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## BRIEF COMMUNICATION

# How fast does the brain recover after an epileptic seizure?

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## Abstract

The postictal state, an abnormal cerebral condition following a seizure until the return to the interictal baseline, is frequently overlooked, despite often exceeding ictal duration and significantly impacting patients' lives. This study analyzes stereo-EEG (SEEG) signal dynamics using permutation entropy to quantify recovery time (postictal alteration time – PAT) in focal epilepsy and its clinical correlations. The average PAT was 4.5 min, extending up to an hour and was highest in temporal epilepsy and hippocampal sclerosis. Correlating with age at seizure onset and at SEEG, PAT provides a solution for operationally defining the postictal state and guiding interventions.

## Introduction

The postictal state is an abnormal brain condition lasting from the end of a seizure until the return to interictal baseline<sup>1</sup> and often exceeds ictal duration. Moreover, the impact of the postictal period on patients' lives might surpass that of the seizures themselves. Hence, the postictal state emerges as a potential target for epilepsy therapy.<sup>2</sup> However, research on this period is still limited. In this regard, analyzing signal dynamics can assist in monitoring EEG changes throughout the ictal and postictal states. Permutation entropy (PE), a signal complexity measure, has shown promise in quantifying (peri)ictal EEG alterations.<sup>3,4</sup>

In this study, we analyzed stereo-EEG (SEEG) signal dynamics using PE to estimate recovery time in different types of focal epilepsy and to correlate it with clinical parameters.

## Methods

### Patients and data acquisition

We analyzed the SEEG recordings of 202 consecutive patients with focal drug-resistant epilepsy who underwent presurgical assessment between 2000 and 2023. We

included patients with unequivocal epileptogenic zone network (EZN) defined to one lobe (or homologous lobes in case of bilaterality) and spontaneous, isolated seizures (with at least 1 h of postictal period per dataset). All patients have given informed written consent, and this study was approved by the Assistance Publique – Hôpitaux de Marseille (PADS A5WSFC).

### SEEG signal analysis

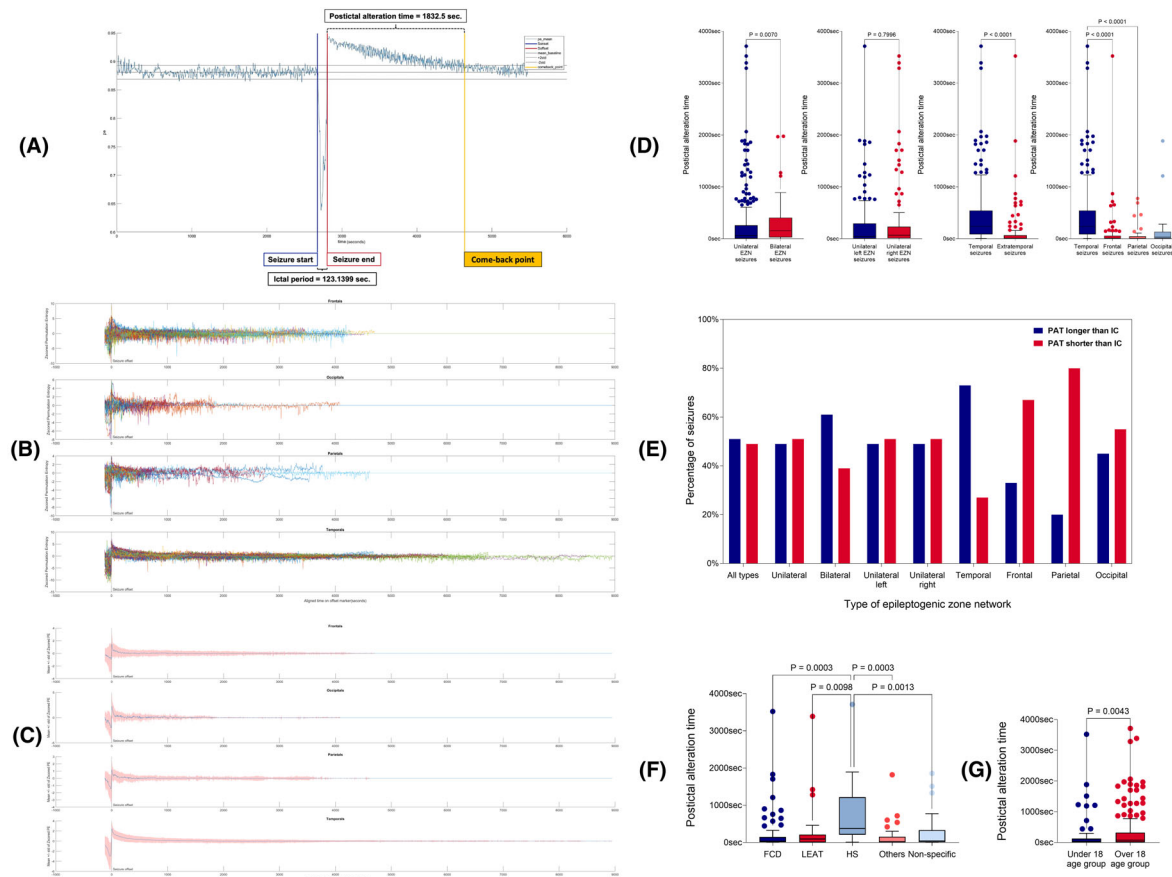
Noninvasive electro-clinical hypothesis-driven SEEG explorations were performed using intracerebral electrodes as previously described.<sup>5</sup>

