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Title:
Postictal suppression and seizure durations: A patient-specific, long-term iEEG analysis

Date:
2018-05-01

Citation:
Payne, D. E., Karoly, P. J., Freestone, D. R., Boston, R., D'Souza, W., Nurse, E., Kuhlmann, L., Cook, M. J. & Grayden, D. B. (2018). Postictal suppression and seizure durations: A patient-specific, long-term iEEG analysis. Epilepsia, 59 (5), pp.1027-1036. https://doi.org/10.1111/epi.14065.

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Article type : Full length original research paper

Title: Postictal suppression and seizure durations: a patient-specific, long-term iEEG analysis

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Running Title: Postictal suppression in long-term iEEG

Key Words: long-term, iEEG, postictal, suppression, patient-specific, SUDEP

Number of text pages: 17

Number of words: 2979

Number of references: 22

Number of figures: 3

Number of tables: 2

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/epi.14065

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Summary

Objective: We report on patient-specific durations of postictal periods in long-term intracranial electroencephalogram (iEEG) recordings. The objective was to investigate the relationship between seizure duration and postictal suppression duration.

Methods: Long-term recordings iEEG from nine patients (>50 seizures recorded) were analyzed. In total, 2310 seizures were recorded during a total of 13.8 years of recording. Postictal suppression duration was calculated as the duration of time after seizure termination until total signal energy returned to background levels. The relationship between seizure duration and postictal suppression duration was quantified using the correlation coefficient (r). The effects of populations of seizures within patients on correlations were also considered. Populations of seizures within patients were distinguished by seizure duration thresholds and k-means clustering along the dimensions of seizure duration and postictal suppression duration. The effects of bursts of seizures were also considered by defining populations based on interseizure interval (ISI).

Results: Seizure duration accounted for 40% of postictal suppression duration variance, aggregated across all patients and seizures. Seizure duration accounted for more than 25% of the variance in postictal suppression duration in two patients and accounted for less than 25% in the remaining seven. In three patients, heat maps showed multiple distinct postictal patterns indicating multiple populations of seizures. When accounting for these populations, seizure duration accounted for less than 25% of the variance in postictal duration in all populations. Variance in postictal suppression duration accounted for less than 10% of ISI variance in all patients.

Significance: We have previously demonstrated that some patients have multiple seizure populations distinguishable by seizure duration. This paper shows that different seizure populations have distinct and consistent postictal behaviors. The existence of multiple populations in some patients has implications for seizure management and forecasting, while the distinct postictal behaviors may have implications for SUDEP prediction and prevention.

Key Words: long-term, iEEG, postictal, suppression, patient-specific, SUDEP

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Key Points

- Long-term iEEG recordings were obtained from nine patients with a total of 2310 seizures over a cumulative recording time of 13.8 years.
- Multiple distinct and reliable postictal iEEG patterns were seen in three patients, illustrating multiple populations of seizures.
- Postictal suppression duration shows minor or no correlation with seizure duration when accounting for multiple populations of seizures.

Introduction

Despite extensive study, the mechanisms of epileptic seizures remain elusive. Much of the focus in epilepsy research is on seizure onset rather than seizure termination. Thus, less is known about the postictal period than about preictal and ictal activity. Understanding seizure onset mechanisms may help guide preventative or predictive strategies. However, studying the seizure termination process may permit new therapeutic approaches[1]. An understanding of seizure dynamics and transitions must be informed by statistical observations from data[2] including mathematical modelling.

Various signal features at the electrographic onsets and offsets of seizures suggest that they are critical transitions in the underlying brain state[3,4]. Critical transition models assume that seizure onsets and offsets may not begin and end entirely as a result of random fluctuations in cortical activity or input, but rather that seizures follow a path that must be completed as the brain transitions to the interictal state. Mathematical modelling of postictal suppression suggests a deterministic process associated with longer inter-clonic intervals and reduced connectivity prior to seizure termination[5]. This agrees with the hypothesis that seizures follow a set pathway through brain states[4,6].

The postictal period is commonly characterized by a period of low energy that slowly returns to interictal norms (referred to here as postictal suppression).[5,7–9] Postictal suppression is often associated with specific clinical features such as immobility, impaired cognition, headache, and psychological depression[10–12]. There is a contentious link between postictal generalized suppression(PGES) and sudden unexpected death in epilepsy (SUDEP)[8,9,13–15].

