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Quantitative EEG analysis of brivaracetam in drug-resistant epilepsy: A pharmaco-EEG study

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HIGHLIGHTS

- The impact of BRV on cortical activity and connectivity can be explored using pharmaco-EEG analysis.
- BRV treatment does not alter power spectral density across various frequency bands in people with epilepsy.
- BRV therapy aligns theta phase locking value connectivity in responders to the drug to levels seen in healthy controls.

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ABSTRACT

Objective: Brivaracetam (BRV) is a recent antiseizure medication (ASM) approved as an add-on therapy for people with focal epilepsy. BRV has a good efficacy and safety profile compared to other ASMs. However, its specific effects on resting-state EEG activity and connectivity are unknown. The aim of this study is to evaluate quantitative EEG changes induced by BRV therapy in a population of adult people with drug-resistant epilepsy (PwE) compared to healthy controls (HC).
Methods: We performed a longitudinal, retrospective, pharmaco-EEG study on a population of 23 PwE and a group of 25 HC. Clinical outcome was dichotomized into drug-responders (i.e., >50% reduction in seizures' frequency; RES) and non-responders (N-RES) after two years of BRV. EEG parameters were compared between PwE and HC at baseline (pre-BRV) and after three months of BRV therapy (post-BRV). We investigated BRV-related variations in EEG connectivity using the phase locking value (PLV).
Results: BRV therapy did not induce modifications in power spectrum density across different frequency bands. PwE presented lower PLV connectivity values compared to HC in all frequency bands. RES exhibited lower theta PLV connectivity compared to HC before initiating BRV and experienced an increase after BRV, eliminating the significant difference from HC.
Conclusions: This study shows that BRV does not alter the EEG power spectrum in PwE, supporting its favourable neuropsychiatric side-effect profile, and induces the disappearance of EEG connectivity differences between PwE and HC.
Significance: The integration of EEG quantitative analysis in epilepsy can provide insights into the efficacy, mechanism of action, and side effects of ASMs.

Abbreviations: ASMs, Anti-Seizure Medications; BRV, Brivaracetam; DC, Direct Current; FFT, Fast Fourier Transform; HC, Healthy Controls; ILAE, International League Against Epilepsy; IQR, Inter-Quartile Range; LEV, Levetiracetam; N-RES, Non-Responders; PwE, people with drug-resistant epilepsy; PLV, Phase Locking Value; PSD, Power Spectrum Density; RES, Drug-Responders; SV2A, Synaptic Vesicle Proteins 2A.

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1. Introduction

Brivaracetam (BRV) is an innovative anti-seizure medication (ASM) approved as an add-on treatment for focal-onset seizures in adults in Italy (Klein et al., 2018). BRV is an effective and safe therapy option for people with drug-resistant epilepsy (PwE) (Lattanzi et al., 2016). Notably, it offers significant advantages for patients with concomitant psychiatric conditions who might not be suitable for levetiracetam (LEV) therapy (Lattanzi et al., 2021). While its clinical efficacy is well-established, the underlying mechanisms by which BRV influences brain activity, especially at the neural network level, remain to be understood.

The influence of ASMs on brain network dynamics is becoming increasingly evident. Recent studies suggest that EEG can provide insights into the effects of ASMs at the cortical level, revealing their influence on cortical rhythms and networks (Ricci et al., 2021). Indeed, the measurement of quantitative EEG parameters to evaluate the effect of specific drugs on the electrical activity of the brain is known as pharmaco-EEG (Höller et al., 2018; Ricci et al., 2022). The significance of pharmaco-EEG is multifaceted, extending its applications from clinical pharmacology to neuropsychiatric research and offering insights into the mechanisms of action, efficacy, and safety profiles of various drugs (Saletu et al., 1987). This is particularly crucial in epilepsy research since pharmaco-EEG can analyse the modulations in brain networks induced by ASMs, potentially contributing to the optimization of therapeutic strategies and the mitigation of undesirable side effects (Ricci et al., 2021). Consistently, previous studies from our group described the EEG effects of a first ASM in drug-naïve people with temporal lobe epilepsy (Croce et al., 2021; Ricci et al., 2022, 2021). Similarly, we also evaluated the EEG modulations induced by new-generation ASMs, perampanel (Lanzone et al., 2021) and eslicarbazepine acetate (Pellegrino et al., 2018), in people with drug-resistant epilepsy.

Along this line, the goal of this study is to measure the effects of BRV on cortical activity and connectivity in a population of drug-resistant epilepsy using resting-state pharmaco-EEG analysis.

We hypothesize that pharmaco-EEG analysis can be utilized to investigate the effect of BRV on cortical activity and connectivity. To test our hypothesis, we performed a multicentric retrospective pharmaco-EEG study on PwE undergoing add-on therapy with BRV. We compared quantitative EEG features between the EEG performed before BRV initiation (pre-BRV) and the EEG performed approximately three months after BRV therapy (post-BRV). We also compared the EEG of PwE with the EEG of a population of healthy controls (HC).

