2012). Degrees of freedom were adjusted using the Greenhouse-Geisser correction when necessary, and Bonferroni correction was applied for multiple comparisons and post hoc analyses to control for Type I errors. Statistical significance was set at $p < 0.05$. Detailed statistical methods were organized into the following three parts:

2.7.1. Rapid and remaining effects of ketamine on LZC

This analysis examined whether ketamine infusion alters EEG signal complexity compared to placebo, either rapidly (during infusion) or sustainedly (24 h post-infusion). We used repeated measures ANOVA to compare relative changes in LZC, calculated as the percent difference from pre-infusion, across treatment condition (start-pre, end-pre and 24 h-pre). For rapid effect analysis in both LZC_T and LZC_S indices, intervention (ketamine vs. placebo) and treatment condition (start-pre vs. end-pre) were included as within-subject factors, while group (responders vs. non-responders) was included as a between-subject factor. Regional LZC_T analyses included brain region (frontal, parietal, temporal, occipital) as additional within-subject factor, while in 1-min block analysis of LZC_S, recording block was included (1 min, 2 min, …, 10 min) as a within-subject factor. Residual effects were modeled similarly, focusing only the 24-hour post-infusion change (24 h-pre). We also conducted partial correlations, adjusted for age and gender, between LZC changes and serum levels of ketamine and norketamine.

2.7.2. Pretreatment LZC and group differences in treatment response

To assess whether pretreatment LZC values differ between ketamine responders and non-responders, we conducted ANOVA models examining pretreatment LZC by group (responders vs. non-responders). To further explore the classification potential of pretreatment LZC as a biomarker, we used logistic regression (without regularization) and computed a receiver operating characteristic (ROC) curve. Metrics such as sensitivity, specificity, and AUC (area under the curve) were derived.

2.7.3. Association between LZC and MADRS scores

This analysis investigated LZC values relate to subjective depressive severity. We used partial correlations (controlling for age and gender) between LZC values (at pretreatment and changes during infusion) and MADRS scores (at pretreatment and subsequent symptom improvement in follow-up days). To account for group-level differences in these associations, correlations were conducted separately for responders and non-responders. Additionally, pretreatment correlations were pooled across ketamine and placebo sessions to increase the sample size and robustness.

3. Results

3.1. Patient demographics

The demographic results were reported in our previous publication (Ip et al., 2024). In brief, 12 patients were classified as responders and 12 as non-responders to ketamine treatment. No significant differences were found in pretreatment MADRS scores, whole-brain LZC_T and 10-min-block LZC_S before ketamine and placebo infusion (p values >0.20, Table 1).

3.2. Rapid ketamine effects on LZC during infusion

The whole-brain model on LZC_T showed a significant intervention effect ($F(1,20) = 9.36$, $p = 0.006$, $\eta^2 = 0.32$), such that ketamine induced a greater change in LZC_T compared to placebo (16.90 % vs. -4.84 %, 95 % CI [4.29, 39.18], $p = 0.015$, Cohen's $d = 0.54$, Fig. 1). The three-way interaction between intervention, conditions, and group was not significant ($F(1,20) = 0.001$, $p = 0.97$, $\eta^2 < 0.001$), suggesting that the observed effect of ketamine on LZC_T was consistent across both responders and non-responders. However, no significant partial correlation was observed between the percentage changes in LZC_T at start-pre or end-pre and the levels of serum ketamine or norketamine (p values >0.15). The regional analyses of LZC_T did not yield significant differences across brain regions (p values >0.23), indicating that ketamine's rapid effects on LZC_T were not region-specific. The analyses on LZC_S did not reveal any significant effects (p values >0.26).

Table 1
Demographics characteristics and comparisons for ketamine and placebo intervention.

	Ketamine (n = 24)	Placebo (n = 24)			
	Mean (SD)	Mean (SD)	*F-value*	95 % CI	*p-value*
Demographics					
Sex (% M/F)	7/17 (29 %/71 %)		/	/	/
Age	43.67 (12.46)		/	/	/
Clinical: MADRS					
Pretreatment MADRS	27.33 (4.84)	27.50 (4.40)	1.34	[−0.05, 1.72]	0.26
Response (% R/NR)	12/12 (50 %/50 %)	1/23 (4 %/96 %)	/	/	**< 0.001**
24 h ΔMADRS (% changes from 24 h to pretreatment)	21.15 (25.05)	−0.31 (15.47)	11.48	[10.69, 32.23]	**0.003**
EEG: LZC					
Pretreatment whole-brain LZC_T	0.41 (0.14)	0.43 (0.12)	1.77	[−0.07, 0.02]	0.20
Pretreatment 10-min-block LZC_S	1.15 (0.057)	0.15 (0.062)	0.95	[−0.02, 0.03]	0.34

Note. M, male; F, female; MADRS, Montgomery-Åsberg Depression Rating Scale; LZC_T, temporospatial LZC; LZC_S, spatiotemporal LZC; R, responders; NR, non-responders. Responders were defined by at least a 33 % improvement in depressive symptoms assessed by the MADRS score 24 h after intervention. Bold values indicate statistically significant results at $p < 0.05$.

3.3. Pretreatment LZC and group differences in treatment response

No significant results were found in the whole-brain LZC_T analysis ($p = 0.69$). The regional LZC_T analysis revealed a significant interaction between brain region, intervention and group ($F(3,60) = 4.21$, $p = 0.035$, $\eta^2 = 0.174$), showing that responders exhibited lower occipital LZC_T values than non-responders before ketamine administration (0.33 vs. 0.46, 95 % CI [0.007, 0.26], $p = 0.040$, Cohen's $d = 0.83$, Fig. 2A). However, no significant difference was observed in frontal LZC_T values between group (0.40 vs. 0.41, 95 % CI [−0.11, 0.11], $p = 0.96$, Cohen's $d = 0.068$, Fig. 2A). The analyses of LZC_S did not yield any significant result (p values >0.32). Occipital LZC_T values were employed as predictive markers for treatment response within a logistic regression model. The analysis revealed a 50 % response rate at an occipital LZC_T threshold of 0.39, and achieved an accuracy of 71 %, with the optimal cutoff distinguishing responders and non-responders at an occipital LZC_T threshold of 0.5 (see supplementary materials S.3). This model yielded a recall of 0.75, precision of 0.69, and a ROC-AUC of 0.75 (Fig. 2B).

3.4. Association between LZC and clinical depressive scores

In all patients, a negative partial correlation was observed between end-pre LZC_T changes and 24-hour MADRS improvement ($r(20) = -0.43$, $p = 0.039$, 95 % CI [−0.71, −0.03], Table 2, Fig. 3), suggesting that greater increase in LZC_T was associated with less short-term symptom improvement. No significant correlation was found between whole-brain LZC_T at other treatment conditions and MADRS scores at other timepoints (p values >0.15, Table 2). As no region-specific ketamine effect was found, the association with regional LZC_T was not investigated. In non-responders specifically, only pretreatment frontal LZC_T was found significantly correlated with pretreatment MADRS scores ($r(20) = 0.41$, $p = 0.049$, 95 % CI [−0.004, 0.70], Table 2, Fig. 4A). In contrast, pretreatment whole-brain ($r(8) = 0.69$, $p = 0.012$, 95 % CI [0.20, 0.91]), frontal ($r(8) = 0.66$, $p = 0.021$, 95 % CI [0.13, 0.89]), temporal ($r(8) = 0.73$, $p = 0.0067$, 95 % CI [0.27, 0.92]) and occipital ($r(8) = 0.83$, $p < 0.001$, 95 % CI [0.49, 0.95]). LZC_T were positively correlated with MADRS score changes at 24 h post-ketamine infusion in responders (Table 2, Fig. 4B), but not in non-responders (p values >0.57). No significant correlation was found in LZC_S (p values >0.096).