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No correlation between postictal suppression length and SUDEP has been established. However, postictal suppression and PGES may reflect similar processes and so it is reasonable to speculate that postictal suppression may also influence SUDEP occurrence. SUDEP has a mortality rate of 0.13-2.7 per 1000 person years, increasing to 3.5-9.3 per 1000 person years for people with refractory epilepsy[16], so understanding any potential link may assist in the development of preventative strategies.

Cook et al. (2016)[17] showed that, in some patients, seizure duration is bimodally distributed, indicating two distinct populations of seizures that have different onset and/or offset mechanisms. However, it is not yet known if these populations also differ in their postictal behavior. Knowledge of postictal statistics could have important implications for SUDEP prevention.

Despite knowledge that many aspects of seizure characterization are highly patient-specific[17–20], such an analysis of the postictal period in long-term data has not yet been conducted. This has been largely due to lack of datasets that contain enough seizures per patient to allow sufficient analysis. The dataset created by the clinical trial of a seizure advisory system has recently provided such data[21]. We use this to investigate patient-specific patterns in the postictal period, and find a relationship between postictal suppression duration and seizure duration.

Methods

The Dataset

The data used in this study has been previously described by Cook et al. (2013)[21]; please refer to this publication for further information on patient demographics, study design, and other details not provided in Table 1. In summary, the 15 patients in the dataset had focal-onset seizures with a lateralized epileptogenic zone. Sixteen intracranial electroencephalogram (iEEG) channels were continuously recorded at 400 Hz. Epilepsy-related events were categorized into three types: seizures that were clinically confirmed (type one), events that were equivalent to type one seizures in the iEEG recordings but without clinical confirmation (type two), and seizure-like events that were different to type one events in iEEG recordings and without clinical confirmation (type three). Type three events were excluded from this

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study as they may not represent true seizures. The first 15 weeks of iEEG recordings were excluded as there were transition periods in the iEEG signal after initial implantation[22]. Patients 2, 4, 5, 7, 12, and 14 were removed as they had less than 50 type one and two seizures.

Some seizures were followed within a few hours by another seizure. To avoid unintentional inclusion of the following seizure's preictal period in the current seizure's post-ictal period, a minimum inter-seizure interval (ISI) of five hours was chosen, except where stated otherwise. Seizures with high iEEG signal loss, defined as more than 10% of the data segment lost, were also removed from the study.

Data processing

Each data sample consisted of 16 channel iEEG from the point of seizure termination until the postictal upper limit, which was defined to identify a start point of the interictal period and was determined on a patient-specific basis (see Table 1). The postictal upper limit is defined here as the longest postictal suppression duration (i.e. time from seizure start until changes in total energy perceived to be due to noise alone) rounded up to the nearest multiple of 10 minutes. Therefore, all postictal suppressions finish before the postictal upper limit.

The mean of each channel was subtracted from that channel to remove DC offset. Energy was calculated in the 10-30 Hz range in each channel after filtering with a zero-phase, second-order Butterworth filter. The energy was then smoothed using a five sec moving average sliding window with 0.0025 sec step size. Smoothed energy across all 16 channels were summed to give the total energy across the recording in the 10-30 Hz frequency band. A five sec median-value filter with 0.0025 sec step size was then applied to smooth the total energy.

The average total energy in the 10 minutes after the postictal upper limit was defined as normal background energy for a given seizure. The end of postictal suppression for each seizure was conservatively estimated as the time of the first total energy value passed the background energy value. To avoid falsely short suppression times due to smoothing windows overlapping with the seizure, the first five sec after each seizure were ignored when calculating postictal suppression length. To ensure that seizures with no suppression period

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were not falsely labeled to have a five sec suppression period, all suppression durations were reduced by five sec.

Correlating seizure and postictal suppression duration

The strength of the correlation between postictal suppression duration and seizure duration was evaluated using the correlation coefficient (r). To account for the effect of multiple seizure populations on the correlation between seizure length and postictal suppression length, correlation was also calculated within seizure populations for selected patients. Seizures in these patients were most easily separated by seizure length and so seizures were separated into short-seizure and long-seizure populations. From herein the term populations refers to these clusters of seizures split by seizure length except where stated otherwise. Thresholds were chosen upon viewing the data. Given that the selection of these thresholds were subjective, seizures were also separated objectively by applying k-means clustering in two dimensions (seizure duration and postictal suppression duration). Correlation was also calculated across all patients as a point of comparison to patient-specific analysis. If all seizures were used, results could vary due to differences in statistical power alone. To avoid this, 17 seizures per patient for a total of 153 seizures were sampled, close to the average of 152.6 seizures per patient (when excluding seizures with an ISI less than five hours).