2. Methods

2.1. Patients and data collection

We retrospectively evaluated the records of twenty-three individuals with drug-resistant epilepsy (PwE), along with a control group consisting of twenty-five HC. Subjects were consecutively enrolled in a period spanning from July 2018 to July 2020 from the epilepsy clinic at the Department of Human Neurosciences of Policlinico Umberto I University Hospital of Rome, Campus Bio-Medico University Hospital Foundation of Rome, and San Filippo Neri Hospital in Rome. We included PwE who met the following inclusion criteria: (i) had a clinical diagnosis of focal drug-resistant epilepsy according to the International League Against Epilepsy (ILAE) diagnostic criteria (Kwan et al., 2010); (ii) >18 years old; (iii) two 19-channel standard EEGs performed before (<30 days) the initiation of BRV (Pre-BRV) and another following approximately 3 months after BRV introduction (Post-BRV) ensuring steady plasmatic levels of BRV for all PwE (Rolan et al., 2008); and (iv) at least 3 min of resting-state EEGs free of relevant artifacts. The exclusion criteria were: (i) PwE taking neuroactive drugs other than ASMs; (ii) PwE abruptly discontinued ASMs or introduced new ASMs (excluding BRV) during the interval between the initial and second EEG recordings; (iii) clinical seizures in the 24 h before the EEG. The EEG data of HC have been previously used for other studies from our group, and their selection criteria can be found elsewhere (Ricci et al., 2021). The study protocol received approval from the ethics committee of Policlinico Umberto I Ethic Board-Rome, Campus Bio-Medico University Hospital Foundation Ethic Board-Rome, and San Filippo Neri Hospital Ethic Board-Rome. All procedures were performed in agreement with the 1964 Helsinki Declaration and its later amendments.

2.2. EEG recording

EEG recording was performed using the same methodology as previously described in previous works from our group (Pellegrino et al., 2018; Ricci et al., 2021). In particular, "nineteen channel-EEG was acquired using a Micromed recorder (Micromed, Modigliano Veneto, IT). The electrodes were placed according to the international 10–20 system (Fp1, Fp2, F3, F4, C3, C4, P3, P4, F7, F8, T3, T4, T5, T6, O1, O2, Fz, Cz, Pz). The reference was placed on FPz and the ground on FCz. Impedance was kept below 5 kOhm for all electrodes. The sampling rate was set to 256 Hz. The resting EEG recording lasted 15 min and was performed with patients and healthy subjects with closed eyes, seated in a comfortable armchair in a quiet room." (Ricci et al., 2021).

2.3. Pharmaco-EEG analysis

Pharmaco-EEG analysis was carried out using the Brainstorm toolbox for Matlab (Tadel et al., 2011) and in-home Matlab code. An experienced neurophysiologist (LR) selected, from each EEG, a total of 180 s of continuous epoch free of relevant artifacts or epileptiform abnormalities to be used for further analysis (Babiloni et al., 2020). Brainstorm was utilized for offline data pre-processing, which encompassed: (i) a visual review by three experienced neurophysiologists (LR, MT, and GA) to exclude potential interictal and ictal epileptiform activities; (ii) removal of Direct Current (DC); (iii) application of a 50-Hz notch filter; (iv) implementation of a bandpass filter ranging from 1 to 70 Hz (utilizing a linear phase finite impulse response filter); (v) re-referencing of EEG to the average; (vi) rectification of pulse and eyeblink artifacts through Independent Component Analysis (Ricci et al., 2021).

To evaluate the influence of BRV on brain networks, we evaluated resting-state brain activity and connectivity. For the quantification of activity, we calculated the Power Spectrum Density (PSD) utilizing the standard Fast Fourier Transform (FFT) method. We averaged PSD measurements across all channels to derive a measure of global cortical activity. Concurrently, we determined the Phase Locking Value (PLV) to gauge global cortical connectivity. We measured the PLV for all possible channel combinations and averaged to obtain a measure of global connectivity. We computed PSD and PLV for the following frequency bands: (i) Delta δ: 2–4 Hz; (ii) Theta θ: 5–7 Hz; (iii) Alpha α: 8–12 Hz; (iv) Beta β: 13–29 Hz; and Gamma γ: 30–60 Hz. Further details about the EEG analysis workflow can be found in our previous publications (Lanzone et al., 2021; Pellegrino et al., 2018; Ricci et al., 2021). The EEG pipeline and study flowchart are summarized in Fig. 1.

2.4. Statistical analysis

We performed statistical analysis using the R statistical packages. Clinical and demographic features were compared among the PwE group and HC using the χ^2 test for categorical variables, and Mann-Whitney U tests for continuous variables. Data distribution of clinical and demographic data was checked by means of Shapiro-Wilk test.

