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Resting-state gamma activity as a discriminative marker for cognitive subtypes in psychosis

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ABSTRACT

Background and hypothesis: Schizophrenia and other psychotic disorders exhibit significant clinical and cognitive heterogeneity, challenging diagnosis and treatment. Given indications of widespread cortical hyperactivity and dysregulation of neural oscillations in schizophrenia, investigating resting-state activity is highly relevant. This study examined resting-state EEG alterations across previously defined cognitive subtypes within the psychosis spectrum.

Study design: We analyzed resting-state EEG data from 141 psychosis patients (64 chronic schizophrenia, 40 first-episode schizophrenia, 37 bipolar disorder) and 80 healthy controls. Patients were a priori classified into two distinct cognitive subgroups: Cluster 1 (severe impairment, n = 47) and Cluster 2 (moderate impairment, n = 94).

Study results: Both patient clusters exhibited increased spectral power across most frequency bands compared to healthy controls. Notably, the more severely impaired Cluster 1 showed significantly higher power in the gamma-1 band (30–45 Hz) compared to Cluster 2. Furthermore, in Cluster 1, a significant positive correlation was found between resting-state gamma-1 power and positive symptom scores.

Conclusions: These results support our hypothesis of distinctive basal hyperactivation linked to the cognitive profile, suggesting that altered intrinsic brain activity, particularly gamma-1 hyperactivation, may underlie cognitive heterogeneity in psychosis. This also suggests that gamma-1 band hyperactivation at rest serves as a distinct neurophysiological marker differentiating both subgroups. Our findings highlight the importance of subdivision approaches to identify more homogeneous patient subgroups and emphasize the potential of resting-state gamma activity as a precise biomarker for specific symptom dimensions and personalized treatment strategies.

1. Introduction

Schizophrenia is a highly heterogeneous psychiatric disorder characterized by a broad spectrum of clinical symptoms as well as variable cognitive impairment (Ahmed et al., 2018; Tandon et al., 2009) which likely reflects distinct underlying neurobiological alterations (Takahashi, 2013). This heterogeneity extends beyond traditional diagnostic boundaries. Accumulating evidence supports a psychosis spectrum, in which schizophrenia and bipolar disorder share overlapping clinical, cognitive and neurobiological characteristics (Craddock and Owen, 2010). This perspective is reinforced by large-scale neurobiological studies that have demonstrated convergent alterations in functional connectivity, network dynamics, and electrophysiological measures across both disorders (Clementz et al., 2016).

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Numerous efforts have recently emerged to classify schizophrenia spectrum into distinct subtypes based on valid biological markers, with a particular focus on altered functional and structural properties of the brain (Chand et al., 2020; Clementz et al., 2015; Planchuelo-Gómez et al., 2020), including task-related connectivity patterns (Fernández-Linsenbarth et al., 2021a; Rodriguez et al., 2019), and endophenotypic and genetic analysis, using neurocognitive data and genome-wide results for linking key features of abnormal neurotransmission and axonal structure (Greenwood et al., 2019; Warren et al., 2024). Key findings from this approach underscore the importance of integrating neurobiological and functional parameters to refine our understanding of plausible subtypes and their relevance for treatment outcomes.

Within this context, cognitive subtyping has emerged as a particularly promising approach. For example, some studies have identified three, (Gilbert et al., 2014; Van Rheenen et al., 2017) and four subgroups (Liu et al., 2011; Seaton et al., 1999). However, studies with larger sample sizes consistently support a two-cluster solution (Cobia et al., 2011; Green et al., 2012a), a pattern that aligns with our own preceding results (Fernández-Linsenbarth et al., 2021a). In this study, we identified a first group of patients with severe cognitive impairment, also showing increased positive and negative symptomatology, thalamic-hippocampal atrophy, reduced frontal connectivity and basal hypersynchrony. In contrast, the second group of patients was characterized by a moderate cognitive impairment, which was accompanied by milder deficits, yet also reduced cortical thickness and connectivity modulation. Importantly, both subgroups included patients with diagnoses of schizophrenia and bipolar disorder (Fernández-Linsenbarth et al., 2021b). To further refine this cognitive-based classification, it is essential to complement this work with a more comprehensive characterization of the underlying neurobiological alterations.

Recent evidence suggests that the neuropathology of psychosis spectrum is not solely dependent on localized structural abnormalities but rather reflects widespread dysfunction in large-scale neural networks (Uhlhaas and Singer, 2012a, 2012b). Electroencephalography (EEG) provides a direct measure of rapidly changing brain dynamics with high temporal resolution (Kirschstein and Köhling, 2009). Task-related studies have shown impaired neural modulation among individuals with schizophrenia, regardless of sensory modality or cognitive domain (Molina et al., 2018; Northoff and Gomez-Pilar, 2021). Our previous work suggests that excessive baseline neural activity (i.e., prior to stimulus onset) in the broadband and theta band in schizophrenia patients is linked to reduced modulation of evoked activity during an oddball/P300 task (Cea-Cañas et al., 2020). Therefore, elevated baseline synchronization may hinder the brain's capacity to modulate responses and adjust resources during task performance (Gomez-Pilar et al., 2018).

These prior assessments of baseline activity were conducted under conditions of cognitive expectancy, so they do not fully capture intrinsic brain activation. Therefore, a better understanding of possible mechanisms underlying baseline hypersynchrony requires the examination of a true resting state in the absence of external stimuli (Lechner and Northoff, 2023b). This setting provides a more direct measure of endogenous neural dynamics in absence of external demands (Northoff et al., 2010). In fact, in a previous study we demonstrated that elevated resting-state theta activity predicts reduced cognitive modulation capacity in schizophrenia (Iglesias-Tejedor et al., 2022). This evidence reinforces the need to investigate how resting-state neural activity relates to cognitive dysfunction and whether it underlies distinct schizophrenia subtypes.

Importantly, resting-state neural activity plays a fundamental role in cognitive processing, as it reflects the baseline excitability and integration of large-scale brain networks upon which task-evoked responses are built (Deco et al., 2015; Lechner and Northoff, 2023a). Differences in resting-state power have been shown to have influence in excitation-inhibition balance and network gain, which critically shape cognitive capacity and flexibility (Shine et al., 2019; Uhlhaas and Singer, 2012b). Therefore, cognitive subtypes are expected to differ not only in task performance but also in their intrinsic activation regimes.

To our knowledge, the profile of resting-state brain activation, within specific cognitive subtypes of schizophrenia, has not yet been explored. Therefore, we aim to calculate resting-state activity across different characteristic frequency bands (from delta to gamma) in patients, and to study its alteration in cognitive subtypes of patients with schizophrenia previously defined (Fernández-Linsenbarth et al., 2021a). Also, given the possible overlap in altered neurophysiological mechanisms between psychotic diagnoses, we studied cognitive clusters in a sample of patients with chronic and first-episode schizophrenia, and bipolar disorder. We hypothesize that patients will exhibit resting-state hyperactivity on the proposed measures, and that this activity will contribute to defining distinctive profiles within the cognitive subtypes of psychosis.

2. Methods

2.1. Participants

The study sample consisted of 141 patients diagnosed with psychosis (64 with chronic schizophrenia, 40 first-episode schizophrenia, and 37 with bipolar disorder), as well as 80 age- and sex-matched healthy controls. Patients were diagnosed according to the criteria of the DSM-5 criteria ('DSM V.', 2013) by one of the psychiatrists in the group (VM). Our exclusion criteria were: (i) any neurological illness; (ii) history of cranial trauma with loss of consciousness longer than one minute; (iii) past or present substance abuse, except nicotine or caffeine; (iv) total intelligence quotient (IQ) under 70; (v) for patients, the presence of any other comorbid psychiatric process; and (vi) for controls, any current psychiatric or neurological diagnosis and/or treatment with drugs known to act on the central nervous system.

Global intelligence quotient (IQ) was measured using the Wechsler Adult Intelligence Scale III (WAIS-III) (Fuentes Durá et al., 2010). Positive and negative psychotic symptoms were assessed in patients using the Spanish versions of, respectively, the positive scale of the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) and the Brief Negative Symptoms Scale (BNSS) (Kirkpatrick et al., 2011). All schizophrenia patients (chronic and first-episodes) were receiving stable doses of atypical antipsychotics for at least 3 months prior to the EEG recordings. Bipolar patients were also under stable lithium treatment and 34 of them were under additional antipsychotic treatment. Antipsychotic doses were converted into chlorpromazine equivalents (mg/day).

A detailed summary of the demographic and clinical characteristics is presented in Table 1. All participants provided written informed consent after receiving comprehensive information about the study. The research was approved by the Ethics Committee of the University Hospital of Valladolid (protocol PI-21-2623).