To investigate possible effects of seizure clusters on the postictal period, the relationship between seizure duration and postictal suppression was investigated in three separate groups distinguished by the inter-seizure interval (ISI) following the seizure: ISI > five hours, two hours < ISI < five hours, and ISI< two hours. Correlation coefficients between postictal duration and ISI duration, as well as postictal duration and the following seizure duration, were also calculated.

Results

Seizure duration vs. postictal suppression duration

Figure 1 shows heat maps of the postictal period for all nine patients, ordered by seizure duration. Blue, white, and red represent periods of low, average, and high energy, respectively. Therefore, postictal suppression can be seen as a segment of blue that starts at the start of the postictal period (left) and gradually fades to white. Comparing across patients,

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the heat maps show very different patterns of postictal behavior, highlighting the importance of patient-specific analysis. Based on the heat maps, the patients can be categorized into two broad types: those with consistent postictal behavior, and those with multiple distinguishable postictal behaviors. These changes in postictal behavior align with changes in seizure duration indicating that the populations identified in the heat map may be the same populations identified previously[17]. Within populations defined by seizure length, postictal suppression length is notably consistent. Patients 6, 9, 13, and 15 fall into the first category. The postictal behaviors of patients 1 and 3 are broadly consistent across all seizures, except that the longest seizures have notably different behavior with a longer suppression period. The postictal periods of patients 8, 10, and 11 show clearly different patterns between populations. Short seizures for patients 8 and 10 show no postictal suppression at all while longer seizures show a clear suppression period. The postictal periods of patient 11 show a similar pattern, though involve a small degree of postictal suppression for short seizures. Additionally, it is likely that patient 11 has three post-ictal patterns with the longest seizures showing notably longer post-ictal periods than medium-length seizures. The postictal periods of patient 10 and, to a lesser degree, patient 11 show a period of postictal excitation after the shorter seizures.

Figure 2 compares seizure duration with postictal suppression duration for each patient, with each data point representing a single seizure. Histograms next to the horizontal and vertical axes show the distributions of seizure length and postictal suppression length, respectively. Blue lines show lines of best fit and red lines show the seizure length threshold chosen to split seizures into two populations. Results varied greatly across patients, for instance patient 11 had the highest correlation at 0.76 ($p < 0.001$) while patient 10 showed the lowest significant correlation at 0.20 ($p = 0.03$) and three patients did not show any significant correlation. Across all patients, $r = 0.6294$ ($r^2 = 0.396$, $p < 0.001$) meaning 40% of postictal duration variance is due to seizure duration when ignoring patient specificity. Full results of the statistical analysis are shown in Table 2.

Patients 8, 10, and 11 were chosen for multiple population analysis based on the observation of multiple postictal patterns in the heat maps. Patients 1 and 3 were also considered for this analysis but both had a relatively small number of seizures in one population and so were excluded. The seizure duration thresholds separating short and long seizures in patients 8, 10, and 11 were set at 40, 35, and 20 seconds, respectively. Both populations for patients 8 and

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10 showed no significant correlation between seizure length and postictal suppression length despite correlation across all seizures for each patient. However, this may be due to a loss in statistical power intrinsic to calculating correlation in a smaller number of seizures. Patient 11 showed significant and reduced correlation for both the short ($r = 0.47$, $p < 0.001$) and long ($r = 0.69$, $p < 0.001$) seizure populations.

K-means clustering with two clusters, across dimensions of seizure duration and postictal suppression duration, was performed on patients 8, 10, and 11 due to the observation of multiple populations in the heat maps. Patient 10 showed no significant correlation in either cluster. Patients 8 and 11 both showed significant and reduced correlation in one cluster, the other cluster showing no significant correlation in each patient. The heat map for Patient 11 also suggested a possible third population and so k-means clustering with three clusters was performed for that patient. No cluster showed significant correlation between seizure length and postictal suppression length.