To test the effect of BRV on the EEG global cortical activity (PSD) and connectivity (PLV), we employed linear mixed-effects models using the *lme4* package in R (Bates et al., 2014). The linear mixed effect model has the advantage of including individual subjects and items as crossed, independent random effects. This feature is particularly suitable for repeated measures data, allowing for the specific consideration of intra-subject variability (Baayen et al., 2008). As fixed effects in the model, we considered *Condition (*i.e., pre-BRV, post-BRV and HC), *Bands* (i.e., Delta, Theta, Alpha, Beta and Gamma) and the interaction term (*Condition* vs. *Bands*). Subjects were incorporated as random effects to control for inter-individual variability. The normality of the residuals for the linear mixed effects model was checked by means of visual inspection using a quantile–quantile (Q-Q) plot. The residuals followed a straight line for Phase-Locking Values (PLV) and log-transformed Power Spectrum Density (PSD), suggesting a normal distribution. P-values were obtained by likelihood ratio tests of the full model with the effect in question against the model without the effect in question (Baayen et al., 2008). In cases of significant interactions, we performed post-hoc tests using the 'glht' function from the *multcomp* package in R (Hothorn et al., 2016) with *Condition* contrasts based on the Tukey method separately for each frequency band. We further applied the Holm correction to adjust the p-values for multiple comparisons.

Subsequently, a secondary analysis was conducted wherein PLV and PSD features were independently tested for PwE and HC according to clinical outcome, distinguishing between patients identified as drug-responders (RES, i.e., those experiencing a reduction in seizures of 50% or more post-BRV introduction) and those who did not meet this criterion (Non-Responder, N-RES). Specifically, we implemented a rank-based nonparametric Kruskal-Wallis test followed by post-hoc multiple comparisons using the Dunn test in instances where the Kruskal-Wallis test indicated significant differences. Post-hoc analysis was corrected for multiple comparisons using the Benjamini-Hochberg procedure. Clinical outcome was defined according to patient self-reporting or clinical diary. Results are reported as mean ± standard deviation unless differently stated.

3. Results

3.1. Patients clinical characteristics and control group

Twenty-three PwE (11 females) satisfied all the selection criteria and were included in the study (Table 1). The mean age at the time of BRV introduction was 47.3 ± 14.9 years (range: 20–76 years). Eight patients (34.8%) experienced a >50% reduction in seizure frequency after the introduction of BRV (RES). Fifteen patients (65.2%) presented a structural cause of their epilepsy, and one patient (4.3%) had a chronic immune-mediated aetiology. The median BRV maintenance daily dose was 100 mg (IQR = 100–175 mg). Six patients (26.1%) experienced non-serious adverse events related to BRV therapy and twelve patients (52.2%) switched from a previous therapy with LEV. Twenty-five healthy subjects (12 females) were considered as the control group. The mean age was 50.7 ± 18.2 years (range: 20–80 years). The mean age did not differ between the epilepsy and control groups (p = 0.48). The median duration of epilepsy was 21.5 years for RES (IQR = 9.5–36.5 years) and 10 years for N-RES (IQR = 8.5–14.5 years), with no significant differences between groups (p = 0.18). The mean BRV maintenance dose did not differ between RES and N-RES (100 mg [IQR = 100–162.5 mg] for RES and 150 mg [IQR = 75–175 mg] for N-RES; p = 0.76). We found no association between the presence of a structural lesion (Table 1) and clinical outcome (62.5% for RES and 73.3% for N-RES; p = 0.66).

3.2. EEG power spectrum density

The linear mixed effect model did not reveal any significant difference in the factor *Conditions* across PwE before and after BRV therapy and HC (factor *Conditions;* χ^2 = 2.49, p = 0.29). Nonetheless, a significant interaction effect was found (*Condition* vs. *Bands*;