2.2. Cognitive assessment and patient clustering

Both patients and controls were cognitively assessed using the Spanish version of the Brief Assessment of Cognition in Schizophrenia Scale (BACS) (Segarra et al., 2011) and the perseverative errors score of the Wisconsin Card Sorting Test (WCST) (Chelune and Baer, 1986). The six BACS dimension scores (verbal memory, working memory, motor speed, verbal fluency, attention and processing speed, and problem solving), as well as the WCST perseverative errors score, were used for patient clustering and for deriving a single principal component analysis (PCA)-driven composite score of cognitive performance for each participant (Table 1).

The clustering of patients into two different cognitive subgroups was calculated in a previous article by our group, where it is described in detail (Fernández-Linsenbarth et al., 2021b). K-means clustering was carried out on the raw cognitive variables to identify cognitive subtypes across psychotic disorders. The optimal number of clusters was determined using the silhouette method (Rousseeuw, 1987), complemented

Table 1
Demographic and clinical characteristics of the groups studied.

	Patients – Whole sample (n = 141)	Patients – Cluster 1 (n = 47)	Patients – Cluster 2 (n = 94)	Healthy Controls (n = 80)
Age, years	39.12 (11.37)	42.00 (9.77) ***	37.68 (11.88)	36.39 (9.9)
Sex, M/F	80:61	26:21	54:40	40:40
Education level, years	13.27 (3.87)***	11.03 (3.11) ###***	14.38 (3.74)*	16.00 (3.3)
Diagnosis assigned according to traditional clinical criteria				
Chronic schizophrenia	64 (45.39%)	27 (57.45%)	37 (39.36%)	NA
First-episode schizophrenia	40 (28.37%)	12 (25.53%)	28 (29.79%)	NA
Bipolar disorder	37 (26.24%)	8 (17.02%)	29 (30.85%)	NA
Pharmacology – number of patients having a specific drug (percentage on its own sample):				
CPZ equivalents	340.69 (248.57)	379.33 (262.17)	321.38 (240.70)	NA
Antipsychotics	101 (71.63%)	44 (93.61%)	57 (60.64%)	NA
Lithium	21 (14.89%)	4 (8.51%)	17 (18.08%)	NA
Antidepressants	13 (9.22%)	6 (12.77%)	7 (7.45%)	NA
Benzodiazepines	28 (19.85%)	14 (29.79%)	14 (14.89%)	NA
Symptoms				
Illness duration, months	147.79 (142.78)	193.59 (160.38)	127.22 (130.70)	NA
PANSS positive	11.27 (4.21)	11.57 (3.81)	11.11 (4.43)	NA
BNSS total	21.76 (17.61)	26.55 (16.11)	19.68 (17.94)	NA
Cognition				
Cognitive factor	−0.38 (0.82)***	−1.29 (0.46) ###***	0.07 (0.54) ***	0.69 (0.59)
IQ. WAIS total	92.27 (15.86)***	83.60 (16.97) ###***	96.71 (13.31)***	113.78 (11.82)

Data are presented as mean (standard deviation) unless otherwise specified. NA: Not Applicable (data not collected in this condition). Significance levels: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.005$ (Patients vs Controls); # $p < 0.05$; ## $p < 0.01$; ### $p < 0.005$ (Cluster 1 vs. Cluster 2). Statistical comparisons were performed using Student's t, one-way ANOVA or $\chi 2$ test, as appropriate.

by 25 additional indices from the *NbClust* package (Charrad et al., 2014). Clustering stability was ensured through 50 random initializations, selecting the configuration with the highest silhouette score, and confirmed using hierarchical clustering. Dimensionality reduction via PCA was conducted for descriptive purposes and for reducing collinearity among cognitive and biological variables. In the current study. The clustering procedure was rerun on the full updated sample following the same methodological pipeline, yielding a highly stable solution with only minimal changes in cluster inclusions.

2.3. EEG resting-state recording and power calculation

Resting-state EEG and task-related EEG recordings were acquired as part of the same experimental protocol at the time of patient inclusion. While the auditory oddball EEG data were previously used to characterize cognitive subtypes (Fernández-Linsenbarth et al., 2021b), the present study focuses exclusively on resting-state EEG measures to further define these subgroups. Data were acquired using a Brain Vision equipment (Brain Products GmbH, Munich, Germany) with two electrode cap configurations: 64-channel and 32-channel caps (both from Electro-Cap International, Inc., Eaton, Ohio, USA). All recordings were acquired using the same amplifier system and preprocessing pipeline, and analyses were performed after reducing both montages to a common 29-channel subset (10/10 International System), ensuring that identical sensor locations were used across all subjects. This approach effectively removes any differences related to sensor density, spatial sampling, or montage configuration and ensures that all spectral and connectivity measures are computed from the same electrodes. The selected electrodes were Fp1, Fp2, F7, F3, Fz, F4, F8, FC5, FC1, FCz, FC2, FC6, T7, C3, Cz, C4, T8, CP5, CP1, CP2, CP6, P7, P3, Pz, P4, P8, O1, Oz, and Fpz, which was used as the ground channel. To monitor ocular artifacts, two additional electro-oculography (EOG) electrodes were positioned to capture both vertical and lateral eye movements. EEG signals were referenced online to Cz and continuously recorded at a sampling rate of 500 Hz. Electrode impedance was maintained below 5 kΩ throughout the recording process. The experimental paradigm consisted of a 5-min resting-state EEG session with eyes closed. Participants were instructed to be as still as possible while comfortably seated and relaxed in a quiet room.

EEG signals were first offline re-referenced to the average activity of all sensors (Bledowski et al., 2004) and band-pass filtered between 1 and 70 Hz. An additional 50 Hz notch filter was applied to suppress power line interference. Artifacts were identified and removed using Independent Component Analysis (ICA) (Delorme et al., 2007). The number of excluded ICA components did not significantly differ between patients and controls (Kruskal-Wallis H(2) = 5.28, $p = 0.071$). Recordings were then divided into 5-s epochs. Those exceeding a range of ±70 μV in any of the 29 EEG channels were automatically rejected. Additionally, a visual inspection was carried out to manually reject remaining epochs that still present clear artifacts. Subject data were included in the analysis only if 20 or more valid epochs were still available after data preprocessing. The average number of valid segments per participant was 136.19 (SD = 90.16). A spectrum analysis based on Fourier transform was applied to the segmented data to estimate the absolute power (expressed in μV^2) across different frequency bands (Iglesias-Tejedor et al., 2022). The following frequency ranges were considered: delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta-1 (12–18 Hz), beta-2 (18–30 Hz), gamma-1 (30–45 Hz), gamma-2 (45–70 Hz), and broadband power (0.5–70 Hz). We used a fixed window length method based on Hanning tapering. Time window length was set to 1 s (1 Hz frequency resolution). Power values were transformed to a logarithmic scale in order to achieve distributions closer to normality.

Data pre-processing and power calculation were conducted in MATLAB R2025a (MathWorks Inc., Natick, MA, USA) using the EEGLAB toolbox v13.6.5b (Delorme and Makeig, 2004), supplemented by custom analysis scripts using the Fieldtrip toolbox v20250318 (Oostenveld et al., 2011).

2.4. Statistical analysis

All statistical analyses were performed using SPSS 29.0 for Windows. Group differences in demographic and clinical characteristics (age, sex, clinical and cognitive scores, and years of education) were assessed using independent-samples *t*-tests or one-way ANOVAs for continuous variables, and chi-square tests for categorical variables, as appropriate.

To evaluate differences in resting-state EEG power across the three groups (Cluster 1, Cluster 2, and Healthy Controls), a Multivariate Analysis of Variance (MANOVA) was conducted. The dependent variables were the absolute power measures from eight frequency bands (delta, theta, alpha, beta-1, beta-2, gamma-1, gamma-2, and broadband). *Post-hoc* pairwise comparisons were then conducted using Tukey's HSD test to identify specific group differences for each significant band.

In addition, Pearson correlation analyses were performed to explore the association between clinical and cognitive variables, and the EEG power measures. These were performed only for those EEG measures that discriminated between both patient clusters according to the results of the previous step.

Finally, for those parameters that were significant in the previous analysis, topographic plots (see Fig. 2) were generated to visualize the spatial distribution of EEG power values, as well as their intergroup differences and statistical significance (*t*-test, FDR corrected). For this purpose, we used the FieldTrip toolbox (Oostenveld et al., 2011) in MATLAB (MathWorks, 2023).

To assess whether resting-state gamma power was associated with pharmacological treatment, we performed a Pearson correlation between gamma power and the daily chlorpromazine-equivalent (CPZ) dose. Additionally, group comparison analyses through permutational ANOVAs were conducted to evaluate potential differences in gamma power according to clozapine and lithium use in addition to a chi-square test for benzodiazepine use between clusters.

3. Results

3.1. Demographic and clinical characteristics

All patients were classified into two clusters according to their cognitive performance. Forty-seven patients belonged to the severely impaired group or Cluster 1 (27 with chronic schizophrenia, 12 first episodes of schizophrenia, and 8 with bipolar disorder) and 94 to the moderately impaired group or Cluster 2 (37 with chronic schizophrenia, 28 first episodes of schizophrenia, and 29 with bipolar disorder). When comparing both patient clusters and controls, there were significant differences in age ($F(2, 218) = 4.15$, $p = 0.017$), with Cluster 1 being older than controls ($p < 0.001$). Conversely, there were no significant differences between Cluster 2 and the control group or between the two patient clusters (Table 1).