3.5. Remaining ketamine effects on LZC 24 h post-infusion

The whole-brain model of LZC_T did not show any significant results (p values >0.50). Neither the regional analyses of LZC_T nor LZC_S showed any significant findings (p values >0.15).

4. Discussion

This placebo-controlled study investigated the effects of subanesthetic doses of ketamine on EEG signal complexity in patients with MDD, focusing particularly on those with TRD. By using Lempel-Ziv complexity (LZC), we assessed both temporospatial (LZC_T) and spatiotemporal (LZC_S) complexity measures to evaluate changes in brain activity over time and across different brain regions. Our primary findings indicate that ketamine significantly elevated whole-brain LZC_T during infusion compared to placebo, suggesting an enhancement in neuronal activity and complexity. Interestingly, elevated LZC_T at the end of ketamine infusion was associated with less short-term symptom improvement the following day. Furthermore, lower baseline LZC_T in the occipital region was identified as a potential predictive biomarker for a favorable response to ketamine, suggesting that individuals with initial lower complexity might benefit more from ketamine's neuroplastic effects.

4.1. Rapid ketamine effects on LZC during infusion

Our findings reveal significant insights into how subanesthetic doses of ketamine modulate EEG signal complexity. Specifically, enhancements in the richness and variability of patterns across EEG channels, quantified by LZC_T, reflect heightened neuronal activity (Hernández et al., 2023; Lempel and Ziv, 1976). This aligns with ketamine's mechanisms involving neuroplasticity and glutamatergic modulation, crucial for its rapid antidepressant effects (Price and Duman, 2020; Wang et al., 2022). The observed peak in LZC_T within 30 min of infusion corroborates findings from Murphy et al. (2023), who reported similar increase in EEG complexity shortly after ketamine administration. Computational models by Khaleghi et al. (2023) further suggest that an increase in the proportion of excitatory neurons under ketamine leads to more complex brain dynamics. This is consistent with the broader literature indicating that ketamine induces increased brain signal complexity and enhanced gamma oscillations (Lijffijt et al., 2021; Newport et al., 2015; Schartner et al., 2017; Sos et al., 2013), further demonstrated by the elevation of EEG vigilance stage B1 (Ip et al., 2021a, 2024). This stage, characterized by low-voltage EEG with dominant beta activity and reduced alpha activity (Ip et al., 2024), signifies a shift towards lower vigilance stages, effectively helping patients transfer from high to low vigilance phases (Ip et al., 2024, 2021a). Furthermore, ketamine's induction of EEG changes extends to increasing beta power and promoting fast oscillations, often observed in therapeutic contexts and experimental settings like status epilepticus (Machado et al., 2022). These modifications suggest a dissociative state of vigilance (Corssen & Domino, 1966; de la Salle et al., 2016; Haaf et al., 2023), where the interplay between enhanced beta power and the overall increase in LZC_T underscores the complex influence of ketamine on brain activity.

Ketamine's ability to enhance EEG signal complexity was observed across all patients with MDD, irrespective of their response to treatment. This general enhancement indicates that ketamine consistently affects neuroplasticity and neural dynamics (Aleksandrova and Phillips, 2021; Kopelman et al., 2023; Price and Duman, 2020; Wang et al., 2022),

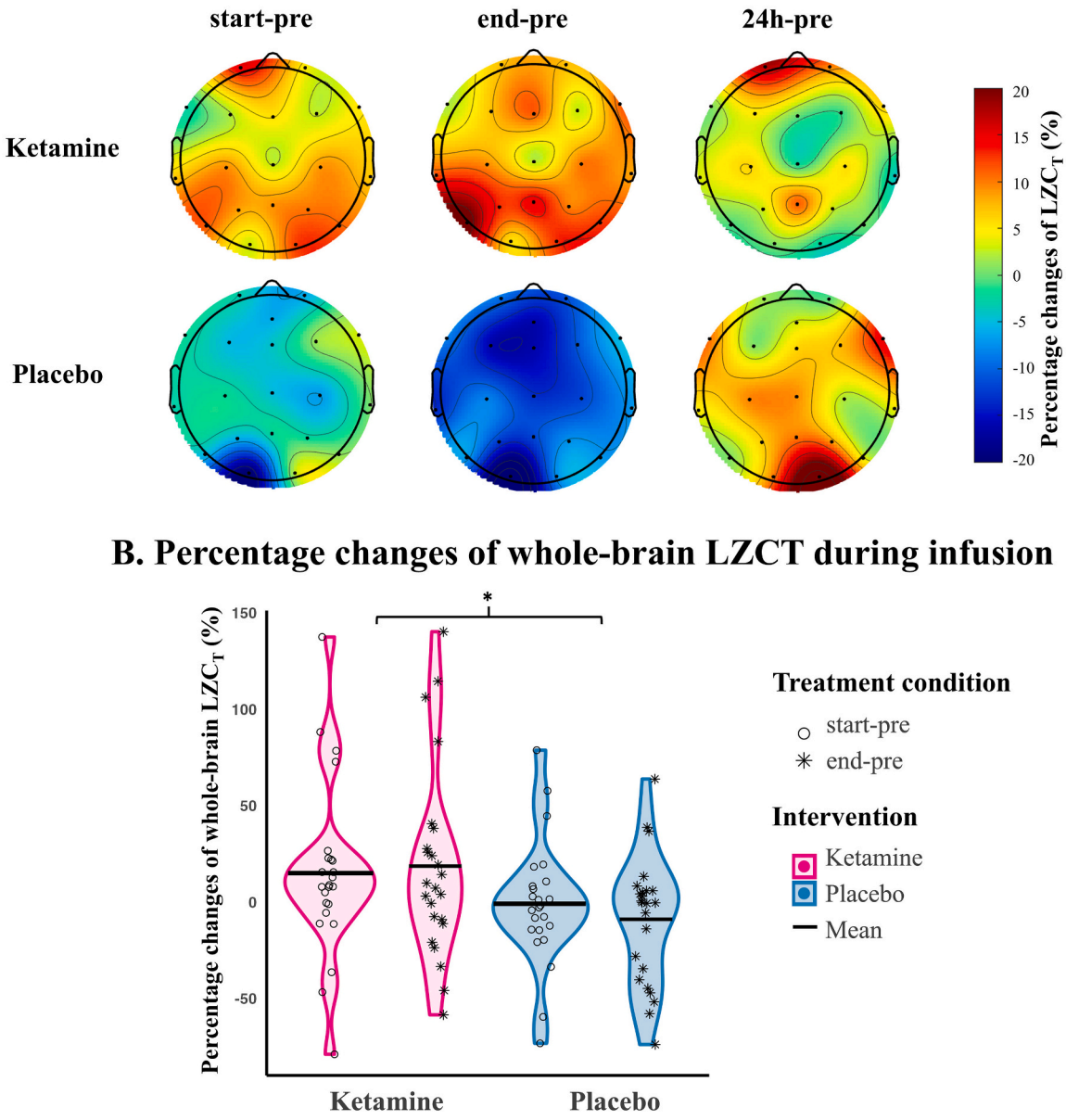

Fig. 1. Effects of ketamine and placebo on LZC$_T$. A. Topographic map of percentage changes of LZC$_T$ at start-pre, end-pre and 24 h-pre in ketamine and placebo infusion. B. Percentage changes of whole-brain LZC$_T$ during infusion. Ketamine led to a greater LZC$_T$ percentage change than placebo in all patients during infusion. Note. *$p < 0.05$.