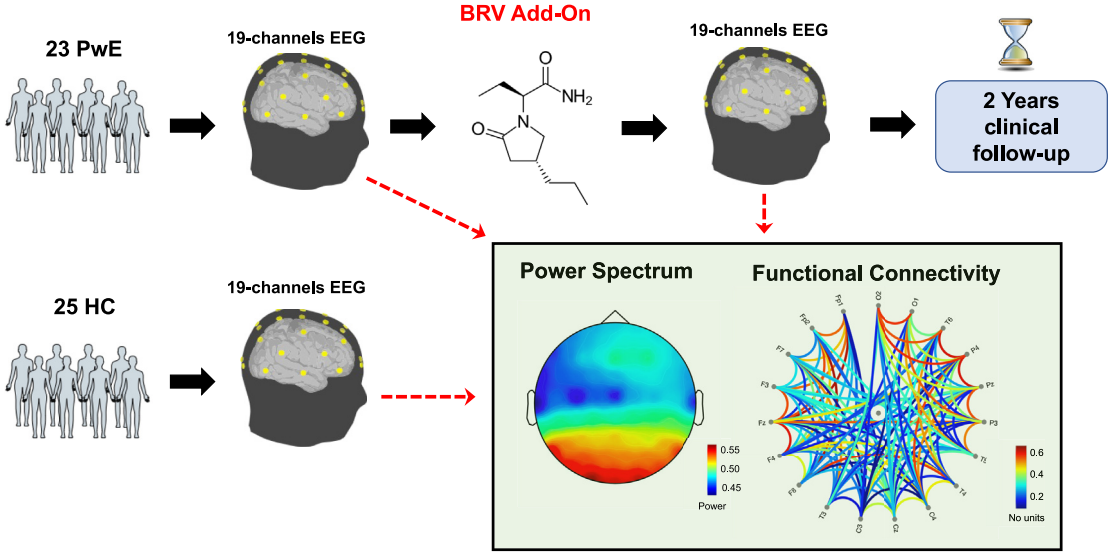

Fig. 1. Methodological Design and workflow of the study. The study involved two groups: 23 people with drug-resistant epilepsy (PwE) and 25 healthy controls (HC). All patients underwent 19-channel scalp EEG before and after approximately 3 months of Brivaracetam (BRV) treatment. The 19-channel scalp EEG data of HC were analysed as well. We analysed quantitative EEG features in the form of power spectrum density and functional connectivity across different frequency bands (delta to gamma). Long-term clinical follow-up (2 years) was collected for all patients to compare EEG features between clinical responders and non-responders to BRV.

Table 1
Patients clinical information and outcome.

Patient	Age (ys)	Sex	Aetiology	Epilepsy Duration (ys)	Seizure Type	Seizure Frequency	Epileptogenic Focus*	Concomitant ASMs(mg/day)	BRV Maintenance dose (mg/day)	Adverse Events	Previous therapy with LEV	Outcome
1	57	M	Immune	9	FIA, FTB	Weekly	Bil. T	CBZ 700, LTG 400, LCM 350, PB 100, CLB 10	50	No	Yes	N-RES
2	69	F	Structural (Post-Traumatic)	5	FIA	Weekly	Bil. T	OXC 1800; LTG 300; PB 100	200	No	Yes	RES
3	45	F	Unknown	9	FTB	Daily	Right T	LCM 450, CZP 10	100	No	No	N-RES
4	66	F	Structural (IH)	45	FPA	Monthly	Left T	LCM 300, LTG 300	100	No	Yes	RES
5	55	F	Unknown	35	FIA, FTB	Monthly	Bil. FT	LCM 350; PER 4	200	No	No	RES
6	35	F	Unknown	9	FIA	Daily	Right FCT	LCM 600, CBZ 1200	150	No	No	N-RES
7	32	M	Structural (Post-Traumatic)	11	FPA	Weekly	Left T	CBZ 1200	50	Distractibility	No	N-RES
8	63	F	Structural (Ischemic Stroke)	11	FPA	Monthly	Right FT	CBZ 1200	150	Irritability, Headache	Yes	RES
9	45	M	Structural (Vascular Malformation)	26	FTB	Weekly	Right T	PB 150; CLB 10	100	No	No	N-RES
10	25	F	Unnown	10	FTB	Daily	Bil. FCT	ESL 1200	200	No	Yes	N-RES
11	44	F	Structural (Vascular Malformation)	23	FTB	Daily	Rigth T	CBZ 1000, PB 10, ACZ 250	200	No	Yes	N-RES
12	37	M	Structural (Glial Tumor)	1	FPA, FTB	Weekly	Left FT	LTG 300, LCM 200	200	No	No	N-RES
13	20	F	Unknown	8	FIA, FTB	Monthly	Right FT	LCM 300, LTG 400, VPA 800	150	No	No	N-RES
14	23	M	Structural (Post-Traumatic)	11	FPA	Monthly	Right T	LCM 400	100	No	Yes	RES
15	58	F	Structural (Ischemic Stroke)	7	FIA, FTB	Mutiple-yearly	Right TP	CBZ 1200	75	Drowsiness, Fatigue	Yes	N-RES
16	76	M	Structural (Vascular Malformation)	24	FIA	Mutiple-yearly	Right T	CBZ 800, PB 50, TPM 100	200	No	Yes	N-RES
17	49	M	Unknown	41	FPA, FTB	Daily	Bil. T	VPA 1000, LTG 150, PB 150	100	Drowsiness, Headache	No	RES
18	44	M	Structural (Vascular Malformation)	13	FIA, FTB	Mutiple-yearly	Right T	VPA 1200, CBZ 1400	150	No	No	N-RES
19	52	M	Unknown	32	FIA	Monthly	Right T	PB 100	100	No	No	RES
20	63	M	Structural (Glial Tumor)	5	FTB	Multiple-yearly	Left F	LCM 200, LTG 200, TPM 100	100	No	No	RES
21	37	M	Structural (Meningioma)	16	FPA	Daily	Left TO	OXC 1200	75	Drowsiness	Yes	N-RES
22	42	M	Structural (Ischemic Stroke)	12	FIA	Daily	Right T	ESL 1800, LTG 200	75	Irritability	Yes	N-RES
23	51	F	Structural (Ischemic Stroke)	4	FPA	Multiple-yearly	Right FTP	PER 8	150	No	Yes	N-RES

