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Title: Seizure evolution can be characterized as path through synaptic gain space of a neural mass model

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Abstract

Physiologically based models could facilitate better understanding of mechanisms underlying epileptic seizures. In this paper, we attempt to reveal the dynamic evolution of intracranial EEG activity during epileptic seizures based on synaptic gain identification procedure of a neural mass model. The distribution of average excitatory, slow and fast inhibitory synaptic gain in the parameter space and their temporal evolution, i.e. the path through the model parameter space, were analyzed in thirty seizures from ten temporal lobe epileptic patients. Results showed that the synaptic gain values located roughly on a plane before seizure onset, dispersed during seizure and returned to the plane when seizure terminated. Cluster analysis was performed on seizure paths and demonstrated consistency in synaptic gain evolution across different seizures from the individual patient. Furthermore, two patient groups were identified, each one corresponding to a specific synaptic gain evolution in the parameter

space during a seizure. Results were validated by a bootstrapping approach based on comparison with random paths. The differences in the path revealed variations in EEG dynamics for patients despite showing identical seizure onset pattern. Our approach may have the potential to classify the epileptic patients into subgroups based on different mechanisms revealed by subtle changes in synaptic gains and further enable more robust decisions regarding treatment strategy.

Introduction

Epilepsy is the third neurological disorder in the world population and affects approximately 50 million people worldwide (Megiddo, 2016). It is defined as "a disorder of the brain characterized by an enduring predisposition to generate epileptic seizure and by the neurobiologic, cognitive, psychological, and social consequences of this condition" (Fisher *et al.*, 2005). The concept of considering epilepsy as a dynamical disease of brain systems has been established (Lopes da Silva *et al.*, 2003a; Lopes da Silva *et al.*, 2003b; Richardson, 2012) based on the fact that seizures occur in a paroxysmal way and an epileptic brain can function normally between seizures (Fisher *et al.*, 2005), i.e. during the interictal state. Therefore, epileptic disorders are now considered as a dynamical disease, characterized by the occurrence of abnormal dynamics. The understanding of dynamical evolution underlying epileptic seizures is of significant importance for the development of effective treatments.

The electroencephalogram (EEG) has become a commonly used technique for capturing macroscopic brain dynamics. The EEG features show a dynamic evolution during interictal to ictal transition (Blenkinsop *et al.*, 2012; Nevado-Holgado *et al.*, 2012). Computational models are efficient tools for studying this evolution, as it can relate EEG activities recorded during seizure to the pathways and mechanisms of seizure evolution (Richardson, 2012; Kuhlmann *et al.*, 2015; Breakspear, 2017) through physiological relevance of the model parameters. In particular, neural mass models (NMMs) have been increasingly popular in the

field of epilepsy due to their capacity to reproduce accurately epileptiform EEG signals (Kameneva, 2017). They emphasize the dynamics of a population of neurons and the interactions among different populations, rather than explicitly describing the behavior of individual neurons, which dramatically reduce the dimensionalities of both parameters and variables (Wendling *et al.*, 2016; Breakspear, 2017). The NMM proposed by Wending et al. (Wendling *et al.*, 2002), based on the work of Jansen and Rit (Jansen & Rit, 1995), has gained increasing attention and become popular in the research community (Suffczynski *et al.*, 2004; Lytton, 2008; Molaee-Ardekani, 2010; Kameneva, 2017), as it was validated to reproduce iEEGs recorded in patients with temporal lobe epilepsy (TLE) during the transition to seizure (Wendling *et al.*, 2002; Wendling *et al.*, 2005).

The study of dynamics underlying epilepsy can be achieved in a purely theoretical way using bifurcation theory, which is a powerful tool for systematically studying the relationship between the output of the model and physiological based parameters (Breakspear *et al.*, 2006; Marten *et al.*, 2009a; Spiegler *et al.*, 2010; Geng, 2014; Sohanian-Haghighi & Markazi, 2017). It can also be achieved by fitting the model with recorded data (Wendling *et al.*, 2005; Havlicek *et al.*, 2011; Freestone *et al.*, 2014; Lopez-Cuevas, 2015), exploring this way the path through parameter space (Nevado-Holgado *et al.*, 2012). Both approaches have the potential to gain a better understanding of the physiology occurring in conjunction with seizure onset and evolution. For instance, Kramer et al. explored the pathways to seizure regions identified with bifurcation analysis on a mesoscale model to reveal potential mechanisms in the causation of seizures (Kramer *et al.*, 2005; Kramer *et al.*, 2007). Alternatively, Dadok et al. proposed a Bayesian framework to produce a probabilistic pathway of the temporal evolution of physiological state in the cortex over the course of individual seizures and allow the comparison among different hypotheses (Dadok *et al.*, 2015). The advantage of combining clinical data with physiological based model is that it