highlighting its broad modulatory impact on brain activity in a clinical population. However, in our study, a greater increase in signal complexity during the second ketamine infusion was associated with less symptom improvement on the following day, which contrasts with the expectation that higher neural complexity would align with better clinical outcomes. A prior report found no significant correlations between ketamine-potentiated EEG complexity and clinical improvement (Murphy et al., 2023). One possible explanation comes from Khaleghi et al.' (2023) computational model, which suggested that increased LZC can reflect an elevated excitation-to-inhibition ratio. When this ratio becomes excessively unbalanced, it may disrupt the regular firing patterns of neuronal populations, leading to abnormal activity underlying neuropathological deficits. This implies that while an increase in neural complexity may be important for the antidepressant effect of ketamine—as supported by the significant difference from placebo—excessive or dysregulated increases may signal a departure from functional homeostasis and could be less beneficial to clinical improvement (Duman et al., 2019; Milak et al., 2016; Möhler, 2012; Prévot and Sibille, 2021). Additionally, research shows that successful long-term mirtazapine treatment often normalizes EEG complexity to levels seen in healthy individuals, indicating that therapeutic success may be associated with the stabilization of brain activity rather than a simple increase in complexity (Méndez et al., 2012).

Previous studies have suggested that increased neural signal complexity correlates with more intense psychedelic experiences (Farnes et al., 2020; Schartner et al., 2017). Notably, transient psychotomimetic effects—including dissociative experiences—elicited by ketamine have been associated with greater antidepressant symptom improvement in the days following administration (Sos et al., 2013). Therefore, while LZC$_T$ might reflect the intensity of acute dissociative

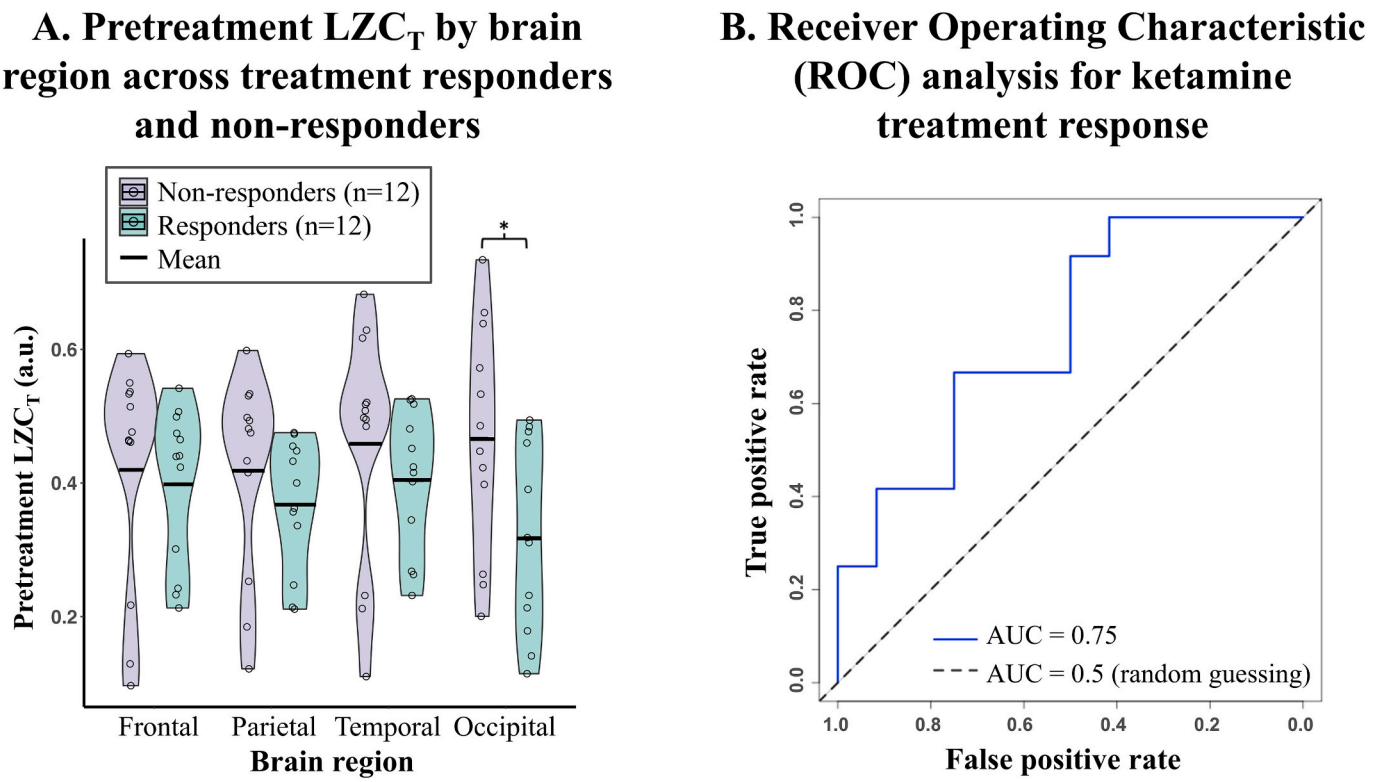

Fig. 2. Occipital LZC$_T$ as an indicator of ketamine response. A. Pretreatment LZC$_T$ by brain region in non-responders and responders. Before ketamine treatment, responders exhibited significantly lower LZC$_T$ values in the occipital region compared to non-responders. B. The logistic regression analysis yielded an area under the curve (AUC) of 0.75.
Note. *$p < 0.05$.

states, this does not necessarily preclude its relevance to antidepressant mechanisms, as these phenomena may be interrelated.

Our results did not show significant regional differences in complexity changes during ketamine infusion, suggesting a more uniform effect across the brain. However, this finding contrasts with other studies that identified significant regional increases in signal complexity in the occipital and parietal regions, which are crucial for visual processing and sensory integration (Schartner et al., 2017; Song et al., 2021; Zhou et al., 2022). While we did not detect changes in LZC 24 h post-infusion, studies have documented neuroplasticity enhancements and connectivity changes in frontal lobe after this time (Abdallah et al., 2017; Kopelman et al., 2023). This implies that the observed increase in regional neuronal connectivity and plasticity may not be captured by LZC changes. This suggests that our measurements might not align with the critical periods of synaptogenesis, which are proposed to peak 24–48 h post-treatment (Moda-Sava et al., 2019; Muscat et al., 2021).