Ys = years; M = Male; F = Female; IH = Intracerebral Hemorrage; FIA: Focal Impaired awareness; FPA: Focal Preserved Awareness; FTB: Focal To Bilateral tonic-clonic; Bil. = Bilateral; T = Temporal; FCT = Fronto-Centro-Temporal; FT = Fronto-Temporal; TP = Temporo-Parietal; TO = Temporo-Occipital; FTP = Fronto-Temporal-Parietal; CBZ = Carbamazepine; LTG = Lamotrigine; LCM = Lacosamide; PB = Phenobarbital; CLB = Clobazam; OXC = Oxcarbazepine; CZP = Clonazepam; ESL = Eslicarbazepine acetate; ACZ = Acetazolamide; VPA = Valproic Acid; TPM = Topiramate; PER = Perampanel; N-RES = Non-Responder; RES = Responder. Ys = years * Presumed epileptogenic focus based on anatomo-electro-clinical correlations.

χ^2 = 637.9, p < 0.001; Fig. 2). Post-hoc tests revealed increased PSD theta values in PwE compared to HC both before BRV therapy (pre-BRV vs. HC; z = −3.67; p < 0.001) and after BRV (post-BRV vs. HC; z = −3.59; p < 0.001; Fig. 2). No significant differences were found in other frequency bands.

When controlling for clinical outcome, the Kruskal-Wallis test yielded similar results, showing increased PSD theta values in PwE compared to HC in both RES (pre-BRV vs. HC; z = 2.99; p < 0.01; post-BRV vs. HC; z = 2.57; p = 0.01) and N-RES (pre-BRV vs. HC; z = 2.47; p = 0.04; post-BRV vs. HC; z = 2.38; p = 0.02).

3.3. Phase-locking value connectivity

The comparison of PLV connectivity values across PwE before and after BRV therapy and HC revealed a significant difference between groups (factor *Conditions;* χ^2 = 4.52, p < 0.001), along with a significant interaction (*Condition* vs. *Bands*; χ^2 = 368.2, p < 0.001; Fig. 3). Post-hoc tests showed reduced PLV values for all the frequency bands in PwE compared to HC both before BRV therapy (z: 4.07 [delta]; 3.4 [theta]; 7.81 [alpha]; 12.62 [beta] and; 7.13 [gamma]; p < 0.001 for all frequency bands) and after BRV (z: 3.86 [delta]; 3.31 [theta]; 7.53 [alpha]; 12.56 [beta] and; 7.58 [gamma]; p < 0.001 for all frequency bands). We found no differences in the comparison of PLV values between pre-BRV and post-BRV (p > 0.05 for all frequency bands; Fig. 3).

After controlling for clinical outcome, the Kruskal-Wallis test yielded similar results, except within the theta frequency band. RES patients exhibited lower theta PLV connectivity compared to HC before initiating BRV (z = −2.58; p = 0.03) and experienced an increase after BRV, eliminating the significant difference from HC (z = −1.68; p = 0.14; Fig. 4). Conversely, N-RES patients showed consistently lower theta PLV both before and after BRV therapy compared to HC (z = −2.54; p = 0.03 [pre-BRV vs. HC], and z = −2.39; p = 0.02 [post-BRV vs. HC]; see Fig. 4).

4. Discussion

In this study, we showed the quantitative EEG features of PwE undergoing BRV therapy through pharmaco-EEG analysis compared to HC. We also compared such EEG components according to clinical outcomes among RES and N-RES patients. Our main findings can be summarized as follows: (i) PwE presented higher theta PSD values compared to HC, regardless of BRV therapy; (ii) BRV did not induce modifications in PSD values across different frequency bands; (iii) PwE presented lower PLV connectivity values compared to HC in all frequency bands; (iv) BRV therapy led to an increase of theta PLV connectivity in patients who responded (RES) to the treatment, bringing their levels in line with those of healthy controls, unlike in patients who showed no response (N-RES).

4.1. PSD results

In most pharmaco-EEG studies examining ASMs, the primary objective was the evaluation of alterations in frequency using either visual inspection or quantitative approaches (Ricci et al., 2021). Numerous old-generation ASMs commonly demonstrated a general reduction of power, as observed in responses to sodium valproate (Sannita et al., 1989), gabapentin (Saletu et al., 1986), and carbamazepine (Wu and Xiao, 1996). Notably, recent work on new-generation ASMs showed mixed results. A recent pharmaco-EEG study from our group examining LEV demonstrated increased EEG power for alpha and decreased theta, with a return to values similar to healthy controls (Ricci et al., 2021). Another recent study showed that the new-generation ASM perampanel increased theta power without altering brain connectivity as measured by 19-channel EEG (Lanzone et al., 2021). Interestingly, we found that BRV therapy did not lead to significant shifts in PSD values across various frequency bands in this study. There are several possible explanations for this finding. Firstly, it should be men-