Permutation entropy (PE) quantification of the SEEG signals was performed using AnyWave software (<https://meg.univ-amu.fr/wiki/AnyWave>)<sup>6</sup> and an in-house Matlab plug-in. PE analysis starts with a one-dimensional time series from which a set of D vectors is generated. These vectors consist of consecutive points separated by a fixed time delay  $\tau$  measured in samples (with  $\tau = 1$  for consecutive samples). Each vector of signal samples is assigned an ordinal pattern  $\pi$ , reflecting the ranks of amplitudes within the vector. In a subsequent step, the probability  $p(\pi)$  of a specific ordinal pattern  $\pi$  occurring within a given time window is calculated. The entropy within the window is consequently defined as  $H(D) = -\frac{1}{\log_2 D!} \sum p(\pi) \log_2(p(\pi))$ .

The values of  $H(D)$  range from 0 to 1, smaller values indicating a more regular and deterministic time series, while values closer to 1 suggesting a noisier and more random time series.<sup>7</sup>

Building on our previous work,<sup>3,8</sup> the parameters used in this PE study were an embedding dimension  $D = 3$  and a time lag  $\tau = 1$ . The analysis was conducted using a sliding time window of 5 sec, with an overlap of 2.5 sec. Global PE values were computed by averaging all PE values of nonartifactual channels. The preictal baseline global complexity was established within 2 standard

deviations (SD) of the mean value. We considered that the SEEG signal returned to its preictal complexity (“come-back point”) when for 25 consecutive seconds onward ( $10 \times 2.5$  sec overlap) the global PE value was again in the 2SD interval (Fig. 1). Seizure onset and termination were visually determined by expert clinicians (I.F.B. and F.B.). Electrical seizure end was based on the moment when the ictal discharge ended in the last pair of involved channels. The period between the electrical seizure termination and the “come-back point” was named postictal alteration time (PAT) (Fig. 1A). We excluded