4.2. Pretreatment LZC as predictive biomarker for treatment response

Our study underscores the potential of using lower baseline occipital LZC$_T$ as a predictive biomarker for positive responses to ketamine in patients with MDD. This finding aligns with earlier evidence suggesting that enhanced LZC in the occipital and parietal lobes—areas active during psychedelic experiences— is associated with vivid imagery and ego dissolution, which are crucial to ketamine's antidepressant effects (Farnes et al., 2020; Schartner et al., 2017). Further studies suggest that individuals with lower occipital complexity may experience more intense visual effects during ketamine, potentially enhancing its therapeutic impact (Grundy et al., 2017; Sos et al., 2013). From the perspective of E/I balance (Khaleghi et al., 2023), patients with inherently lower complexity who benefit from ketamine intervention may derive greater benefits from ketamine's ability to modulate GABAergic interneurons. Furthermore, our recent findings also indicate that responders to ketamine typically start with a higher vigilance state and may achieve a lower vigilance state more rapidly (Ip et al., 2024). To further optimize treatment efficiency, practical strategies might include facilitating relaxation with pre-selected music, employing cognitive training with visual tasks to adjust occipital signal complexity, or encouraging patients to keep their eyes closed during infusion to reduce sensory input (Ibáñez-Molina et al., 2015; Muscat et al., 2021; Song et al., 2021; Zhou et al., 2018). These approaches aim to modulate the occipital region's signal complexity, potentially lowering it to maximize the therapeutic effects of ketamine by adjusting the E/I balance in favor of treatment efficacy.

4.3. Association between LZC and clinical depressive scores

While no direct correlation was found between pretreatment LZC$_T$ values and symptom severity across all patients, distinct patterns emerged when analyzing responders and non-responders to ketamine. Responders demonstrated a positive correlation between LZC$_T$ in all regions, except for the parietal area, and symptom improvement the following day. Conversely, non-responders exhibited a positive correlation between frontal LZC$_T$ and symptom severity, supporting literature that emphasizes the role of prefrontal and frontal complexities in depression (Ćukić et al., 2020; Zhao et al., 2020). This pattern suggests that increased signal complexity in these regions might contribute to the persistence of symptoms, potentially impeding the therapeutic response to ketamine. These nuanced findings underscore the potential of LZC$_T$ to help delineate clinical subtypes within TRD and suggest that different neural patterns may indicate underlying pathophysiological differences that influence treatment responsiveness.

Our study has several limitations. A primary methodological constraint concerns our ability to detect spatiotemporal complexity

Table 2
LZC_T values in association with MADRS scores.

LZC_T		MADRS	partial *r*	95 % CI	*p*-value	*df*
Pretreatment	Whole-brain	Pretreatment	0.18	[−0.11, 0.44]	0.22	44
		24 h	0.17	[−0.25, 0.54]	0.43	20
		4d	−0.07	[−0.46, 0.34]	0.75	20
		7d	0.20	[−0.22, 0.56]	0.35	20
		14d	0.14	[−0.31, 0.54]	0.56	17
	Frontal	Pretreatment	0.19	[−0.10, 0.45]	0.19	44
		24 h	0.30	[−0.12, 0.63]	0.15	20
	Parietal	Pretreatment	0.18	[−0.11, 0.44]	0.21	44
		24 h	0.11	[−0.31, 0.49]	0.61	20
	Temporal	Pretreatment	0.13	[−0.16, 0.40]	0.38	44
		24 h	0.12	[−0.30, 0.50]	0.58	20
	Occipital	Pretreatment	0.16	[−0.13, 0.42]	0.28	44
		24 h	−0.10	[−0.48, 0.32]	0.65	20
	Responders Only (n = 12)					
	Whole-brain	Pretreatment	−0.30	[−0.63, 0.11]	0.15	20
		24 h	0.69	[0.20, 0.91]	**0.012**	8
	Frontal	Pretreatment	−0.36	[−0.67, 0.05]	0.085	20
		24 h	0.66	[0.13, 0.89]	**0.021**	8
	Parietal	Pretreatment	−0.28	[−0.61, 0.14]	0.19	20
		24 h	0.57	[−0.006, 0.86]	0.053	8
	Temporal	Pretreatment	−0.25	[−0.60, 0.17]	0.24	20
		24 h	0.73	[0.27, 0.92]	**0.007**	8
	Occipital	Pretreatment	−0.13	[−0.51, 0.29]	0.55	20
		24 h	0.83	[0.49, 0.95]	**< 0.001**	8
	Non-Responders Only (n = 12)					
	Whole-brain	Pretreatment	0.38	[−0.03, 0.68]	0.068	20
		24 h	−0.0009	[−0.57, 0.57]	>0.99	8
	Frontal	Pretreatment	0.41	[−0.004, 0.70]	**0.049**	20
		24 h	0.11	[−0.50, 0.64]	0.74	8
	Parietal	Pretreatment	0.39	[−0.02, 0.69]	0.060	20
		24 h	0.02	[−0.56, 0.59]	0.96	8
	Temporal	Pretreatment	0.28	[−0.14, 0.61]	0.19	20
		24 h	−0.13	[−0.65, 0.48]	0.70	8
	Occipital	Pretreatment	0.34	[−0.08, 0.65]	0.11	20
		24 h	−0.18	[−0.68, 0.44]	0.57	8
Start-pre	Whole-brain (changes)	Pretreatment	0.15	[−0.27, 0.52]	0.50	20
		24 h	−0.31	[−0.63, 0.11]	0.15	20
		4d	−0.22	[−0.57, 0.20]	0.30	20
		7d	−0.22	[−0.57, 0.20]	0.31	20
		14d	−0.28	[−0.64, 0.17]	0.22	17
End-pre	Whole-brain (changes)	Pretreatment	0.09	[−0.33, 0.47]	0.69	20
		24 h	−0.42	[−0.71, −0.03]	**0.039**	20
		4d	−0.24	[−0.59, 0.18]	0.25	20
		7d	−0.23	[−0.58, 0.19]	0.28	20
		14d	−0.20	[−0.58, 0.25]	0.38	17

Note. r, correlation coefficients; *df*, degree of freedom. LZC_T values at start-pre and end-pre were determined by the percentage changes in LZC_T values at start-infusion and end-infusion respectively, compared to the pre-infusion values. MADRS scores at 24 h, 4 d, 7 d, and 14 d were calculated as percentage improvements from the pretreatment scores following ketamine infusion at each respective timepoint. Bold values indicate statistically significant results at $p < 0.05$.

changes using LZC_S. The present study employed resting-state EEG under a subanesthetic ketamine dose, without accompanying behavioral transitions such as loss or recovery of consciousness. This limited both temporal and state-related variability, which may have reduced sensitivity to dynamic brain state changes. Additionally, the use of a 22-channel EEG cap restricted spatial resolution, likely to constrain the ability of LZC_S to detect topographic variability. While we applied regional averaging in the analysis of LZC_T to enhance spatial interpretability, this approach may be insufficient for fully capturing the spatial complexity that LZC_S is designed to assess. Second, the study focused exclusively on patients with moderate to severe depression, excluding individuals with mild depression or those experiencing suicidal ideation, which limits the broader applicability of our findings. Moreover, the small sample size may compromise the statistical power and robustness of our conclusions. The use of a single-blind, fixed-sequence design introduces potential biases. Although this sequence was selected to minimize pharmacological carryover from ketamine and ensure a clean EEG baseline, it may have contributed to order effects and expectancy-related bias, especially in subjective outcome measures such as the MADRS. Lastly, while the finding that lower baseline occipital LZC_T may predict treatment response is promising, it should be interpreted cautiously, as it is based on a single cohort. Replication in independent datasets is necessary before it can be considered as a reliable marker.