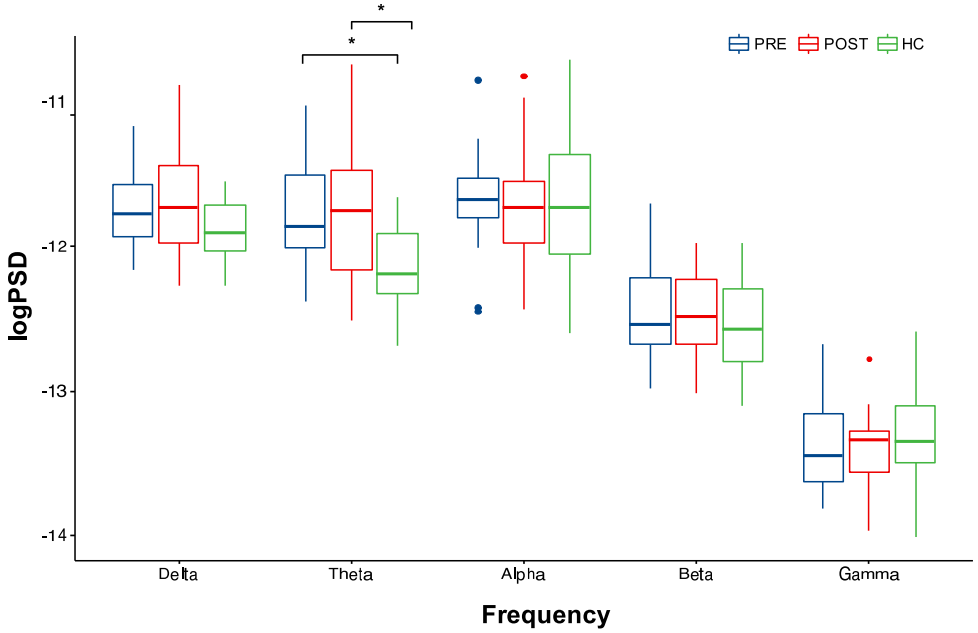

Fig. 2. EEG power spectrum density (PSD). Boxplot distributions of PSD modifications comparing people with drug-resistant epilepsy before (PRE) and after three months (POST) of Brivaracetam therapy and healthy controls (HC). Circles denote values that are farther than 1.5 interquartile ranges. PSD values are represented on a logarithmic scale (logPSD) for visual purposes. *p < 0.05.

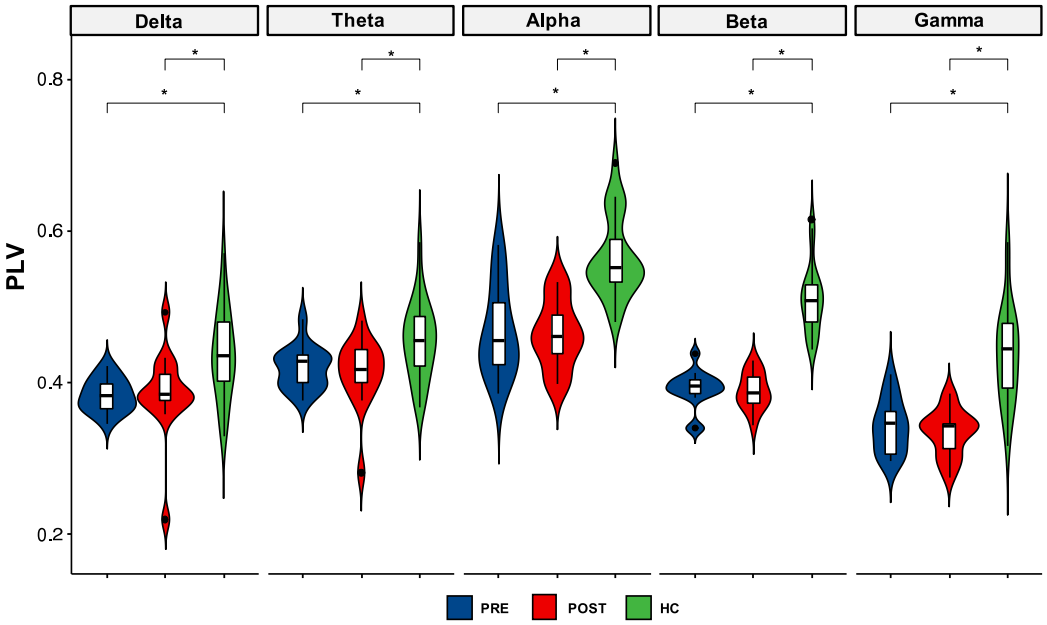

Fig. 3. EEG phase locking value (PLV) connectivity. Boxplot and violin plot distributions of PLV EEG connectivity across conditions (PRE, POST and healthy controls – HC). Circles denote values that are farther than 1.5 interquartile ranges. Pre EEG performed before the initiation of Brivaracetam (BRV) therapy. Post EEG performed after approximately 3 months of BRV therapy.*$p < 0.05$.