Significant differences were also observed among the three groups in both the cognitive factor score ($F(2, 205) = 185.679$, $p < 0.001$), and years of education ($F(2, 160) = 22.033$, $p < 0.001$). Post hoc analysis showed that both patient clusters obtained significantly lower cognitive performance and fewer years of education than healthy controls ($p < 0.001$ in all cases), although Cluster 2 showed an intermediate position in both variables among the three groups (Table 1). Both patient clusters also differed significantly from each other in both cognitive performance and years of education ($p < 0.001$ in both cases). No significant differences were found between the two clusters of patients in clinical measures: years of illness, positive and negative symptoms, or CPZ equivalents.

1.1 EEG results

Regarding the analysis of the resting state EEG measures, the MANOVA revealed a significant multivariate effect of the cluster factor on the eight frequency ranges evaluated (Wilks' Lambda = $F(16, 422) = 2.647$, $p < 0.001$). Subsequent tests of inter-subject effects showed significant differences between groups for all frequency bands (Table 2), with the strongest effect observed in the gamma-1 band ($F(2,218) = 10.91$, $p \leq 0.001$, partial $\eta^2 = 0.091$). Post hoc pairwise comparisons revealed significant differences between Cluster 1 patients and healthy controls in beta-1, beta-2, gamma-1, gamma-2, and broadband. Cluster 2, however, differed significantly from the control group across all frequency bands (Fig. 1 and Table 2). In all instances, patients exhibited higher power values than healthy controls. When comparing the two patient clusters, Cluster 1 showed higher power values than Cluster 2 only for the gamma-1 band (MD = 0.088, SE = 0.037, $p = 0.045$, 95% CI [0.002–0.175]), with a moderate standardized effect size (Cohen's d = 0.40). Receiver Operating Characteristic (ROC) curve analysis was performed to assess the ability of resting-state gamma 1 power to discriminate between patient Cluster 1 and Cluster 2 resulting with an area under the curve (AUC) of 0.618, indicating a modest discriminative performance (see also Fig. 1 and Table 2). Topographic analysis confirms the results in a frontal-medial and temporo-parietal distribution (Fig. 2).

For each cognitive subgroup, possible associations between clinical and cognitive variables and resting EEG power were explored. Only the gamma-1 band was studied as it is the only frequency range that differed between the two cognitive clusters. Additionally, we conducted exploratory correlation analyses to assess the potential influence of age on this measure. Age showed a small but statistically significant positive association with this band ($r = 0.17$, $p = 0.009$), accounting for approximately 3% of the variance. *The correlation between gamma-1 resting-state power and the cognitive factor score across the whole psychosis sample was negative but not statistically significant (Pearson's $r = -0.133$, $p = 0.121$).* In Cluster 1, only a significant positive correlation was found between resting-state gamma-1 power and positive symptom scores on the PANSS ($r = 0.45$, $p = 0.001$). No other significant correlations were observed between gamma-1 power and clinical or cognitive measures.

Finally, the correlation analysis revealed no significant association between resting-state gamma power and CPZ equivalents ($r = -0.086$, $p = 0.325$). Similarly, the permutational ANOVAs indicated no statistically significant differences in gamma power between clusters with or without clozapine treatment ($F(1,216) = 1.079$, $p = 0.300$), or between those with or without lithium treatment ($F(1,216) = 2.002$, $p = 0.159$). There were also no differences in the use of benzodiazepines (Pearson's $\chi^2(1) = 1.21$, $p = 0.545$).

Table 2
Mean (SD) values of EEG absolute power (μV^2) across eight frequency bands (delta, theta, alpha, beta-1, beta-2, gamma-1, gamma-2, and total power) for patients in Cluster 1, patients in Cluster 2, and healthy controls. A fourth column reports the overall group effect obtained from MANOVA.

	Patients – Cluster 1 ($n = 47$)	Patients – Cluster 2 ($n = 94$)	Healthy Controls ($n = 80$)	Group effect (MANOVA)
Power – Delta band	1.15 (0.27)	1.17 (0.26) ***	1.04 (0.24)	$F(2) = 5.778$, $p = 0.004$, $\eta^2 = 0.050$
Power – Theta band	1.17 (0.28)	1.18 (0.26) ***	1.05 (0.27)	$F(2) = 5.774$, $p = 0.004$, $\eta^2 = 0.050$
Power – Alpha band	1.14 (0.28)	1.15 (0.26) ***	1.01 (0.30)	$F(2) = 5.778$, $p = 0.004$, $\eta^2 = 0.050$
Power – Beta-1 band	0.99 (0.26) *	0.99 (0.25) **	0.86 (0.31)	$F(2) = 6.034$, $p = 0.003$, $\eta^2 = 0.052$
Power – Beta-2 band	0.56 (0.27) ***	0.49 (0.22) *	0.39 (0.23)	$F(2) = 7.846$, $p < 0.001$, $\eta^2 = 0.067$
Power – Gamma-1 band	−0.11 (0.23)#***	−0.20 (0.21)*	−0.28 (0.19)	$F(2) = 10.908$, $p < 0.001$, $\eta^2 = 0.091$
Power – Gamma-2 band	−0.48 (0.24)***	−0.53 (0.27)*	−0.63 (0.23)	$F(2) = 5.862$, $p = 0.003$, $\eta^2 = 0.051$
Power – Broadband	0.20 (0.18) ***	0.15 (0.18) ***	0.05 (0.19)	$F(2) = 11.712$, $p < 0.001$, $\eta^2 = 0.097$

Data are presented as mean (standard deviation). Significance levels: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.005$ (Patients vs Controls); # $p < 0.05$ (Cluster 1 vs. Cluster 2). Statistical comparisons were performed using MANOVA and Tukey's HSD post hoc test.

4. Discussion

This study aimed to explore alterations in resting-state activity, measured by EEG, and their potential differential profiles across cognitive subtypes of patients with schizophrenia and other psychotic spectrum disorders. Building upon previous findings that revealed two clear cognitive subtypes within the patient sample, characterized by distinct cognitive impairment profiles, (Fernández-Linsenbarth et al., 2021b) our current results demonstrate significant differences in resting-state EEG power that are consistent with these classifications. Specifically, the severely impaired patient subgroup (Cluster 1) exhibited higher gamma-1 band power compared to the moderately impaired subgroup (Cluster 2), supporting our hypothesis of a distinctive resting-state hyperactivation linked to their cognitive profile. These results suggest that alterations in intrinsic brain activity might underlie the cognitive heterogeneity observed in schizophrenia and related