5. Conclusion

This study confirms that subanesthetic doses of ketamine significantly enhance EEG signal complexity in treatment-resistant depression, reflecting heightened neuroplasticity and neuronal dynamics. Crucially, lower baseline occipital LZC_T serves as a promising predictor of treatment outcome for favorable ketamine responses, emphasizing its potential in treatment personalization. These insights into EEG complexity not only deepen our understanding of ketamine's mechanisms but also suggest a path forward for stratifying therapeutic approaches in major depressive disorder, potentially enhancing treatment efficacy and patient outcomes.

CRediT authorship contribution statement

Weng-Lam Chan: Writing – review & editing, Writing – original draft, Visualization, Formal analysis. **Sebastian Olbrich:** Writing – review & editing. **Xinwen Jiang:** Writing – review & editing, Formal

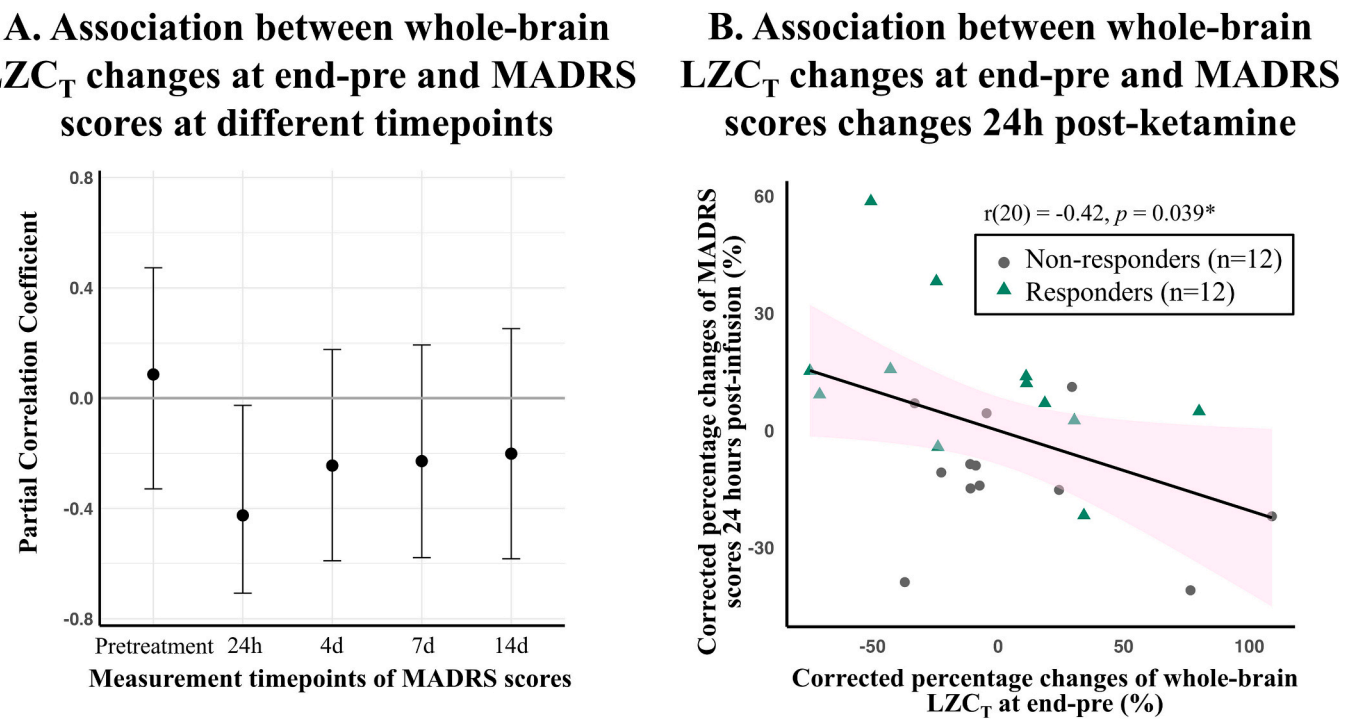

Fig. 3. Whole-brain LZC_T at end-pre in association with MADRS scores measured at pretreatment and various timepoints post-ketamine. A, B. A negative partial correlation was observed only between whole-brain LZC_T changes at end-pre and changes in MADRS scores at 24 h post-ketamine across all patients, with no significant correlations observed at other timepoints.
Note. * $p < 0.05$. Error bars represent 95 % confidence intervals.