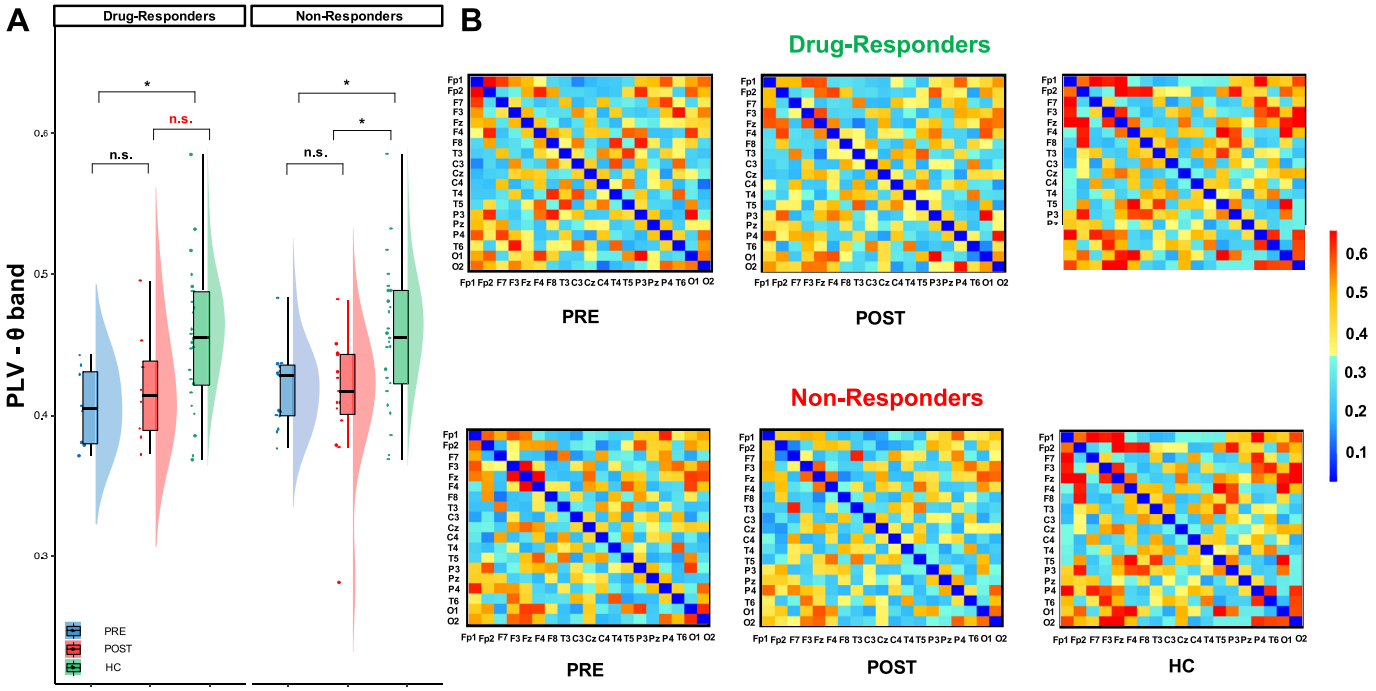

Fig. 4. Comparison of Phase Locking Value (PLV) in the theta band among Drug-Responders, Non-Responders, and Healthy Controls (HC). A. Raincloud plot and boxplot distribution of PLV comparing the EEG performed before Brivaracetam (BRV) initiation (PRE) and the EEG performed after 3 months of BRV therapy (POST) among people with drug-resistant epilepsy presenting a clinical response to BRV (drug-responder; RES) and non-responder (N-RES) and HC. Black lines represent mean values. Circles denote mean metric value for each subject. We found that RES patients experienced an increase in theta PLV after BRV, eliminating the significant difference from HC. **B. Connectivity matrices**. The matrices illustrate the PLV in the theta band between pairs of EEG electrodes before and after BRV treatment for RES (top row) and N-RES (bottom row), as well as for healthy controls (HC, far right).Each cell within the matrices corresponds to the PLV between the EEG electrode pair labelled on the x and y axes, with colour intensity reflecting the strength of connectivity (ranging from low [blue] to high [red]). n.s. = non-significant. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

tioned that more than half of the patients in our cohort (52.2%) shifted from a previous therapy with LEV to BRV. LEV and BRV are thought to exert their anticonvulsant action by binding to SV2A and modulating its effect on neurotransmitter release (Klein et al., 2018) and BRV differs from LEV only for its selectivity and high affinity for SV2A (15- to 30-fold higher affinity than LEV) (Klein et al., 2018). Therefore, it is reasonable to assume that switching to an ASM with the same molecular target might not