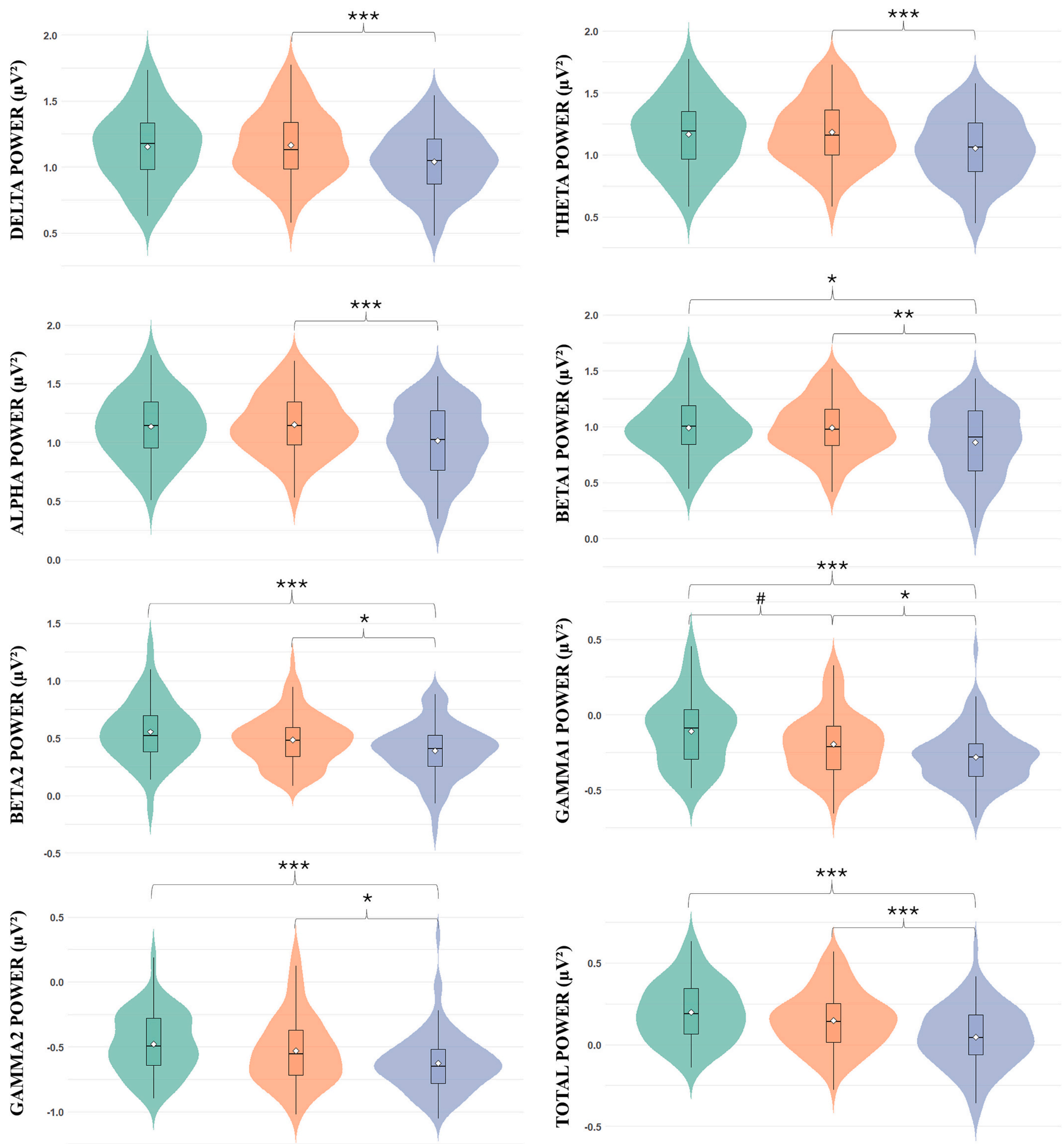

Fig. 1. Violin plots showing group differences in EEG power (μV^2) across eight frequency bands: delta, theta, alpha, beta-1, beta-2, gamma-1, gamma-2, and total power (broadband). The three groups correspond to Cluster 1 patients (green), Cluster 2 patients (orange), and healthy controls (blue). Significance levels: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.005$ (Patients vs Controls); # $p < 0.05$ (Cluster 1 vs. Cluster 2). Statistical comparisons were performed using MANOVA and Tukey's HSD post hoc test. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

disorders.

The identification of a two-cluster model of psychosis patients, differentiated by the severity of cognitive impairment, is consistent with prior large-scale studies that have consistently supported this two-cluster solution (Cobia et al., 2011; Green et al., 2012b). Importantly, both subgroups included patients with diagnoses of chronic schizophrenia, first-episodes of schizophrenia, and bipolar disorder, highlighting the transdiagnostic relevance of these cognitive classifications (Bora, 2016; Green et al., 2020; Van Rheenen et al., 2017). Both patient clusters exhibited increased spectral power relative to healthy controls across most frequency bands, consistent with prior studies indicating widespread cortical hyperactivity and dysregulation of neural oscillations in schizophrenia (Andreou et al., 2015b; Gordillo et al., 2023). Importantly, similar alterations have also been observed in

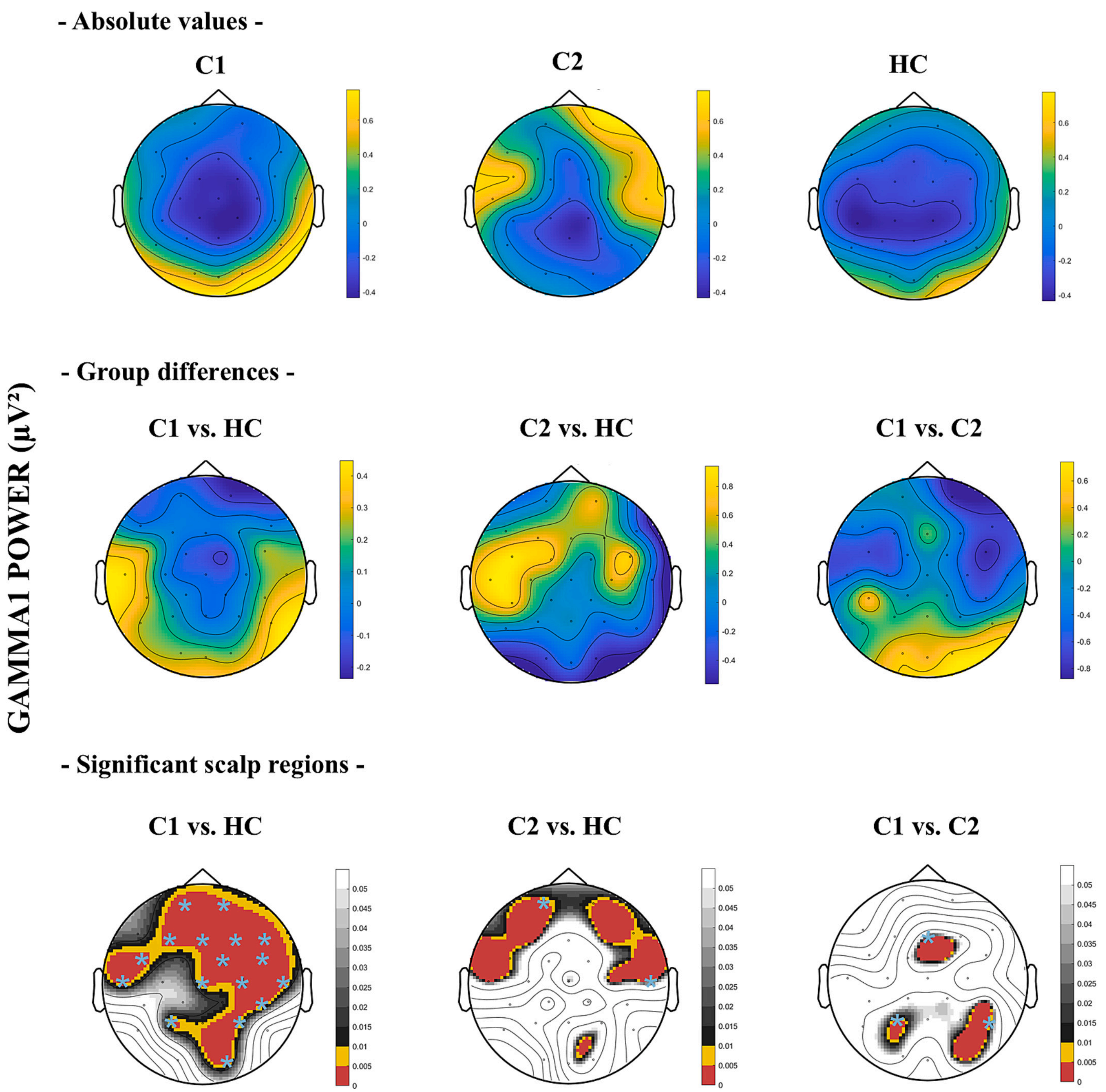

Fig. 2. Topographical distribution of resting-state EEG gamma-1 power (μV^2). The first row shows absolute power values for Cluster 1 patients (C1), Cluster 2 patients (C2), and healthy controls (HC). The second row depicts group differences (C1 vs. HC, C2 vs. HC, and C1 vs. C2). The third row highlights scalp regions with significant differences identified using independent-samples *t*-tests at each electrode ($p < 0.05$, FDR-corrected). Electrodes with significant effects are marked with asterisks. Color scales represent the range of power values or statistical differences, as indicated by the corresponding bars.

bipolar disorder, with increased power particularly in high-frequency bands and coherence abnormalities, though less pronounced than in schizophrenia (Kam et al., 2013). These findings highlight that oscillatory dysfunction is not exclusive to schizophrenia but reflects broader pathophysiological mechanisms shared across severe mental illnesses.

Distinct spectral profiles were observed across the two patient subgroups. While high-frequency bands (beta and gamma) were altered in both, low-frequency bands (such as theta) were exclusively altered in the moderately impaired subgroup (Cluster 2). Specifically, alterations in Cluster 1 were more concentrated in the higher frequency bands, whereas Cluster 2 showed a more homogeneous pattern of alteration across multiple frequency ranges. Indeed, increasing evidence implicates theta and gamma frequency bands as particularly disrupted in schizophrenia during resting-state and task-related conditions. For instance, previous studies have found a task-related EEG spectral entropy modulation deficit in schizophrenia linked to theta band hyperactivation during resting-state (Andreou et al., 2015a; Iglesias-Tejedor et al., 2022; Won et al., 2018). Conversely, a recent review highlighted considerable variability in findings across resting-state gamma frequencies, potentially attributable to patient heterogeneity (De Pieri et al., 2025). Our findings are thus consistent with existing literature but highlight the pressing need to adopt subdivision approaches that allow for the identification of more homogeneous patient subgroups. Crucially the only significant difference between the two clinical clusters emerged in the gamma-1 band (30–45 Hz), with Cluster 1 showing significantly higher activity values than Cluster 2. This suggests that gamma-band brain activity may serve as a key neurophysiological marker sensitive to the distinction between the two described psychotic subgroups.