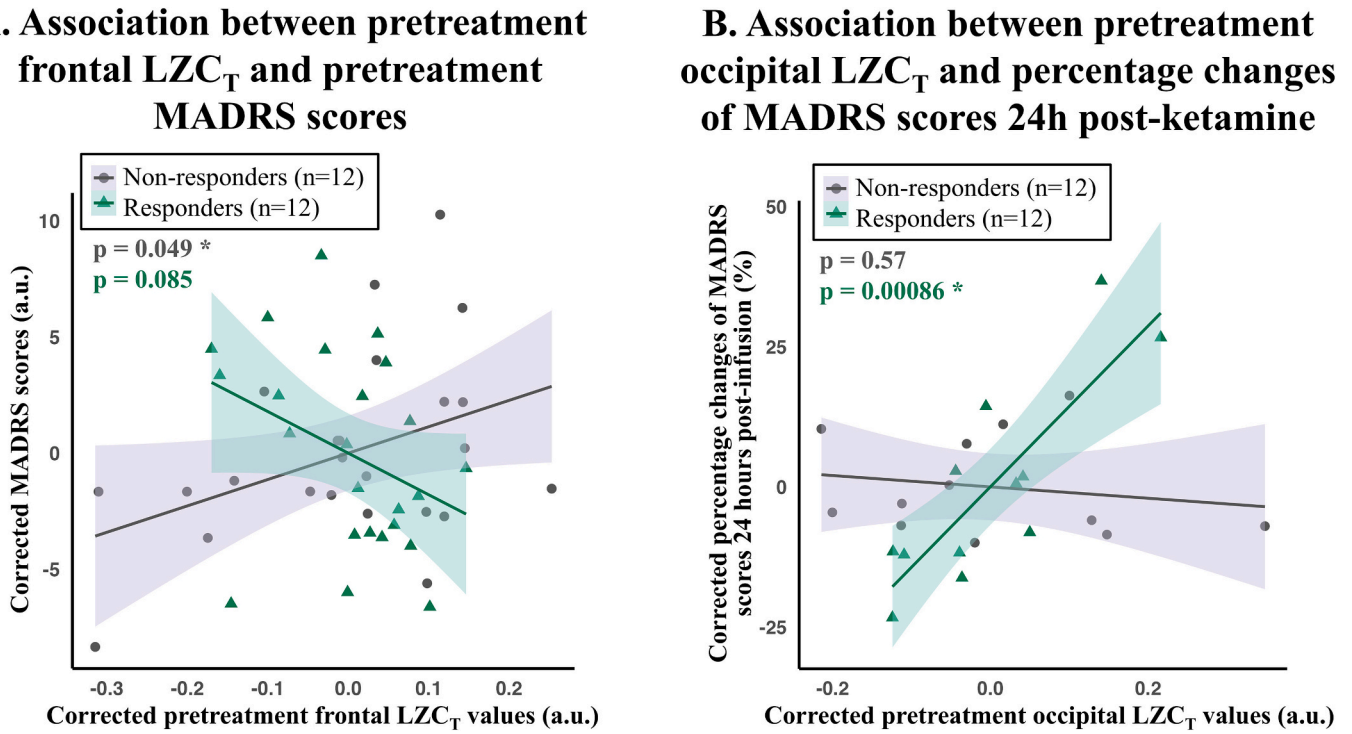

Fig. 4. Pretreatment regional LZC_T in association with MADRS scores at pretreatment and 24 h post-ketamine, in responders and non-responders, respectively. A. A positive partial correlation was observed between pretreatment frontal LZC_T and pretreatment MADRS scores in non-responders. B. In responders, a positive partial correlation was observed between pretreatment whole-brain, frontal, temporal and occipital LZC_T and MADRS scores changes 24 h post-ketamine.
Note. *$p < 0.05$.

analysis. **Haoyun Zhang:** Writing – review & editing, Formal analysis. **Cheng-Teng Ip:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Conceptualization. **Martin Brunovsky:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization.

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Declaration of competing interest

SO is a co-founder and shareholder of DeepPsy AG. CTI is a shareholder of DeepPsy AG. MB is a co-founder and shareholder of the psychedelic clinic Psyon s.r.o.. All other authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2025.119477.

References

Aamodt, A., Sevenius Nilsen, A., Markhus, R., Kusztor, A., HasanzadehMoghadam, F., Kauppi, N., Thürer, B., Storm, J.F., Juel, B.E., 2023. EEG Lempel-Ziv complexity varies with sleep stage, but does not seem to track dream experience. Front. Hum. Neurosci. 16. https://doi.org/10.3389/fnhum.2022.987714.

Abdallah, C.G., Jackowski, A., Salas, R., Gupta, S., Sato, J.R., Mao, X., Coplan, J.D., Shungu, Di.C., Mathew, S.J., 2017. The nucleus accumbens and ketamine treatment in major depressive disorder. Neuropsychopharmacology 42, 1739–1746. https://doi.org/10.1038/npp.2017.49.

Abdallah, C.G., Sanacora, G., Duman, R.S., Krystal, J.H., 2018. The neurobiology of depression, ketamine and rapid-acting antidepressants: is it glutamate inhibition or activation? Pharmacol. Ther. https://doi.org/10.1016/j.pharmthera.2018.05.010.

Aboy, M., Hornero, R., Abásolo, D., Álvarez, D., 2006. Interpretation of the Lempel-Ziv complexity measure in the context of biomedical signal analysis. IEEE Trans. Biomed. Eng. 53, 2282–2288. https://doi.org/10.1109/TBME.2006.883696.

Aleksandrova, L.R., Phillips, A.G., 2021. Neuroplasticity as a convergent mechanism of ketamine and classical psychedelics. Trends Pharmacol. Sci. https://doi.org/10.1016/j.tips.2021.08.003.

Arns, M., Gordon, E., Boutros, N.N., 2017. EEG abnormalities are associated with poorer depressive symptom outcomes with escitalopram and venlafaxine-XR, but not sertraline. Clin. EEG Neurosci. 48, 33–40. https://doi.org/10.1177/1550059415621435.

Bachmann, M., Kalev, K., Suhhova, A., Lass, J., Hinrikus, H., 2015. Lempel Ziv complexity of EEG in depression. In: IFMBE Proceedings. Springer Verlag, pp. 58–61. https://doi.org/10.1007/978-3-319-11128-5_15.

Casali, A.G., Gosseries, O., Rosanova, M., Boly, M., Sarasso, S., Casali, K.R., Casarotto, S., Bruno, M.-A., Laureys, S., Tononi, G., Massimini, M., 2013. A theoretically based index of consciousness independent of sensory processing and behavior. Sci. Transl. Med. 5, 198ra105.

Čukić, M., Stokić, M., Radenković, S., Ljubisavljević, M., Simić, S., Savić, D., 2020. Nonlinear analysis of EEG complexity in episode and remission phase of recurrent depression. Int. J. Methods Psychiatr. Res. 29. https://doi.org/10.1002/mpr.1816.

Deyama, S., Kaneda, K., 2023. Role of neurotrophic and growth factors in the rapid and sustained antidepressant actions of ketamine. Neuropharmacology. https://doi.org/10.1016/j.neuropharm.2022.109335.

Duman, R.S., Sanacora, G., Krystal, J.H., 2019. Altered connectivity in depression: GABA and glutamate neurotransmitter deficits and reversal by novel treatments. Neuron. https://doi.org/10.1016/j.neuron.2019.03.013.

Farnes, N., Juel, B.E., Nilsen, A.S., Romundstad, L.G., Storm, J.F., 2020. Increased signal diversity/complexity of spontaneous EEG, but not evoked EEG responses, in ketamine-induced psychedelic state in humans. PLoS One 15. https://doi.org/10.1371/journal.pone.0242056.

Fitzgerald, P.B., Srithiran, A., Benitez, J., Daskalakis, Z.Z., Oxley, T.J., Kulkarni, J., Egan, G.F., 2008. An fMRI study of prefrontal brain activation during multiple tasks in patients with major depressive disorder. Hum. Brain Mapp. 29, 490–501. https://doi.org/10.1002/hbm.20414.

Gonda, X., Dome, P., Neill, J.C., Tarazi, F.I., 2023. Novel antidepressant drugs: beyond monoamine targets. CNS Spectr. https://doi.org/10.1017/S1092852921000791.

Grundy, J.G., Anderson, J.A.E., Bialystok, E., 2017. Bilinguals have more complex EEG brain signals in occipital regions than monolinguals. Neuroimage 159, 280–288. https://doi.org/10.1016/j.neuroimage.2017.07.063.

Hernández, M., Ponce-Meza, J., Saavedra-López, M., Campos Ugaz, W., Chanduvi, R., Monteza, W., 2023. Brain complexity and psychiatric disorders. Iran. J. Psychiatry 18, 493–502.

Ibáñez-Molina, A.J., Iglesias-Parro, S., Soriano, M.F., Aznarte, J.I., 2015. Multiscale Lempel-Ziv complexity for EEG measures. Clin. Neurophysiol. 126, 541–548. https://doi.org/10.1016/j.clinph.2014.07.012.

Ionescu, D.F., Rosenbaum, J.F., Alpert, J.E., 2015. Pharmacological approaches to the challenge of treatment-resistant depression. Dialogues Clin. Neurosci. 17, 111–126. https://doi.org/10.31887/dcns.2015.17.2/dionescu.

Ip, C.T., Ganz, M., Dam, V.H., Ozenne, B., Rüesch, A., Köhler-Forsberg, K., Jørgensen, M. B., Frokjaer, V.G., Søgaard, B., Christensen, S.R., Knudsen, G.M., Olbrich, S., 2021a. NeuroPharm study: EEG wakefulness regulation as a biomarker in MDD. J. Psychiatr. Res. 141, 57–65. https://doi.org/10.1016/j.jpsychires.2021.06.021.