Notably, when considering all seizures for each patient, only patients 8 and 11 showed correlation coefficients greater than 0.5 meaning that, for all other patients, seizure duration accounts for less than 25% of the variance of postictal suppression duration (i.e. $r^2<0.25$). When considering two populations of seizures within patient 8, all correlation coefficients fall below 0.5, and when seizures are separated by seizure length no significant correlation is found at all. In contrast, patient 11 shows one population that has a correlation coefficient above 0.5 for both methods for defining populations. However, if three populations are considered, there are no longer any clusters with significant correlation. Patient 10 shows no significant correlation when using either method of defining populations. Therefore, assuming that patients 8 and 10 have two populations and that patient 11 has three populations, as supported by the heat maps, we find that within all seizure populations seizure duration accounts for less than 25% of the variance of postictal suppression duration.

Postictal duration in seizure bursts

To investigate postictal behavior during bursts of seizures, events were grouped according to the duration of the following inter-seizure interval (ISI). Patient 6 shows the highest correlation between postictal suppression length and inter-seizure interval ($r = 0.31$, $p = 0.03$). A few other patients show lower and significant correlations while the majority show

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no significant correlation. Figure 3 shows the relationship between seizure duration and postictal suppression duration with seizures labeled according to ISI length. No patient showed significant correlation between postictal suppression length and duration of the following seizure.

Discussion

We have shown that populations of seizures have distinct postictal activity within individual patients. For most if not all populations of seizures, less than 25% of postictal suppression variance is attributable to variance in seizure duration. However, the relationship is stronger when all populations within a patient are combined. The populations themselves are distinguished by seizure length, and so we propose that the increase in postictal suppression duration variance accounted for by seizure duration is attributable to population membership. Therefore, postictal suppression duration is a consequence of the population the seizure belonged to, in addition to the differences in seizure duration that the populations represent. The consistent duration of the postictal suppression within each population also highlights the deterministic nature of the seizure process.

When combining all seizures across all patients, 40% of the variance of postictal suppression is accounted for by seizure duration variance. However when accounting for different populations within patients this value is below 25%. As when considering a similar discrepancy within individual patients, we speculate that membership in a population influences postictal suppression length in addition to the effects of seizure length. This discrepancy also highlights the importance of performing patient specific analysis or even population specific analysis, where possible.

The detection of multiple populations of seizures has significant implications for the prediction, detection, and management of seizures. This work shows that populations of seizures can have very different postictal patterns. It follows that these populations are likely to also have differing ictal patterns. If the ictal patterns differ, the seizure class within a detector would necessarily be defined broadly and therefore the seizure detector would likely suffer from poor performance. To counter this, each population could be classified separately. So, instead of distinguishing seizure and non-seizure states, the detector would distinguish non-seizure, short-seizure and long-seizure. In addition to improving seizure detection

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performance, a detector that is population specific would also enable population specific diagnosis and management. For example, triggers may be identified that are specific to a population, or a prescribed antiepileptic drug may be found to only suppress one population of seizures.

While still contentious, there is evidence that postictal generalized suppression (PGES) is associated with SUDEP in patients with generalized tonic-clonic seizures[8,9,13–15]. Postictal suppression, as defined in this paper, differs from PGES and so findings from studies on PGES cannot be directly related to this study. However, postictal suppression and PGES show some similarities, so findings relating to PGES may also hold true for postictal suppression, though this remains to be proven. If an association between postictal suppression and SUDEP could be established, our results suggest that long-seizure populations may represent high-risk populations for SUDEP, which may inform preventative strategies. This contrasts with findings that suggest seizure length does not correlate with PGES length[13]. The identification of seizures that may lead to a longer suppression period could enable clinicians to more aggressively manage the high-risk seizures while more conservatively managing low-risk seizures. This targeting of high-risk seizures may also apply to long seizures in patients that do not have defined seizure sub-populations, although such seizures may be harder to identify and target.

An extension of detecting high-risk seizures would be to predict or forecast them. If high-risk seizures can be identified during the preictal period, they may be entirely preventable. A therapeutic system would ideally prevent all seizures, though there is always a balance between false positives and false negatives in any real-world predictive system. For those seizures that are perceived to pose a higher health risk, the system could be altered in favor of fewer false negatives, whilst keeping the false positives low for lower risk seizures. These results also assist seizure prediction as a refinement of the problem. Analogous to seizure detection, most seizure prediction algorithms treat all seizures (or their preictal periods) as one class distinguished only against interictal periods. The results presented in this work suggest that for some patients, seizures should be split into two or even three different classes, making seizure prediction a two-, three-, or four-class classification problem, depending on the individual patient.