These findings are consistent with previous studies that have also identified more pronounced alterations in the severely impaired subgroup. For instance, a recent systematic review emphasized that patients with severe cognitive impairment exhibited reduced cortical thickness and larger structural brain abnormalities (Karantonis et al., 2023). Functionally, severely impaired subgroups often show resting-state hyperconnectivity in a broad range of brain regions (Meda et al., 2025; Yasuda et al., 2020). Conversely, less impaired clusters tend to exhibit preserved neuroanatomical features and more normative functional organization (Lewandowski et al., 2019; Weinberg et al., 2016). These converging results support the idea that the more affected subgroup represents a distinct biotype characterized by more severe disruptions, while the less impaired subgroup may reflect a more preserved neurobiological profile (Fernández-Linsenbarth et al., 2021a, 2021b; Planchuelo-Gómez et al., 2020).

Our finding of the discriminative ability of this high-frequency activity during resting state is particularly relevant given the role of gamma oscillations in higher-order cognitive processes, including attention, working memory, and consciousness (Uhlhaas and Singer, 2010). This could imply distinct underlying neurobiological mechanisms between clusters involved in efficient information processing, whereby resting-state hyperactivation in high-frequency bands might hinder the brain's adaptive and problem-solving capacities during subsequent cognitive tasks. Cognitive functions rely on the finely tuned spatial and temporal coordination between excitatory pyramidal neurons and inhibitory GABAergic interneurons, which together regulate dynamic neural network interactions (Kepecs and Fishell, 2014). Among the diverse classes of interneurons, parvalbumin-positive (PV+) cells are particularly crucial for the generation and synchronization of gamma band oscillations (Carlén et al., 2012; Sohal et al., 2009). Dysfunction in PV+ interneurons, and their subsequent involvement in GABAergic hypofunction, has been widely documented in schizophrenia (Gonzalez-Burgos and Lewis, 2012; Rotaru et al., 2012). This is consistent with other results showing fronto-central and temporo-parietal spatial distribution, which aligns with other studies suggesting altered frontal GABAergic inhibitory activity in schizophrenia patients (Radhu et al., 2015; Rogasch et al., 2014). Thus, abnormalities in the microcircuitry responsible for generating gamma oscillations may represent a core pathophysiological mechanism contributing to the deficits in cognitive integration and executive functioning (Rotaru et al., 2012; Sun et al., 2011). Through these mechanisms, the significantly higher gamma-1 power in Cluster 1 (compared to Cluster 2 and HC) may reflect a state of aberrant high-frequency activity during rest, potentially indexing inefficient cortical regulation rather than adaptive information processing, further supporting the hypothesis of different neurophysiological substrates within cognitive subtypes. This finding aligns with recent growing evidence suggesting that gamma-band alterations may not follow a uniform pattern but rather serve to demarcate neurophysiological subgroups among individuals. On one hand, some patients may exhibit only a modest increase (or even a lack of enhancement), potentially reflecting subtle inhibitory-excitatory imbalance with limited clinical or cognitive impact, (Lewandowski et al., 2019) as seen in Cluster 2; whereas, markedly elevated gamma-1 power observed in Cluster 1 could represent a hyperexcitable cortical state that is pathologically amplified, possibly driven by severe GABAergic dysfunction (Carlén et al., 2012).

From a clinical perspective, such inefficient cortical processing related to increased gamma activity has been associated with worse cognitive performance (Sohal, 2022) and more pronounced clinical symptoms. Our results provide evidence in Cluster 1 for resting-state gamma hyperactivity directly related to positive symptomatology (PANSS positive scale), suggesting that gamma power may serve as a dimensional biomarker of pathophysiological severity across the psychosis spectrum. This association reinforces previous findings linking abnormal gamma activity to the severity of hallucinations and delusional beliefs (Spencer et al., 2004; Tada et al., 2014). Particularly, in the resting-state, this may indicate hyperactivity or dysregulated thalamocortical loops, which have been implicated in the genesis of positive symptoms (Mulert et al., 2011). These results suggest that severely elevated gamma may help distinguish cognitive subtypes and could serve as a biomarker for specific symptom dimensions. The selective association between increased gamma activity and positive symptoms highlights the importance of integrating neurophysiological markers into the clinical approach, which could enhance early detection and inform more tailored therapeutic interventions. These findings may explain inconsistencies in studies that rely solely on traditional diagnoses, as ignoring cognitive subtypes likely introduces variability that masks neurophysiological patterns.

Our study presents certain limitations. First, while the sample was large and transdiagnostic, the size of specific diagnosis subgroups within the clusters might limit the generalizability of results to more specific populations. Secondly, while gamma activity is always suspected of being contaminated with fast activity from the eye and muscle artifact itself, our significant results for gamma-1 differences between clusters are found in central positions far from those peripheral ones that are potentially more contaminated. Thirdly, it would be valuable to investigate the stability of these subtypes over time and their response to different pharmacological and non-pharmacological interventions. Furthermore, the absence of a drug-naive group limits the interpretation of medication effects on gamma activity. Even though our sample included several first-episode patients with short treatment exposure who were well distributed across clusters, the potential influence of medication cannot be entirely ruled out. The correlation analysis revealed no significant association between resting-state gamma power and CPZ equivalents, suggesting that gamma activity was not influenced by antipsychotic dosage in our sample. In support of this, additional analyses indicated that no significant interaction was observed between antipsychotic treatment and cluster membership associated with gamma-1 power. Clozapine, given its distinctive pharmacological profile, was also examined separately, but no significant effects were found nor when the effect of lithium was analyzed. This could imply that the observed group differences are unlikely to be driven by medication exposure, although subtle modulatory influences cannot be entirely excluded. For these reasons, future longitudinal studies and larger sample sizes, including drug-naive patients, are advisable. Another limitation is that resting-state gamma-band power is sensitive to multiple factors, such as muscle tension, microsaccades or vigilance fluctuations, among others. These factors warrant cautious interpretation of gamma-band findings, particularly when inferring underlying neurobiological mechanisms. Lastly, while both patient clusters were well-balanced for age and sex, only patients in Cluster 1 were significantly older than controls. Importantly, although age and gamma power correlated significantly, our across-group analysis showed a small amount of explained variance, so the magnitude of this effect was limited and unlikely to explain the observed differences between both clusters.

In summary, alterations in resting-state brain activity, particularly gamma-1 hyperactivation, may represent distinctive characteristics of cognitive subtypes in patients with psychosis. These findings not only deepen our understanding of the complex neurobiology of schizophrenia but also pave the way for the development of more precise biomarkers and personalized treatment strategies that address the inherent heterogeneity of the disorder.

CRediT authorship contribution statement

Emma Osorio-Iriarte: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Álvaro Díez:** Writing – review & editing, Writing – original draft, Supervision, Software, Methodology, Formal analysis, Conceptualization. **Inés Fernández-Linsenbarth:** Writing – review & editing, Supervision, Investigation. **Antonio Arjona-Valladares:** Writing – review & editing, Resources, Investigation. **Rosa-Beño-Ruiz-de-la-Sierra:** Writing – review & editing, Resources, Investigation. **Alejandro Roig-Herrero:** Writing – review & editing, Software, Methodology, Investigation. **José María Martínez-Sánchez:** Resources, Investigation, Conceptualization. **Luis Sobrino-Conde:** Resources, Investigation. **Vicente Molina:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization.

Ethical statement

The study entitled, "Resting-State Gamma Activity as a Differentiating Discriminative Marker for Cognitive Subtypes in Psychosis," was conducted in strict compliance with the ethical standards for research involving human subjects.

All procedures performed were in accordance with the relevant institutional guidelines and applicable national and international laws. The research protocol received full approval from the appropriate institutional committee: The Ethics Committee of the University Hospital of Valladolid. The approval was granted under the following reference: protocol PI-21-2623.

Furthermore, the privacy rights of all human participants were strictly observed. It is confirmed that all participants provided written informed consent after receiving comprehensive information concerning the study's methodology and potential implications. The authors affirm that the study was conducted ethically, adhering to the principles outlined in the Declaration of Helsinki.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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Data availability

Data will be made available on request.

References

Ahmed, A.O., Strauss, G.P., Buchanan, R.W., Kirkpatrick, B., Carpenter, W.T., 2018. Schizophrenia heterogeneity revisited: clinical, cognitive, and psychosocial correlates of statistically-derived negative symptoms subgroups. J. Psychiatr. Res. 97, 8–15. https://doi.org/10.1016/j.jpsychires.2017.11.004.

Andreou, C., Leicht, G., Nolte, G., Polomac, N., Moritz, S., Karow, A., Hanganu-Opatz, I. L., Engel, A.K., Mulert, C., 2015a. Resting-state theta-band connectivity and verbal memory in schizophrenia and in the high-risk state. Schizophr. Res. 161 (2–3), 299–307. https://doi.org/10.1016/J.SCHRES.2014.12.018.