Ip, C.T., Olbrich, S., Ganz, M., Ozenne, B., Köhler-Forsberg, K., Dam, V.H., Beniczky, S., Jørgensen, M.B., Frokjaer, V.G., Søgaard, B., Christensen, S.R., Knudsen, G.M., 2021b. Pretreatment qEEG biomarkers for predicting pharmacological treatment outcome in major depressive disorder: independent validation from the NeuroPharm study. Eur. Neuropsychopharmacol. 49, 101–112. https://doi.org/10.1016/j.euroneuro.2021.03.024.

Ip, C.T., de Bardeci, M., Kronenberg, G., Pinborg, L.H., Seifritz, E., Brunovsky, M., Olbrich, S., 2024. EEG-vigilance regulation is associated with and predicts ketamine response in major depressive disorder. Transl. Psychiatry 14. https://doi.org/10.1038/s41398-024-02761-x.

Khaleghi, A., Mohammadi, M.R., Shahi, K., Nasrabadi, A.M., 2023. Possible neuropathological mechanisms underlying the increased complexity of brain electrical activity in schizophrenia: a computational study. Iran. J. Psychiatry 18, 127–133.

Kopelman, J., Keller, T.A., Panny, B., Griffo, A., Degutis, M., Spotts, C., Cruz, N., Bell, E., Do-Nguyen, K., Wallace, M.L., Mathew, S.J., Howland, R.H., Price, R.B., 2023. Rapid neuroplasticity changes and response to intravenous ketamine: a randomized controlled trial in treatment-resistant depression. Transl. Psychiatry 13. https://doi.org/10.1038/s41398-023-02451-0.

Krystal, J.H., Sanacora, G., Duman, R.S., 2013. Rapid-acting glutamatergic antidepressants: the path to ketamine and beyond. Biol. Psychiatry. https://doi.org/10.1016/j.biopsych.2013.03.026.

Lempel, A., Ziv, J., 1976. On the complexity of finite sequences. IEEE Trans. Inf. Theory 22, 75–81.

Li, D., Mashour, G.A., 2019. Cortical dynamics during psychedelic and anesthetized states induced by ketamine. Neuroimage 196, 32–40. https://doi.org/10.1016/j.neuroimage.2019.03.076.

Lijffijt, M., Murphy, N., Iqbal, S., Green, C.E., Iqbal, T., Chang, L.C., Haile, C.N., Hirsch, L.C., Ramakrishnan, N., Fall, D.A., Swann, A.C., Al Jurdi, R.K., Mathew, S.J., 2021. Identification of an optimal dose of intravenous ketamine for late-life treatment-resistant depression: a Bayesian adaptive randomization trial. Neuropsychopharmacology 47, 1088–1095. https://doi.org/10.1038/s41386-021-01242-9.

López-Solà, C., Subirà, M., Serra-Blasco, M., Vicent-Gil, M., Navarra-Ventura, G., Aguilar, E., Acebillo, S., Palao, D.J., Cardoner, N., 2020. Is cognitive dysfunction involved in difficult-to-treat depression? Characterizing resistance from a cognitive perspective. Eur. Psychiatr. 63. https://doi.org/10.1192/j.eurpsy.2020.65.

Lord, B., Allen, J.J.B., 2023. Evaluating EEG complexity metrics as biomarkers for depression. Psychophysiology 60. https://doi.org/10.1111/psyp.14274.

Marcantoni, W.S., Akoumba, B.S., Wassef, M., Mayrand, J., Lai, H., Richard-Devantoy, S., Beauchamp, S., 2020. A systematic review and meta-analysis of the efficacy of intravenous ketamine infusion for treatment resistant depression: January 2009 – January 2019. J. Affect. Disord. https://doi.org/10.1016/j.jad.2020.09.007.

McIntyre, R.S., Carvalho, I.P., Lui, L.M.W., Majeed, A., Masand, P.S., Gill, H., Rodrigues, N.B., Lipsitz, O., Coles, A.C., Lee, Y., Tamura, J.K., Iacobucci, M., Phan, L., Nasri, F., Singhal, N., Wong, E.R., Subramaniapillai, M., Mansur, R., Ho, R., Lam, R.W., Rosenblat, J.D., 2020. The effect of intravenous, intranasal, and oral ketamine in mood disorders: a meta-analysis. J. Affect. Disord. https://doi.org/10.1016/j.jad.2020.06.050.

McIntyre, R.S., Alsuwaidan, M., Baune, B.T., Berk, M., Demyttenaere, K., Goldberg, J.F., Gorwood, P., Ho, R., Kasper, S., Kennedy, S.H., Ly-Uson, J., Mansur, R.B., McAllister-Williams, R.H., Murrough, J.W., Nemeroff, C.B., Nierenberg, A.A., Rosenblat, J.D., Sanacora, G., Schatzberg, A.F., Shelton, R., Stahl, S.M., Trivedi, M.H., Vieta, E., Vinberg, M., Williams, N., Young, A.H., Maj, M., 2023. Treatment-resistant depression: definition, prevalence, detection, management, and investigational interventions. World Psychiatry 22, 394–412. https://doi.org/10.1002/wps.21120.

Méndez, M.A., Zuluaga, P., Hornero, R., Gómez, C., Escudero, J., Rodríguez-Palancas, A., Ortiz, T., Fernández, A., 2012. Complexity analysis of spontaneous brain activity: effects of depression and antidepressant treatment. J. Psychopharmacol. 26, 636–643. https://doi.org/10.1177/0269881111408966.

Meyer, T., Brunovsky, M., Horacek, J., Novak, T., Andrashko, V., Seifritz, E., Olbrich, S., 2021. Predictive value of heart rate in treatment of major depression with ketamine in two controlled trials. Clin. Neurophysiol. 132, 1339–1346. https://doi.org/10.1016/j.clinph.2021.01.030.

Milak, M.S., Proper, C.J., Mulhern, S.T., Parter, A.L., Kegeles, L.S., Ogden, R.T., Mao, X., Rodriguez, C.I., Oquendo, M.A., Suckow, R.F., Cooper, T.B., Keilp, J.G., Shungu, D. C., Mann, J.J., 2016. A pilot in vivo proton magnetic resonance spectroscopy study of amino acid neurotransmitter response to ketamine treatment of major depressive disorder. Mol. Psychiatry 21, 320–327. https://doi.org/10.1038/mp.2015.83.

Moda-Sava, R.N., Murdock, M.H., Parekh, P.K., Fetcho, R.N., Huang, B.S., Huynh, T.N., Witztum, J., Shaver, D.C., Rosenthal, D.L., Alway, E.J., Lopez, K., Meng, Y., Nellissen, L., Grosenick, L., Milner, T.A., Deisseroth, K., Bito, H., Kasai, H., Liston, C., 2019. Sustained rescue of prefrontal circuit dysfunction by antidepressant-induced spine formation. Science 364 (1979). https://doi.org/10.1126/science.aat8078.

Mohammadi, Y., Moradi, M.H., 2021. Prediction of depression severity scores based on functional connectivity and complexity of the EEG signal. Clin. EEG Neurosci. 52, 52–60. https://doi.org/10.1177/1550059420965431.