All patients in the study have focal seizures, limiting conclusions to this seizure type. iEEG

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recordings are not accompanied by clinical reporting for every seizure, which restricts clinical interpretation of the findings. This limitation means seizure length and postictal length cannot be confirmed by clinical manifestations. However, the long term nature provides the best clues for the characterization of postictal suppression on a patient specific basis.

The consistency of postictal suppression duration within seizure populations supports the hypothesis that seizures occur due to a deterministic process, with stochasticity within each population around population means. Previous work has shown similarly consistent patterns during the ictal period, suggesting that this behavior is maintained from seizure onset through to the return to normal interictal state. This may even extend to the pre-ictal period allowing algorithms to predict or forecast not just when a seizure occurs, but its duration, the duration of the postictal suppression and possibly even likelihood of SUDEP.

Figure Legends

Figure 1

Energy heat maps of all seizures, ordered by seizure duration. Each row represents an individual postictal period, starting at the endpoint of the seizure and finishing at the postictal upper limit. The colour of each pixel represents total energy standardised to each seizure's threshold. Seizures are ordered by duration with the shortest at the top. The figures on the left show seizure durations, matched to the rows of the heat map.

Figure 2

Seizure duration vs postictal suppression duration. Type one and two seizures with an interseizure interval greater than five hours. Each data point represents a single seizure. Histograms on the horizontal and vertical axes show the individual distributions of seizure duration and postictal suppression duration respectively. Blue lines represent lines of best fit. Sold red lines show seizure length threshold used to split seizures into two populations for patients 8, 10 and 11. Dashed red lines show lines of best fit within each population for patients 8, 10 and 11.

Figure 3

Postictal suppression duration vs seizure duration in seizures of varied ISI. Blue circles

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indicate seizures with at least five hours until the next seizure, orange indicate between two and five hours and red indicate less than two hours until the next seizure. Histograms on the horizontal and vertical axes show the individual distributions of seizure duration and postictal suppression duration respectively.

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Acknowledgements

The authors acknowledge the support of the National Health and Medical Research Council, Project Grant ID No: 1065638, and the support of the University of Melbourne, Melbourne Research Scholarship.

Disclosure of Conflicts of Interest

No conflicts of interest to disclose.

Ethical Statement

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

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Table 1: Patient information

	Age (years)	Gender	Epileptogenic Zone	Recording Time (years)	Seizures	Seizures, ISI > five hrs
Patient 1	26	Male	Parietal-temporal	2.1	120	74
Patient 3	22	Female	Parietal-temporal	1.5	325	163
Patient 6	62	Male	Temporal	1.2	52	38
Patient 8	48	Male	Frontotemporal	1.5	309	222
Patient 9	51	Female	Occipitoparietal	1.1	161	142
Patient 10	50	Female	Frontotemporal	1.0	475	165
Patient 11	53	Female	Frontotemporal	2.0	343	212
Patient 13	50	Male	Temporal	2.0	465	300
Patient 15	36	Male	Temporal	1.3	60	57

	Average seizure duration (seconds)	Average postictal suppression duration (seconds)	Postictal upper limit (minutes)	Bimodal	Multiple subpopulations investigated
Patient 1	26	54	30	-	-
Patient 3	18	17	10	Yes	-
Patient 6	110	1269	60	-	-
Patient 8	37	56	10	Yes	Yes
Patient 9	58	22	10	Yes	-
Patient 10	37	34	10	-	Yes
Patient 11	32	137	20	Yes	Yes
Patient 13	25	42	10	-	-
Patient 15	55	171	40	-	-

ISI: Inter-seizure interval. Age shown is age at the start of the study. Seizure number represents the number of type one and type two seizures after the initial 15 weeks of recording. Bimodal refers to findings from Cook et al. (2016)[17] where some patients were found to have a bimodal distribution of seizure durations when considering all three seizure types. Patients were selected for multiple subpopulation analysis based on Figures 1 and 2.