**Figure 1.** Postictal state quantification in focal epilepsy. (A) Global complexity dynamics of cerebral electrical activity as measured by the stereo-electroencephalography recording contacts and depicted after permutation entropy quantification. y axis – permutation entropy (PE) values, x axis – timeline in seconds. The vertical bars indicate the seizure onset, termination, and “come-back point” (the point at which for 25 consecutive seconds the global PE value is in the 2SD interval of the preictal period). The interval between the seizure start and end is called “ictal period,” and the interval between the seizure end and the “come-back point” is the postictal alteration time (PAT). (B) Z-scored global complexity dynamics in the postictal period as plotted from the global permutation entropy curves of all analyzed seizures and subgrouped according to the epileptogenic zone network (EZN). (C) Mean  $\pm$  standard deviation of Z-scored global complexity dynamics in the postictal period as plotted from the global permutation entropy curves of all analyzed seizures and subgrouped according to the EZN. (D) Comparison of the postictal alteration time in unilateral EZN versus bilateral EZN, unilateral left EZN versus unilateral right EZN, temporal versus extratemporal and between, temporal, frontal, parietal, and occipital seizures. (E) Percentage of seizures in which the postictal alteration time (PAT) was longer or shorter than the ictal duration (IC) according to the type of epileptogenic zone network. (F) Comparison of the postictal alteration time according to the histopathology exam result of the epilepsy surgery resection piece. FCD, focal cortical dysplasia; HS, hippocampal sclerosis; LEAT, long-term epilepsy-associated tumor. (G) Comparison of the postictal alteration time according to age groups.

from analysis seizures without “come-back point” reached in the available SEEG datasets and/or focal to bilateral tonic-clonic evolution.

## Statistical analysis

Spearman rank correlation was used to examine covariance between PAT and clinical variables. A Mann–Whitney *U* test was applied to assess differences between groups. One-way ANOVA was used to measure the difference between groups with more than two categories.

## Results

A total of 202 patients were included (Table 1). The mean age at epilepsy onset was 11.75 years (first day of life–55 years), and the mean epilepsy duration at the time of SEEG exploration was 17.07 years (0.5–50). The EZN was temporal in 120 patients and extratemporal in 82 patients. In total, 68% of patients benefited from post-SEEG epilepsy surgery (Engel class I in 53%).

### Postictal alteration time in focal seizures

PE was computed on 372 focal seizures (Table 2). The mean PAT was ~4.5 min and ranged from 0 to ~1 h and 2 min. PAT was higher in bilateral seizures (mean ~5 min) than in unilateral seizures (mean ~4.5 min) ( $p = 0.007$ ) (Fig. 1D). There was no significant difference between PAT of left vs. right seizures ( $p = 0.79$ ) (Fig. 1D).

### Postictal alteration time in temporal vs. extratemporal epilepsies

Overall, temporal seizures ( $n = 179$ ) had a higher PAT than extratemporal seizures ( $n = 193$ ) (Fig. 1D). These differences were significant for temporal seizures compared to frontal and parietal seizures. ( $p < 0.0001$ ). In temporal seizures, mean PAT was ~7.5 min, ranging from 5 sec to ~1 h and 2 min, whereas in extratemporal seizures mean PAT was ~1.5 min, ranging from 0 to ~58 min. The longest PAT in temporal epilepsy seizures occurred within the mesial group, ranging from 10 sec to approximately 1 h and 2 min, with an average duration of 10 min. PAT was significantly higher in mesial-temporal seizures compared to lateral-mesial-temporal ones ( $p < 0.05$ ). However, PAT was not significantly different between left and right temporal seizures or their respective subgroups (mesial/lateral/lateral-mesial-temporal) ( $p > 0.05$ ). The PAT in frontal seizures ranged from 0 to ~58 min (~1.5 min mean). In parietal seizures, PAT ranged from 0 to ~13 min (~1 min), and in occipital seizures, it ranged from 0 to ~31 min. There was no