Andreou, C., Nolte, G., Leicht, G., Polomac, N., Hanganu-Opatz, I.L., Lambert, M., Engel, A.K., Mulert, C., 2015b. Increased resting-state gamma-band connectivity in first-episode schizophrenia. Schizophr. Bull. 41 (4), 930–939. https://doi.org/10.1093/schbul/sbu121.

Bledowski, C., Prvulovic, D., Hoechstetter, K., Scherg, M., Wibral, M., Goebel, R., Linden, D.E.J., 2004. Localizing P300 generators in visual target and distractor processing: a combined event-related potential and functional magnetic resonance imaging study. J. Neurosci. 24 (42), 9353–9360. https://doi.org/10.1523/JNEUROSCI.1897-04.2004.

Bora, E., 2016. Differences in cognitive impairment between schizophrenia and bipolar disorder: considering the role of heterogeneity. Psychiatry Clin. Neurosci. *70* (10), 424–433. https://doi.org/10.1111/PCN.12410.

Carlén, M., Meletis, K., Siegle, J.H., Cardin, J.A., Futai, K., Vierling-Claassen, D., Rühlmann, C., Jones, S.R., Deisseroth, K., Sheng, M., Moore, C.I., Tsai, L.H., 2012. A critical role for NMDA receptors in parvalbumin interneurons for gamma rhythm induction and behavior. Mol. Psychiatry 17 (5), 537–548. https://doi.org/10.1038/mp.2011.31.

Cea-Cañas, B., Gomez-Pilar, J., Núñez, P., Rodríguez-Vázquez, E., de Uribe, N., Díez, Á., Pérez-Escudero, A., Molina, V., 2020. Connectivity strength of the EEG functional network in schizophrenia and bipolar disorder. Prog. Neuro-Psychopharmacol. Biol. Psychiatry *98*, 109801. https://doi.org/10.1016/J.PNPBP.2019.109801.

Chand, G.B., Dwyer, D.B., Erus, G., Sotiras, A., Varol, E., Srinivasan, D., Doshi, J., Pomponio, R., Pigoni, A., Dazzan, P., Kahn, R.S., Schnack, H.G., Zanetti, M.V., Meisenzahl, E., Busatto, G.F., Crespo-Facorro, B., Pantelis, C., Wood, S.J., Zhuo, C., Davatzikos, C., 2020. Two distinct neuroanatomical subtypes of schizophrenia revealed using machine learning. Brain 143 (3). https://doi.org/10.1093/brain/awaa025.

Charrad, M., Ghazzali, N., … V. B.-J. of statistical, & 2014, undefined. (n.d.). NbClust: an R package for determining the relevant number of clusters in a data set. *J. Stat. Softw.*, 2014 Retrieved 10 June 2025, from https://www.jstatsoft.org/article/view/2194/0.

Chelune, G.J., Baer, R.A., 1986. Developmental norms for the Wisconsin card sorting test. J. Clin. Exp. Neuropsychol. 8 (3). https://doi.org/10.1080/01688638608401314.

Clementz, B.A., Sweeney, J.A., Hamm, J.P., Ivleva, E.I., Ethridge, L.E., Pearlson, G.D., Keshavan, M.S., Tamminga, C.A., 2015. Identification of distinct psychosis biotypes using brain-based biomarkers. Am. J. Psychiatry 173 (4), 373–384. https://doi.org/10.1176/APPI.AJP.2015.14091200.

Cobia, D.J., Csernansky, J.G., Wang, L., 2011. Cortical thickness in neuropsychologically near-normal schizophrenia. Schizophr. Res. 133 (1–3), 68–76. https://doi.org/10.1016/J.SCHRES.2011.08.017.

Craddock, N., Owen, M.J., 2010. The kraepelinian dichotomy – going, going … but still notgone. Br. J. Psychiatry 196 (2), 92–95. https://doi.org/10.1192/BJP.BP.109.073429.

De Pieri, M., Sabe, M., Rochas, V., Poglia, G., Bartolomei, J., Kirschner, M., Kaiser, S., 2025. Resting-state EEG and MEG gamma frequencies in schizophrenia: a systematic review and exploratory power-spectrum meta-analysis. Schizophrenia *11* (*1*), *1*–26. https://doi.org/10.1038/s41537-025-00596-z.

Deco, G., Tononi, G., Boly, M., Kringelbach, M.L., 2015. Rethinking segregation and integration: contributions of whole-brain modelling. Nat. Rev. Neurosci. 16 (7), 430–439. https://doi.org/10.1038/NRN3963.

Delorme, A., Makeig, S., 2004. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. J. Neurosci. Methods *134* (1), 9–21. https://doi.org/10.1016/J.JNEUMETH.2003.10.009.

Delorme, A., Sejnowski, T., Makeig, S., 2007. Enhanced detection of artifacts in EEG data using higher-order statistics and independent component analysis. Neuroimage *34* (4), 1443–1449. https://doi.org/10.1016/J.NEUROIMAGE.2006.11.004.

Fernández-Linsenbarth, I., Planchuelo-Gómez, Á., Beño-Ruiz-de-la-Sierra, R.M., Díez, A., Arjona, A., Pérez, A., Rodríguez-Lorenzana, A., del Valle, P., de Luis-García, R., Mascialino, G., Holgado-Madera, P., Segarra-Echevarría, R., Gomez-Pilar, J., Núñez, P., Bote-Boneaechea, B., Zambrana-Gómez, A., Roig-Herrero, A., Molina, V., 2021a. Search for schizophrenia and bipolar biotypes using functional network properties. Brain Behav. 11 (12). https://doi.org/10.1002/BRB3.2415.

Fernández-Linsenbarth, I., Planchuelo-Gómez, Á., Díez, Á., Arjona-Valladares, A., de Luis, R., Martín-Santiago, Ó., Benito-Sánchez, J.A., Pérez-Laureano, Á., González-Parra, D., Montes-Gonzalo, C., Melero-Lerma, R., Morante, S.F., Sanz-Fuentenebro, J., Gómez-Pilar, J., Núñez-Novo, P., Molina, V., 2021b. Neurobiological underpinnings of cognitive subtypes in psychoses: a cross-diagnostic cluster analysis. Schizophr. Res. 229, 102–111. https://doi.org/10.1016/j.schres.2020.11.013.

Fuentes Durá, I., Peris, M.R., Vivó, C.D., Ruiz, J.C.R., 2010. Versión abreviada del WAIS-III para su uso en la evaluación de pacientes con diagnóstico de esquizofrenia. Psicothema 22, 202–207.

Gilbert, E., Mérette, C., Jomphe, V., Émond, C., Rouleau, N., Bouchard, R.H., Roy, M.A., Paccalet, T., Maziade, M., 2014. Cluster analysis of cognitive deficits may mark heterogeneity in schizophrenia in terms of outcome and response to treatment. Eur. Arch. Psychiatry Clin. Neurosci. 264 (4), 333–343. https://doi.org/10.1007/S00406-013-0463-7/TABLES/4.

Gomez-Pilar, J., de Luis-García, R., Lubeiro, A., de Uribe, N., Poza, J., Núñez, P., Ayuso, M., Hornero, R., Molina, V., 2018. Deficits of entropy modulation in schizophrenia are predicted by functional connectivity strength in the theta band and structural clustering. Neuroimage Clin. *18*, 382–389. https://doi.org/10.1016/J.NICL.2018.02.005.

Gonzalez-Burgos, G., Lewis, D.A., 2012. NMDA receptor hypofunction, parvalbumin-positive neurons, and cortical gamma oscillations in schizophrenia. Schizophr. Bull. 38 (5), 950–957. https://doi.org/10.1093/SCHBUL/SBS010.

Gordillo, D., da Cruz, J.R., Chkonia, E., Lin, W.H., Favrod, O., Brand, A., Figueiredo, P., Roinishvili, M., Herzog, M.H., 2023. The EEG multiverse of schizophrenia. Cereb. Cortex 33 (7), 3816–3826. https://doi.org/10.1093/cercor/bhac309.

Green, M.J., Cairns, M.J., Wu, J., Dragovic, M., Jablensky, A., Tooney, P.A., Scott, R.J., Carr, V.J., 2012. Genome-wide supported variant MIR137 and severe negative symptoms predict membership of an impaired cognitive subtype of schizophrenia. Mol. Psychiatry 18 (7), 774–780. https://doi.org/10.1038/mp.2012.84.

Green, M.J., Girshkin, L., Kremerskothen, K., Watkeys, O., Quidé, Y., 2020. A systematic review of studies reporting data-driven cognitive subtypes across the psychosis spectrum. Neuropsychol. Rev. 30 (4), 446–460. https://doi.org/10.1007/S11065-019-09422-7/TABLES/3.