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Table 2: Correlation statistics for selected patients across A: all seizures B: two subpopulations, defined by seizure length thresholds C: two subpopulations, defined by k-means clustering D: three subpopulations, defined by k-means clustering

A

	r	p	Slope
Patient 1	0.358	*0.03*	2.25
Patient 3	0.256	*0.005*	0.486
Patient 6	0.131	0.43	2.89
Patient 8	0.528	*<0.001*	1.66
Patient 9	0.319	*0.004*	0.377
Patient 10	0.200	*0.03*	0.683
Patient 11	0.764	*<0.001*	5.61
Patient 13	0.110	0.09	0.650
Patient 15	0.150	0.30	6.66
All Patients	0.6286	*<0.001*	8.995

B

		Short Seizures			Long Seizures		
	Threshold (s)	r	p	Slope	r	p	Slope
Patient 8	40	0.09427	0.25	-1.732	0.1729	0.24	-1.047
Patient 10	20	0.01979	0.87	0.2249	0.003387	0.98	-0.01689
Patient 11	35	0.4737	*<0.001*	3.694	0.6909	*<0.001*	8.264

C

	Cluster 1			Cluster 2		
	r	p	Slope	r	P	Slope
Patient 8	-0.02566	0.76	-0.06304	0.4805	*<0.001*	-0.8176
Patient 10	0.17482	0.22	-0.2522	0.08791	0.46	0.08403
Patient 11	0.5767	*<0.001*	0.2533	0.2014	0.22	0.4205

D

	Cluster 1			Cluster 2			Cluster 3		
	r	p	Slope	r	p	Slope	r	p	Slope
Patient 11	0.1335	0.40	0.09042	0.0872	0.51	-0.05143	0.2754	0.16	0.4696

r, correlation coefficient. p, p-value. Slope (s/s), gradient of linear best fit.

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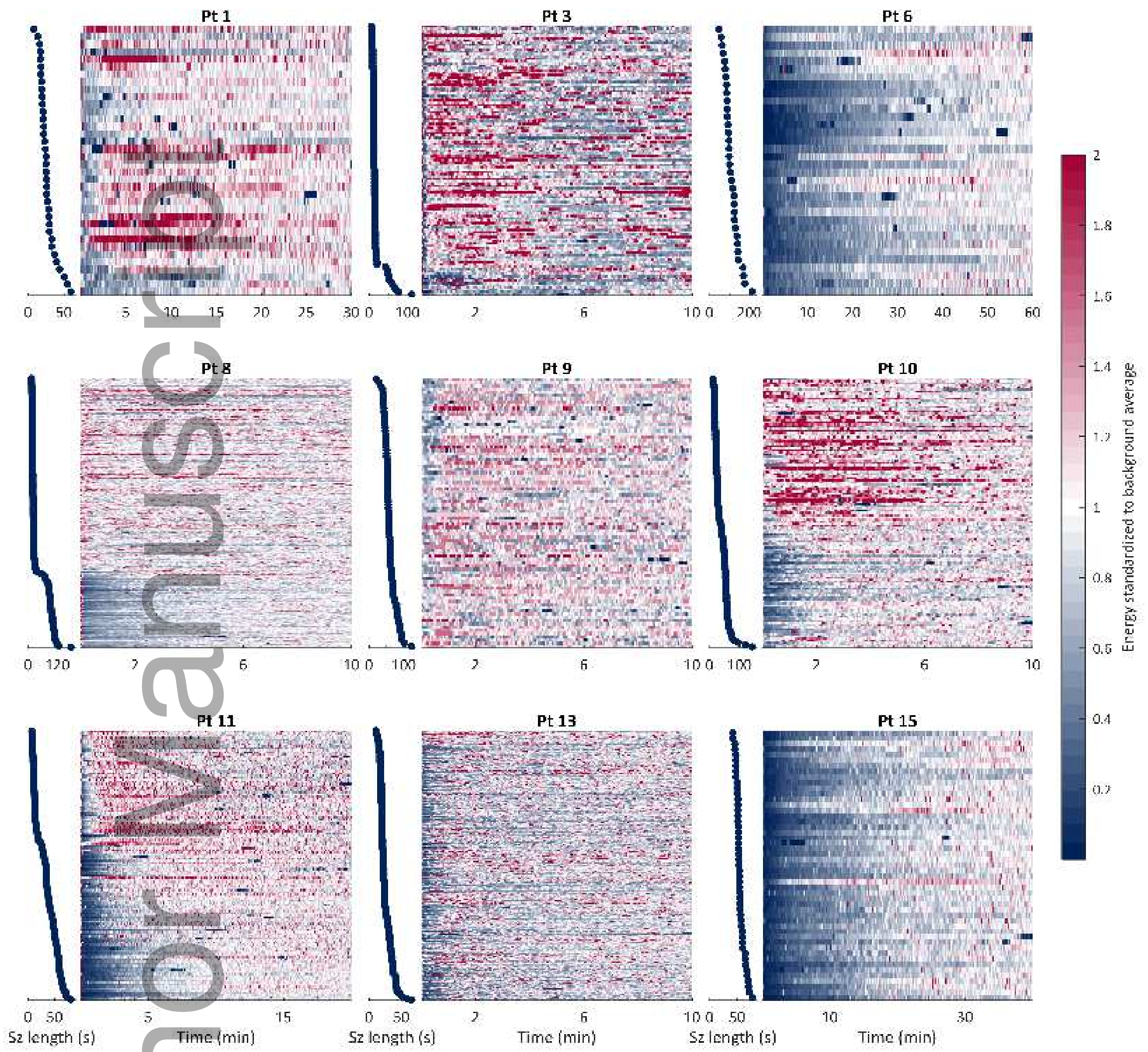