**Table 1.** Electro-clinical characteristics of the patients.

Age at epilepsy onset, years, mean $\pm$ standard deviation (range)	11.75 $\pm$ 9.66 (0–55)
Epilepsy duration until SEEG, years, mean $\pm$ standard deviation (range)	17.07 $\pm$ 10.57 (0.5–50)
Epilepsy duration until surgery, years, mean $\pm$ standard deviation (range)	17.18 $\pm$ 10.46 (1.5–51)
Epilepsy type, localization of the epileptogenic zone network, number of patients	
All types	202
Unilateral	166
Left	79
Right	87
Bilateral	36
Temporal	120
Temporal lateral	13
Temporal mesial	68
Temporal lateral-mesial	14
Extratemporal	82
Frontal	53
Parietal	21
Occipital	8
Surgery, % (number of patients)	
Yes	68% (137)
No	32% (65)
Outcome, Engel class, % (number of patients)	
I	53% (72)
Non-I	47% (65)
Histopathology results, % (number of patients)	
Available	111
Not available	26
Focal cortical dysplasia	34% (38)
Long-term epilepsy-associated tumors	13.5% (15)
Hippocampal sclerosis	12% (13)
Gliosis	20% (22)
Tuberous sclerosis lesion	1% (1)
Non-specific	21% (23)

significant difference between the PAT of the three groups of extratemporal seizures (frontal, parietal, and occipital) or their left and right subgroups ( $p > 0.05$ ).

### Postictal alteration time and seizure duration

In 51% of focal seizures, PAT exceeded the ictal duration (Fig. 1E). This percentage was consistent between left and right EZN seizures and varied between 20% in parietal seizures and 73% in temporal seizures. PAT was positively correlated with seizure duration ( $\rho = 0.48$ ,  $p < 0.0001$ ). Postictally, 18.5% of seizures were immediately followed by a return to baseline cerebral activity complexity. This occurred in at least one seizure for 20% of patients (40 patients) and consistently across seizures for 3% of cases (6 patients).

**Table 2.** Postictal alteration time quantification (seconds) in seizures with focal onset without secondary generalization.

Epilepsy type	Laterality of epilepsy	Specific subgroup	Analyzed seizures	Range	Mean	Std. dev.
All types	All		372	0–3712.5	269.04	519.97
	Unilateral all		305	0–3712.5	264.23	541.11
	Unilateral left		149	0–3712.5	267.43	499.80
	Unilateral right		156	0–3522.5	261.18	579.43
	Bilateral		67	0–1975	290.93	413
Temporal	All		179	5–3712.5	457.21	617.87
	Unilateral all		132	10–3712.5	497.31	666.91
		Lateral	15	12.5–1332.5	247.5	326.37
		Mesial	98	10–3712.5	592.45	737.55
		Lateral-mesial	19	12.5–575	203.82	174.43
	Unilateral left		65	10–3712.5	529.12	619.77
		Lateral	2	255–422.5	338.75	118.44
		Mesial	54	10–3712.5	578.24	665.72
		Lateral-mesial	9	27.5–575	276.67	195.02
	Unilateral right		67	12.5–3390	466.46	712.99
		Lateral	13	12.5–1332.5	233.46	348.57
		Mesial	44	22.5–3390	609.89	824.81
		Lateral-mesial	10	12.5–357.5	138.25	130.23
	Bilateral		47	5–1975	344.57	439.36
Extratemporal	All		193	0–3522.5	94.53	328.88
Frontal	All		116	0–3522.5	88.83	350.44
	Unilateral all		103	0–3522.5	83.07	361.99
	Unilateral left		52	0–227.5	29.66	49.44
	Unilateral right		51	0–3522.5	137.53	508.76
	Bilateral		13	0–715	134.42	246.02
Parietal	All		55	0–775	65.09	158.89
	Unilateral all		52	0–775	65.24	162.99
	Unilateral left		26	0–775	67.69	197.21
	Unilateral right		26	0–462.5	62.79	123.66
	Bilateral		3	22.5–137.5	62.5	65
Occipital	All		22	0–1885	198.18	455.98
	Unilateral all		18	0–1885	166.53	436.82
	Unilateral left		6	0–1885	358.75	749.81
	Unilateral right		12	0–280	70.42	95.44
	Bilateral		4	0–1210	340.63	584.02