Greenwood, T.A., Lazzeroni, L.C., Maihofer, A.X., Swerdlow, N.R., Calkins, M.E., Freedman, R., Green, M.F., Light, G.A., Nievergelt, C.M., Nuechterlein, K.H., Radant, A.D., Siever, L.J., Silverman, J.M., Stone, W.S., Sugar, C.A., Tsuang, D.W., Tsuang, M.T., Turetsky, B.I., Gur, R.C., Braff, D.L., 2019. Genome-wide association of endophenotypes for schizophrenia from the Consortium on the Genetics of Schizophrenia (COGS) study. JAMA Psychiatry 76 (12), 1274–1284. https://doi.org/10.1001/JAMAPSYCHIATRY.2019.2850.

Iglesias-Tejedor, M., Díez, Á., Llorca-Bofí, V., Núñez, P., Castaño-Díaz, C., Bote, B., Segarra, R., Sanz-Fuentenebro, J., Molina, V., 2022. Relation between EEG resting-state power and modulation of P300 task-related activity in theta band in schizophrenia. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 116. https://doi.org/10.1016/j.pnpbp.2022.110541.

Kam, J.W.Y., Bolbecker, A.R., O'Donnell, B.F., Hetrick, W.P., Brenner, C.A., 2013. Resting state EEG power and coherence abnormalities in bipolar disorder and schizophrenia. J. Psychiatr. Res. 47 (12), 1893–1901. https://doi.org/10.1016/J.JPSYCHIRES.2013.09.009.

Karantonis, J.A., Carruthers, S.P., Burdick, K.E., Pantelis, C., Green, M., Rossell, S.L., Hughes, M.E., Cropley, V., Van Rheenen, T.E., 2023. Brain morphological characteristics of cognitive subgroups of schizophrenia-spectrum disorders and bipolar disorder: a systematic review with narrative synthesis. Neuropsychol. Rev. 33 (1), 192–220. https://doi.org/10.1007/S11065-021-09533-0/FIGURES/2.

Kay, S., Fiszbein, A., Bulletin, L. O.-S., & 1987, undefined. (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull.*,* 13(2), 261–276. doi:https://doi.org/10.1093/SCHBUL/+13.2.261.

Kepecs, A., Fishell, G., 2014. Interneuron cell types are fit to function. Nature 505 (7483), 318–326. https://doi.org/10.1038/nature12983.

Kirkpatrick, B., Strauss, G.P., Nguyen, L., Fischer, B.A., Daniel, D.G., Cienfuegos, A., Marder, S.R., 2011. The brief negative symptom scale: psychometric properties. Schizophr. Bull. 37 (2), 300–305. https://doi.org/10.1093/SCHBUL/SBQ059.

Kirschstein, T., Köhling, R., 2009. What is the source of the EEG? Clin. EEG Neurosci. 40 (3), 146–149. https://doi.org/10.1177/155005940904000305;PAGE:STRING:ARTICLE/CHAPTER.

Lechner, S., Northoff, G., 2023a. Prolonged intrinsic neural timescales dissociate from phase coherence in schizophrenia. Brain Sci. 13 (4), 695. https://doi.org/10.3390/BRAINSCI13040695/S1.

Lechner, S., Northoff, G., 2023b. Temporal imprecision and phase instability in schizophrenia resting state EEG. Asian J. Psychiatr. 86. https://doi.org/10.1016/j.ajp.2023.103654.

Lewandowski, K.E., McCarthy, J.M., Öngür, D., Norris, L.A., Liu, G.Z., Juelich, R.J., Baker, J.T., 2019. Functional connectivity in distinct cognitive subtypes in psychosis. Schizophr. Res. 204, 120–126. https://doi.org/10.1016/J.SCHRES.2018.08.013.

Liu, C.M., Fann, C.S.J., Chen, C.Y., Liu, Y.L., Oyang, Y.J., Yang, W.C., Chang, C.C., Wen, C.C., Chen, W.J., Hwang, T.J., Hsieh, M.H., Liu, C.C., Faraone, S.V., Tsuang, M. T., Hwu, H.G., 2011. ANXA7, PPP3CB, DNAJC9, and ZMYND17 genes at chromosome 10q22 associated with the subgroup of schizophrenia with deficits in attention and executive function. Biol. Psychiatry 70 (1), 51–58. https://doi.org/10.1016/J.BIOPSYCH.2011.02.033.

MathWorks. https://www.mathworks.com.

Meda, S.A., Dykins, M.M., Hill, S.K., Clementz, B.A., Keedy, S.K., McDowell, J.E., Ivleva, E.I., Gershon, E.S., Keshavan, M.S., Tamminga, C., Pearlson, G.D., 2025. Neural fingerprints of data driven cognitive subtypes across the psychosis spectrum: a B-SNIP study. Transl. Psychiatry 15 (1), 1–11. https://doi.org/10.1038/s41398-025-03422-3.

Molina, V., Bachiller, A., Gomez-Pilar, J., Lubeiro, A., Hornero, R., Cea-Cañas, B., Valcárcel, C., Haidar, M.K., Poza, J., 2018. Deficit of entropy modulation of the EEG in schizophrenia associated to cognitive performance and symptoms. A replication study. Schizophr. Res. 195, 334–342. https://doi.org/10.1016/J.SCHRES.2017.08.057.

Mulert, C., Kirsch, V., Pascual-Marqui, R., Mccarley, R.W., Spencer, K.M., 2011. Long-range synchrony of gamma oscillations and auditory hallucination symptoms in schizophrenia. Int. J. Psychophysiol. 79 (1), 55–63. https://doi.org/10.1016/J.IJPSYCHO.2010.08.004.

Northoff, G., Gomez-Pilar, J., 2021. Overcoming rest-task divide-abnormal temporospatial dynamics and its cognition in schizophrenia. Schizophr. Bull. *47* (3), 751–765. https://doi.org/10.1093/schbul/sbaa178.

Northoff, G., Qin, P., Nakao, T., 2010. Rest-stimulus interaction in the brain: a review. Trends Neurosci. *33* (6), 277–284. https://doi.org/10.1016/J.TINS.2010.02.006/ASSET/DAD874FC-2E98-4E7C-8223-EA89D5801972/MAIN.ASSETS/GR2.JPG.

Oostenveld, R., Fries, P., Maris, E., Schoffelen, J.M., 2011. FieldTrip: open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. Comput. Intell. Neurosci. 2011. https://doi.org/10.1155/2011/156869.

Planchuelo-Gómez, Á., Lubeiro, A., Núñez-Novo, P., Gomez-Pilar, J., de Luis-García, R., del Valle, P., Martín-Santiago, Ó., Pérez-Escudero, A., Molina, V., 2020. Identificacion of MRI-based psychosis subtypes: replication and refinement. Prog. Neuro-Psychopharmacol. Biol. Psychiatry *100*. https://doi.org/10.1016/j.pnpbp.2020.109907.

Radhu, N., Dominguez, L.G., Farzan, F., Richter, M.A., Semeralul, M.O., Chen, R., Fitzgerald, P.B., Daskalakis, Z.J., 2015. Evidence for inhibitory deficits in the prefrontal cortex in schizophrenia. Brain 138 (2), 483–497. https://doi.org/10.1093/BRAIN/AWU360.

Rodriguez, M., Zaytseva, Y., Cvrčková, A., Dvořaček, B., Dorazilová, A., Jonáš, J., Šustová, P., Voráčková, V., Hájková, M., Kratochvílová, Z., Španiel, F., Mohr, P., 2019. Cognitive profiles and functional connectivity in first-episode schizophrenia spectrum disorders - linking behavioral and neuronal data. Front. Psychol. *10* (APR). https://doi.org/10.3389/fpsyg.2019.00689.

Rogasch, N.C., Daskalakis, Z.J., Fitzgerald, P.B., 2014. Cortical inhibition, excitation, and connectivity in schizophrenia: a review of insights from transcranial magnetic stimulation. Schizophr. Bull. 40 (3), 685–696. https://doi.org/10.1093/SCHBUL/SBT078.

Rotaru, D.C., Lewis, D.A., Gonzalez-Burgos, G., 2012. The role of glutamatergic inputs onto parvalbumin-positive interneurons: relevance for schizophrenia. Rev. Neurosci. 23 (1), 97–109. https://doi.org/10.1515/REVNEURO-2011-0059/MACHINEREADABLECITATION/RIS.

Rousseeuw, P.J., 1987. Silhouettes: a graphical aid to the interpretation and validation of cluster analysis. J. Comput. Appl. Math. 20, 53–65. https://doi.org/10.1016/0377-0427(87)90125-7.

Seaton, B.E., Allen, D.N., Goldstein, G., Kelley, M.E., Van Kammen, D.P., 1999. Relations between cognitive and symptom profile heterogeneity in schizophrenia. J. Nerv. Ment. Dis. 187 (7). https://doi.org/10.1097/00005053-199907000-00004.

Segarra, N., Bernardo, M., Gutierrez, F., Justicia, A., Fernadez-Egea, E., Allas, M., Safont, G., Contreras, F., Gascon, J., Soler-Insa, P.A., Menchon, J.M., Junque, C., Keefe, R.S.E., 2011. Spanish validation of the brief assessment in cognition in schizophrenia (BACS) in patients with schizophrenia and healthy controls. Euro. Psychiatry 26 (2), 69–73. https://doi.org/10.1016/J.EURPSY.2009.11.001.