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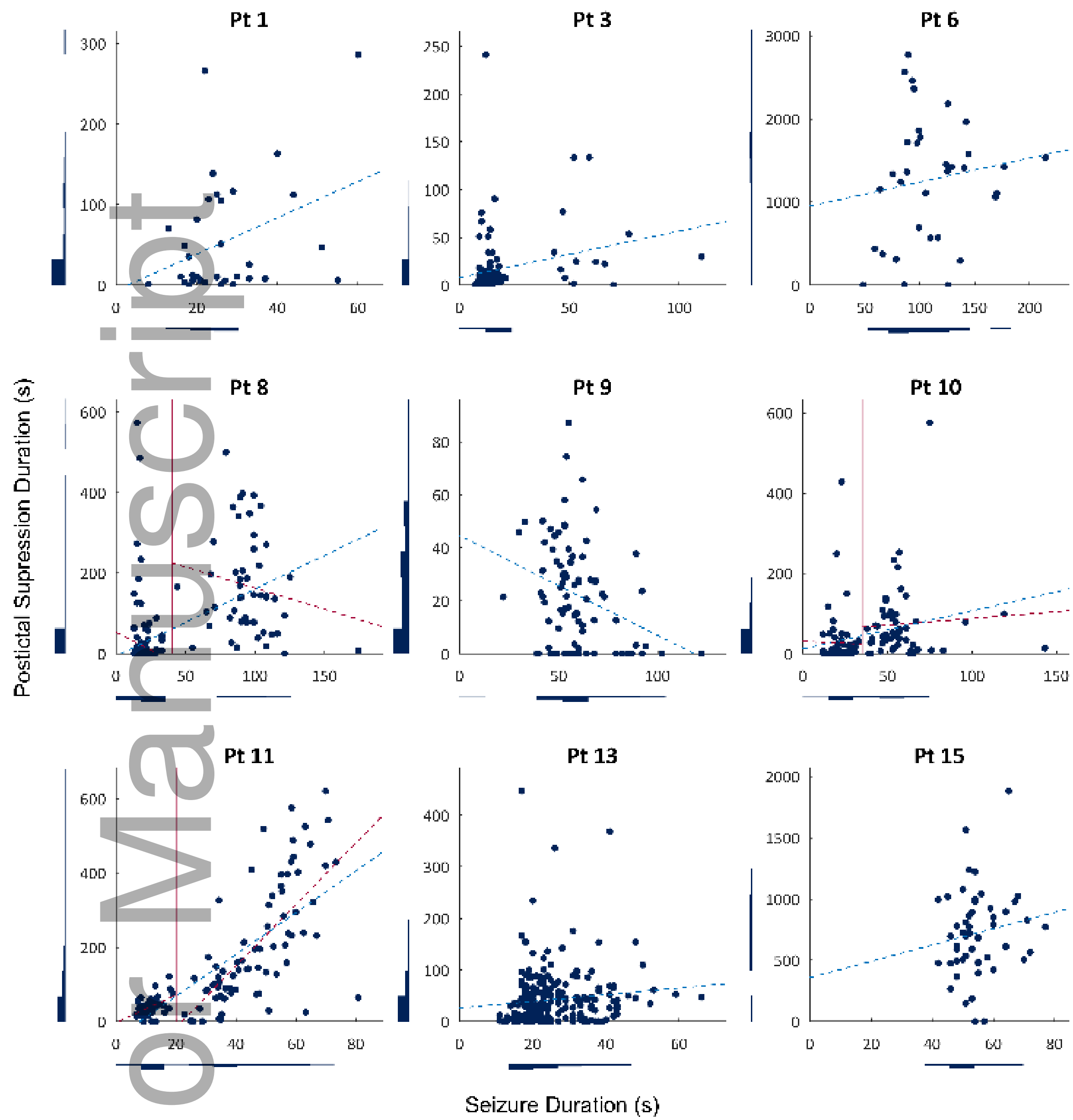