## Postictal alteration time and clinical variables

The PAT values showed no significant differences between seizures grouped by surgical outcome – seizure-free versus nonseizure-free ( $p > 0.05$ ). Seizures that occurred in epilepsies caused by hippocampus sclerosis had a significantly higher PAT than other pathologies (focal cortical dysplasia, long-term epilepsy-associated tumors, others, and negative-non-specific histopathology) (Fig. 1F). PAT was positively correlated with age at epilepsy onset ( $\rho = 0.22$ ,  $p < 0.0001$ ), but not with epilepsy duration ( $p > 0.05$ ). Nevertheless, PAT values differed significantly among age groups – under 18 versus 18+ years old ( $p = 0.004$ ) (Fig. 1G) with higher values in the adult group.

## Discussion

This study quantified, for the first time, complexity alterations of SEEG signals and their dynamics during the postictal period. Previous postictal period quantifications had been done using surface signals and visual analysis.<sup>9,10</sup> The recovery times observed by direct analysis of scalp EEG were considerably longer than those measured in the current work. This could arise from the narrower perspective provided by the sampling of intracerebral sensors compared to scalp sensors (which capture a more global view of brain activity<sup>11</sup>) or from the different techniques of estimation.

The average postictal period evaluated by the measure of a parameter called the PAT lasted approximately 4.5 min, but this period could extend up to an hour, indicating a potential prolonged impact on brain physiology

due to altered complexity dynamics. Persistent changes in brain activity complexity may contribute to postictal cognitive deficits, as evidenced by associations with ictal (e.g., loss of awareness<sup>8</sup>) and postictal deficits (e.g., transient epileptic amnesia<sup>12</sup> linked to postictal complexity alterations in the medial temporal regions).

Despite the bias of a significantly larger number of publications on the comorbidities and consequences of temporal lobe epilepsy, it appears that the latter is responsible for the majority of cases of postictal-related disabilities.<sup>13</sup> Thus, especially in cases of focal temporal lobe epilepsy, interventions like neuromodulation (thalamic<sup>14</sup> or vagal<sup>15</sup> stimulation) or specific medications (e.g., levetiracetam<sup>16</sup> or lamotrigine<sup>17</sup>) could significantly improve quality of life by shortening recovery time.

Our quantification re-emphasizes the fact that the duration of the postictal state frequently exceeds that of the ictus itself.<sup>18</sup> In contrast, 20% of the patients had seizures followed by an instantaneous return to baseline cerebral activity complexity, which is in the range of 15–50% reported in other studies.<sup>10</sup>

We found a relationship between values of PAT, age at seizure onset, and age at which the seizures were recorded by on SEEG. These findings agree with existing literature concerning the effects of age on the duration of the postictal period.<sup>19</sup> Inferences can be drawn regarding the brain plasticity reserve and how changes in cerebral activity complexity are influenced by it.

The variation of PAT according to the histopathological substrate, in our case – higher PAT in hippocampal sclerosis cases, might be accounted for by chronic alterations in the functional organization of lesional tissue and their large-scale network implications.<sup>20</sup>

To conclude, the notion of PAT offers a potential solution for operationally defining the postictal state. Furthermore, it may advance our comprehension of postictal disturbances, guiding interventions in epilepsy therapy.

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## Conflict of Interest

The authors involved in the present study have confirmed that they do not have any conflict of interest.

## Author Contributions

Ionut-Flavius Bratu: Conception and design of the study, Data analysis, Statistical analysis, Methodology, Validation, Visualization, Writing – Original Draft Preparation, Review & Editing. Samuel Medina Villalon: Data analysis, Validation, Visualization. Elodie Garnier: Data analysis. Christian Bénar: Conception, Methodology, Supervision, Validation, Writing – Review & Editing. Fabrice Bartolomei: Conception and design of the study, Methodology, Supervision, Validation, Visualization, Writing – Original Draft Preparation, Review & Editing.

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## Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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