result in specific changes in the electrical activity of the brain as measured by PSD. Secondly, the absence of significant alterations in PSD following BRV administration might be related to its established safety profile concerning neuropsychiatric adverse events (Lattanzi et al., 2021). Indeed, theta (and delta) oscillations have been associated with various cognitive processes, including memory formation, attention, and spatial navigation (Assenza et al., 2015; Pellegrino et al., 2018, 2017). Similarly, alpha oscillations are involved in visual processing and attention (Thut et al., 2006), beta activity pertains to motor network regulation (Engel and Fries, 2010; Pellegrino et al., 2012), and gamma oscillations promote synchronization of neural circuits (Larsen et al., 2018). This trend was also observed in our group of PwE, where 26.1% of patients experienced non-serious adverse events related to BRV therapy. Finally, our results showed increased theta activity in PwE compared to HC. The elevated theta PSD in PwE may reflect underlying dysregulation in the neural circuits involved in cognitive processes. The increased theta activity could represent a compensatory mechanism in response to the epileptic pathology or a consequence of chronic seizure activity (Croce et al., 2021; Ricci et al., 2022). Such alteration might also be the consequence of the concomitant ASM therapy already taken by patients. Alternatively, it could indicate an imbalance in inhibitory and excitatory neural networks, which is commonly observed in epilepsy (Englot et al., 2015; Iandolo et al., 2021). That is, this finding aligns with previous research that reported alterations in theta oscillations in people with epilepsy compared to HC (Lanzone et al., 2021; Ricci et al., 2021).

4.2. PLV connectivity

Epilepsy is increasingly identified as a neurological condition impacting the organization of cortical networks, and numerous investigations have indicated that the epileptogenic focus can modify brain functional connectivity and cortical network topology (Iandolo et al., 2021). Indeed, several studies suggest that healthy interactions across various regions deteriorate in people with epilepsy, leading to abnormally increased connectivity in neural networks proximate to the epileptic focus (i.e., local networks) (Englot et al., 2015; Ricci et al., 2021) and diminished global connectivity in extended-range networks (Pellegrino et al., 2018). As a result, people with epilepsy often exhibit reduced overall connectivity compared to healthy individuals (Pellegrino et al., 2018; Ricci et al., 2021). Our findings are consistent with this notion: PwE patients presented globally reduced phase locking value (PLV) connectivity values compared to HC, suggesting an impairment in physiological extended-range networks. The observed reduction in PLV connectivity in PwE aligns with the concept of 'functional disconnection' in epilepsy, where the physiological interactions between different brain regions are disrupted by the epileptic network (Chericoni et al., 2023). This disruption may eventually lead to the characteristic manifestations of epilepsy, including seizures and cognitive deficits (Tombini et al., 2021).

Finally, BRV therapy increased theta PLV connectivity in RES, eliminating the significant difference from HC, as opposed to patients with no response (N-RES). That is, the possibility of characterizing the prognostic phenotype of PwE using quantitative EEG is promising, possibly allowing us to obtain a data-driven prognostic index of long-term therapeutic efficacy for various ASMs based on EEG data (Croce et al., 2021). However, it is important to highlight that we did not find direct modifications of PLV connectivity induced by BRV (i.e., pre-BRV vs. post-BRV). This suggests that a combination of factors, including clinical heterogeneity, concurrent ASMs therapy, or individual variability, might influence the observed changes. Further prospective research with a larger sample size is needed to validate these findings and to explore the mechanisms through which BRV and other ASMs may influence neural connectivity.

4.3. Limitations and future directions

Our study has some limitations which should be stated. The first limitation is the non-randomized, retrospective nature of the study design since our experiment was not specifically intended for direct clinical applications. Future research should make use of a sample size that is large enough to enable the comparison of pharmaco-EEG characteristics with other clinical factors (i.e., epilepsy duration and aetiology, localization of the epileptic focus, seizures' semiology). The limited sample size of PwE is another limitation, particularly when dividing for clinical outcomes (8 RES and 15 N-RES). Yet, it is important to highlight that the population size of PwE aligns with other pharmaco-EEG studies from our group (Lanzone et al., 2021; Pellegrino et al., 2018; Ricci et al., 2021).

Secondly, since BRV is not licensed as monotherapy in Italy, we were not able to evaluate the effects of BRV alone due to the heterogeneity of therapy combinations and dosages in our PwE cohort. Further investigation is required to verify the reproducibility of our results across varied datasets, specifically among patients with epilepsy who do not meet drug-resistant criteria or those who have not transitioned from previous LEV therapy. Finally, it is important to note that standard EEG may have limitations due to its lower spatial resolution and less comprehensive coverage of certain brain regions (Seeck et al., 2017). More sophisticated techniques (i.e., high-density EEG and MEG) could provide deeper insights into the potential of pharmaco-EEG for measuring the activity and possible effectiveness of ASMs.

5. Conclusion

This study provides insights into the quantitative EEG features of PwE undergoing BRV therapy. Our findings highlight that BRV treatment does not affect EEG power spectrum activity in PwE, supporting its favourable neuropsychiatric profile in terms of side effects. Our results also support the notion that PwE exhibit aberrant and disrupted EEG connectivity compared to HC. Importantly, BRV may facilitate neural synchrony in patients who respond favourably to treatment, as evidenced by the 'normalization' of EEG connectivity patterns in theta band following BRV therapy. The integration of pharmaco-EEG analysis in epilepsy can provide insights into the efficacy, mechanism of action, and potential side effects of ASMs, paving the way for more personalized treatment strategies for people with epilepsy.

Ethical publication statement

All the authors confirm that they have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Conflict of interest statement

None of the authors have potential conflicts of interest to be disclosed.

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