Möhler, H., 2012. The GABA system in anxiety and depression and its therapeutic potential. Neuropharmacology 42–53. https://doi.org/10.1016/j.neuropharm.2011.08.040.

Murphy, N., Tamman, A.J.F., Lijffijt, M., Amarneh, D., Iqbal, S., Swann, A., Averill, L.A., O'Brien, B., Mathew, S.J., 2023. Neural complexity EEG biomarkers of rapid and post-rapid ketamine effects in late-life treatment-resistant depression: a randomized control trial. Neuropsychopharmacology 48, 1586–1593. https://doi.org/10.1038/s41386-023-01586-4.

Muscat, S.A., Hartelius, G., Crouch, C.R., Morin, K.W., 2021. An integrative approach to ketamine therapy may enhance multiple dimensions of efficacy: improving therapeutic outcomes with treatment resistant depression. Front. Psychol. 12. https://doi.org/10.3389/fpsyt.2021.710338.

Newport, D.J., Carpenter, L.L., McDonald, W.M., Potash, J.B., Tohen, M., Nemeroff, C.B., 2015. Ketamine and other NMDA antagonists: early clinical trials and possible mechanisms in depression. Am. J. Psychiatry. https://doi.org/10.1176/appi.ajp.2015.15040465.

Nugent, A.C., Ballard, E.D., Gould, T.D., Park, L.T., Moaddel, R., Brutsche, N.E., Zarate, C.A., 2019. Ketamine has distinct electrophysiological and behavioral effects in depressed and healthy subjects. Mol. Psychiatry 24, 1040–1052. https://doi.org/10.1038/s41380-018-0028-2.

Perrin, F., Pernier, J., Bertrand, O., Giard, M.H., Echallier, J.F., 1987. Mapping of scalp potentials by surface spline interpolation. Electroencephalogr. Clin. Neurophysiol. 66, 75–81.

Prévot, T., Sibille, E., 2021. Altered GABA-mediated information processing and cognitive dysfunctions in depression and other brain disorders. Mol. Psychiatry. https://doi.org/10.1038/s41380-020-0727-3.

Price, R.B., Duman, R., 2020. Neuroplasticity in cognitive and psychological mechanisms of depression: an integrative model. Mol. Psychiatry. https://doi.org/10.1038/s41380-019-0615-x.

Rengasamy, M., Mathew, S., Howland, R., Griffo, A., Panny, B., Price, R., 2024. Neural connectivity moderators and mechanisms of ketamine treatment among treatment-resistant depressed patients: a randomized controlled trial. EBioMedicine 99. https://doi.org/10.1016/j.ebiom.2023.104902.

Salvadore, G., Cornwell, B.R., Sambataro, F., Latov, D., Colon-Rosario, V., Carver, F., Holroyd, T., Diazgranados, N., MacHado-Vieira, R., Grillon, C., Drevets, W.C., Zarate, C.A., 2010. Anterior cingulate desynchronization and functional connectivity with the amygdala during a working memory task predict rapid antidepressant response to ketamine. Neuropsychopharmacology 35, 1415–1422. https://doi.org/10.1038/npp.2010.24.

Schartner, M.M., Carhart-Harris, R.L., Barrett, A.B., Seth, A.K., Muthukumaraswamy, S. D., 2017. Increased spontaneous MEG signal diversity for psychoactive doses of ketamine, LSD and psilocybin. Sci. Rep. 7. https://doi.org/10.1038/srep46421.

Song, X.M., Hu, X.W., Li, Z., Gao, Y., Ju, X., Liu, D.Y., Wang, Q.N., Xue, C., Cai, Y.C., Bai, R., Tan, Z.L., Northoff, G., 2021. Reduction of higher-order occipital GABA and impaired visual perception in acute major depressive disorder. Mol. Psychiatry 26, 6747–6755. https://doi.org/10.1038/s41380-021-01090-5.

Sos, P., Klirova, M., Novak, T., Kohutova, B., Horacek, J., Palenicek, T., 2013. Relationship of ketamine's antidepressant and psychotomimetic effects in unipolar depression. Neuroendocrinol. Lett. 34, 287–293.

Vasavada, M.M., Leaver, A.M., Espinoza, R.T., Joshi, S.H., Njau, S.N., Woods, R.P., Narr, K.L., 2016. Structural connectivity and response to ketamine therapy in major depression: a preliminary study. J. Affect. Disord. 190, 836–841. https://doi.org/10.1016/j.jad.2015.11.018.

Wang, Y.T., Zhang, N.N., Liu, L.J., Jiang, H., Hu, D., Wang, Z.Z., Chen, N.H., Zhang, Y., 2022. Glutamatergic receptor and neuroplasticity in depression: implications for ketamine and rapastinel as the rapid-acting antidepressants. Biochem. Biophys. Res. Commun. https://doi.org/10.1016/j.bbrc.2022.01.024.

Xue, S., Wang, S., Kong, X., Qiu, J., 2017. Abnormal neural basis of emotional conflict control in treatment-resistant depression: an event-related potential study. Clin. EEG Neurosci. 48, 103–110. https://doi.org/10.1177/1550059416631658.

Zhang, X., Hu, Bin, Zhou, L., Moore, P., Chen, J., 2013. An EEG based pervasive depression detection for females. In: Zu, Q., Hu, Bo, Elçi, A. (Eds.), Pervasive computing and the networked world. Springer Berlin Heidelberg, Berlin, Heidelberg, pp. 848–861.

Zhang, Y., Wang, C., Sun, C., Zhang, X., Wang, Y., Qi, H., He, F., Zhao, X., Wan, B., Du, J., Ming, D., 2015. Neural complexity in patients with poststroke depression: a resting EEG study. J. Affect. Disord. 188, 310–318. https://doi.org/10.1016/j.jad.2015.09.017.

Zhao, L., Yang, L., Li, B., Su, Z., Liu, C., 2020. Frontal alpha complexity of different severity depression patients. J. Healthc. Eng. 2020. https://doi.org/10.1155/2020/8854725.

Zhou, W., Wang, N., Yang, C., Li, X.M., Zhou, Z.Q., Yang, J.J., 2014. Ketamine-induced antidepressant effects are associated with AMPA receptors-mediated upregulation of mTOR and BDNF in rat hippocampus and prefrontal cortex. Eur. Psychiatr. 29, 419–423. https://doi.org/10.1016/j.eurpsy.2013.10.005.

Zhou, Y., Zheng, W., Liu, W., Wang, C., Zhan, Y., Li, H., Chen, L., Li, M., Ning, Y., 2018. Neurocognitive effects of six ketamine infusions and the association with antidepressant response in patients with unipolar and bipolar depression. J. Psychopharmacol. 32, 1118–1126. https://doi.org/10.1177/0269881118798614.

Zhou, Y., Wang, C., Lan, X., Zheng, W., Li, H., Chao, Z., McIntyre, R.S., Ning, Y., 2022. The effectiveness of repeated intravenous ketamine on subjective and objective psychosocial function in patients with treatment-resistant depression and suicidal ideation. J. Affect. Disord. 304, 78–84. https://doi.org/10.1016/j.jad.2022.02.032.