Shine, J.M., Breakspear, M., Bell, P.T., Ehgoetz Martens, K., Shine, R., Koyejo, O., Sporns, O., Poldrack, R.A., 2019. Human cognition involves the dynamic integration of neural activity and neuromodulatory systems. Nat. Neurosci. 22 (2), 289–296. https://doi.org/10.1038/s41593-018-0312-0.

Sohal, V.S., 2022. Transforming discoveries about cortical microcircuits and gamma oscillations into new treatments for cognitive deficits in schizophrenia. Am. J. Psychiatry 179 (4), 267–276. https://doi.org/10.1176/APPI.AJP.20220147/ASSET/IMAGES/LARGE/APPI.AJP.20220147F1.JPEG.

Sohal, V.S., Zhang, F., Yizhar, O., Deisseroth, K., 2009. Parvalbumin neurons and gamma rhythms enhance cortical circuit performance. Nature 459 (7247), 698–702. https://doi.org/10.1038/nature07991.

Spencer, K.M., Nestor, P.G., Perlmutter, R., Niznikiewicz, M.A., Klump, M.C., Frumin, M., Shenton, M.E., McCarley, R.W., 2004. Neural synchrony indexes disordered perception and cognition in schizophrenia. KM Spencer, PG Nestor, R Perlmutter, MA Niznikiewicz, MC Klump, M Frumin, ME Shenton, 2004•pnas.Org Proc. Natl. Acad. Sci. 101 (49), 17288–17293. https://doi.org/10.1073/PNAS.0406074101.

Sun, Y., Farzan, F., Barr, M.S., Kirihara, K., Fitzgerald, P.B., Light, G.A., Daskalakis, Z.J., 2011. Gamma oscillations in schizophrenia: mechanisms and clinical significance. Brain Res. 1413, 98–114. https://doi.org/10.1016/J.BRAINRES.2011.06.065.

Tada, M., Nagai, T., Kirihara, K., Koike, S., Suga, M., Araki, T., Kobayashi, T., Kasai, K., 2014. Differential alterations of auditory gamma oscillatory responses between pre-onset high-risk individuals and first-episode schizophrenia. Cerebral Cortex. https://doi.org/10.1093/cercor/bhu278.

Takahashi, S., 2013. Heterogeneity of schizophrenia: genetic and symptomatic factors. Am. J. Med. Genet. B Neuropsychiatr. Genet. 162 (7). https://doi.org/10.1002/ajmg.b.32161.

Tandon, R., Nasrallah, H.A., Keshavan, M.S., 2009. Schizophrenia, 'just the facts' 4. Clinical features and conceptualization. Schizophr. Res. 110 (1–3), 1–23. https://doi.org/10.1016/j.schres.2009.03.005.

Uhlhaas, P.J., Singer, W., 2010. Abnormal neural oscillations and synchrony in schizophrenia. Nat. Rev. Neurosci. 11 (2), 100–113. https://doi.org/10.1038/nrn2774.

Uhlhaas, P.J., Singer, W., 2012. Neuronal dynamics and neuropsychiatric disorders: toward a translational paradigm for dysfunctional large-scale networks. Neuron 75 (6), 963–980. https://doi.org/10.1016/J.NEURON.2012.09.004/ASSET/90F4B2BA-5AA4–4486-B7CB-2379048D2C20/MAIN.ASSETS/GR5.JPG.

V., D.S.M., 2013. J. Dev. Behav. Pediatr. 34 (4). https://doi.org/10.1097/dbp.0b013e3182978a90.

Van Rheenen, T.E., Lewandowski, K.E., Tan, E.J., Ospina, L.H., Ongur, D., Neill, E., Gurvich, C., Pantelis, C., Malhotra, A.K., Rossell, S.L., Burdick, K.E., 2017. Characterizing cognitive heterogeneity on the schizophrenia–bipolar disorder spectrum. Psychol. Med. 47 (10), 1848–1864. https://doi.org/10.1017/S0033291717000307.

Warren, T.L., Tubbs, J.D., Lesh, T.A., Corona, M.B., Pakzad, S.S., Albuquerque, M.D., Singh, P., Zarubin, V., Morse, S.J., Sham, P.C., Carter, C.S., Nord, A.S., 2024. Association of neurotransmitter pathway polygenic risk with specific symptom profiles in psychosis. Mol. Psychiatry 29 (8), 2389–2398. https://doi.org/10.1038/s41380-024-02457-0.

Weinberg, D., Lenroot, R., Jacomb, I., Allen, K., Bruggemann, J., Wells, R., Balzan, R., Liu, D., Galletly, C., Catts, S.V., Weickert, C.S., Weickert, T.W., 2016. Cognitive subtypes of schizophrenia characterized by differential brain volumetric reductions and cognitive decline. JAMA Psychiatry 73 (12), 1251–1259. https://doi.org/10.1001/JAMAPSYCHIATRY.2016.2925.

Won, G.H., Kim, J.W., Choi, T.Y., Lee, Y.S., Min, K.J., Seol, K.H., 2018. Theta-phase gamma-amplitude coupling as a neurophysiological marker in neuroleptic-naïve schizophrenia. Psychiatry Res. 260, 406–411. https://doi.org/10.1016/J.PSYCHRES.2017.12.021.

Yasuda, Y., Okada, N., Nemoto, K., Fukunaga, M., Yamamori, H., Ohi, K., Koshiyama, D., Kudo, N., Shiino, T., Morita, S., Morita, K., Azechi, H., Fujimoto, M., Miura, K., Watanabe, Y., Kasai, K., Hashimoto, R., 2020. Brain morphological and functional features in cognitive subgroups of schizophrenia. Psychiatry Clin. Neurosci. *74* (3), 191–203. https://doi.org/10.1111/PCN.12963;PAGE:STRING:ARTICLE/CHAPTER.

Glossary

Independent Component Analysis (ICA): A signal processing technique used to separate a multivariate signal into additive, statistically independent components. In EEG, it is commonly applied to identify and remove artifacts such as eye movements or muscle activity.

BACS (Brief Assessment of Cognition in Schizophrenia): A brief cognitive battery designed to assess cognitive performance in patients with schizophrenia.

BNSS (Brief Negative Symptoms Scale): A scale used to assess the severity of negative symptoms in patients with psychosis.

PANSS (Positive and Negative Syndrome Scale): A clinical rating scale used to quantify the severity of positive symptoms (delusions, hallucinations) and negative symptoms (blunted affect, anhedonia) in patients with schizophrenia.

WCST (Wisconsin Card Sorting Test): A neuropsychological test assessing executive function, abstract reasoning, and cognitive flexibility, by evaluating the ability to shift response strategies based on feedback.

Gamma activity: Neuronal oscillations typically in the 30–70 Hz range, associated with higher-order cognitive processes such as attention, working memory, and perception. Sub-bands of interest in this study were gamma-1 (30–45 Hz) and gamma-2 (45–70 Hz).

Alpha band: EEG frequency range typically between 8 and 12 Hz, prominently observed during resting state with eyes closed, reflecting relaxation and alert vigilance.

Beta band: EEG frequency range typically between 12 and 30 Hz, often subdivided into beta-1 (12–18 Hz) and beta-2 (18–30 Hz), associated with alertness, active attention, and motor processing.

Delta band: EEG frequency range typically between 0.5 and 4 Hz, dominant during deep sleep and certain pathological states.

Theta band: EEG frequency range typically between 4 and 8 Hz, associated with memory, spatial navigation, and relaxed wakefulness.

K-means clustering: An unsupervised clustering algorithm that partitions a dataset into a predefined number of "k" clusters, assigning each data point to the cluster with the nearest centroid (mean).

Resting-state EEG: Recording of brain electrical activity via electroencephalography while the participant is awake, relaxed, with eyes closed, and not engaged in a specific task.

Chlorpromazine (CPZ) equivalents: A standardized measure used to compare doses of different antipsychotic medications by converting them into an equivalent dose of chlorpromazine, a typical antipsychotic.

GABAergic hypofunction: A reduction in the activity or effectiveness of the GABA (gamma-aminobutyric acid) neurotransmitter system, the brain's main inhibitory system, implicated in the pathophysiology of schizophrenia and in dysregulation of gamma oscillations.

Parvalbumin-positive (PV+) interneurons: A subtype of cortical GABAergic interneurons crucial for regulating pyramidal cell activity and generating gamma oscillations. Their dysfunction has been linked to schizophrenia.

Neural oscillations: Rhythmic patterns of electrical brain activity, measurable as brain waves in EEG and classified by frequency bands (delta, theta, alpha, beta, gamma).

Spectral power: A measure of the intensity or amplitude of electrical activity within a specific EEG frequency range, often calculated using Fourier transform and expressed in units such as μV^2.