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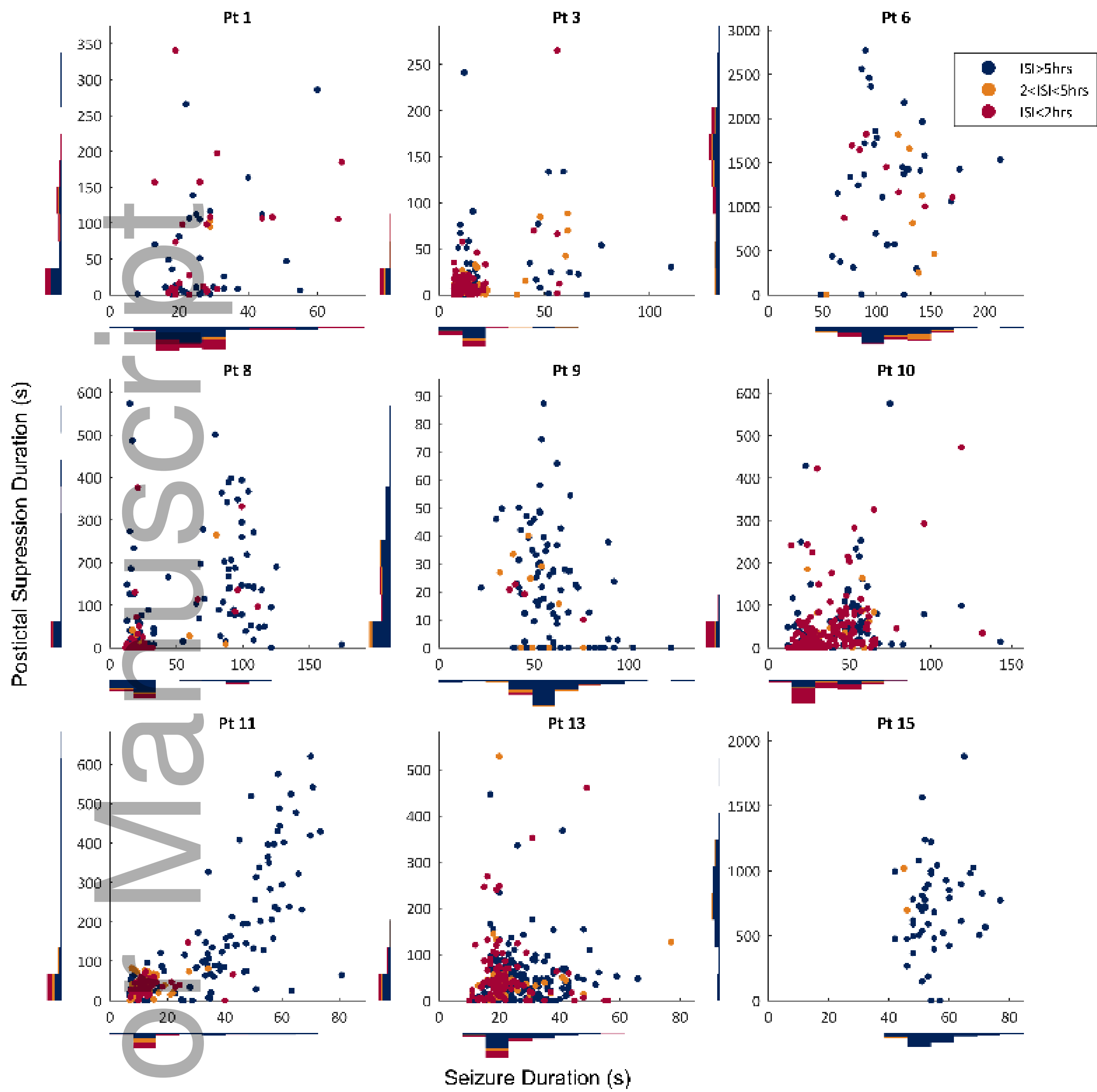

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