may provide an opportunity of revealing patient-specific mechanisms. This is of significant importance because patients with epilepsies which seem identical might have different underlying dynamic mechanisms (Marten *et al.*, 2009b) and may require different treatment. Nevado-Holgado et al. proposed an approach to fit the model to clinical EEG data and characterized the dynamics of EEG waveforms in idiopathic generalized epilepsies as the path through parameter space of a NMM, which provides an opportunity to understand how system parameters change before, during and at the termination of a real seizure in a person with epilepsy (Nevado-Holgado *et al.*, 2012). Focusing on TLE, Blenkinsop et al. mapped out a path by matching temporal features of each identified epoch to regions of parameter space identified from numerical continuation (Blenkinsop *et al.*, 2012). Both studies compared the paths through parameter space against randomly generated paths and discovered consistency in parameter evolution across different seizures from a given patient (Blenkinsop *et al.*, 2012; Nevado-Holgado *et al.*, 2012). However, these comparisons were performed on seizure pairs within individual patients and no analysis was reported across different patients.

In this paper, a NMM (Wendling *et al.*, 2002) was implemented and automatically fitted to 30 SEEG signals recorded from 10 TLE patients during interictal to ictal transition. To achieve a fine temporal resolution, the recordings were processed within a sliding window and three physiologically meaningful parameters, i.e. the average excitatory (A), as well as the slow and fast inhibitory synaptic gains (B and G), were identified within each window to reproduce those recordings. We have shown previously the global trend of temporal evolution of excitation/inhibition synaptic gain ratios during interictal to ictal transition (Fan *et al.*, 2018). In this paper, we analyzed the distribution of synaptic gains in the parameter space and their temporal evolution. Paths through synaptic gain parameter space during seizures were analyzed to characterize seizure evolution. Applying cluster analysis on those paths with a larger cohort, we were able to evaluate not only the consistency across seizures

within individual patients, but also the diversity across patients. Our results were validated statistically by a bootstrapping test based on comparing the seizure path pairs with random path pairs.

Materials and Methods

Clinical data

The same database was used as in our previous study (Fan *et al.*, 2018), which includes thirty depth-EEG recordings recorded from ten patients diagnosed with TLE (Table 1). The seizure onset, offset and seizure onset patterns (SOP) were determined by an expert epileptologist. The seizure onset was defined as the first unequivocal iEEG change visually distinguishable from background activity that followed by clear seizure discharges (Spanedda *et al.*, 1997; Perucca *et al.*, 2014). All seizure onset patterns were classified as low-voltage fast activity (LVFA), which is not surprising since it is the most frequent pattern in iEEG recorded from drug-resistant patients with focal epilepsy (Perucca *et al.*, 2014; de Curtis & Avoli, 2016). Surgical outcome has been regularly evaluated based on Engel surgical outcome classification (Engel, 1993). The study was approved by the Ethics Committee of Hôpital Erasme.

EEG modeling and parameter identification

The model we use can be described mathematically by 10 first order differential equations, as previously described (Wendling *et al.*, 2002). It macroscopically describes the interactions among four subsets of neurons (see Fig. 1A). The main population is composed of the principal cells (i.e. pyramidal cells in the hippocampus or neocortex), the summated postsynaptic potential of which is considered the main contributor of EEG activities. It projects to and receives feedback from other populations of local interneurons, either excitatory or inhibitory. Previous studies have demonstrated the existence of two types of $GABA_A$ synaptic responses in CA1 pyramidal neurons of the hippocampus: a slow one

targeting dendrites and a fast one targeting the soma (Miles *et al.*, 1996). They correspond to two groups of inhibitory interneurons (Banks *et al.*, 2000). The two subsets of inhibitory interneurons are included in the model and interact with the pyramidal neurons through slow synaptic kinetics ($GABA_{A, slow}$) and faster synaptic kinetics ($GABA_{A, fast}$), respectively. Moreover, the $GABA_{A, slow}$ interneurons inhibit $GABA_{A, fast}$ cells (Banks *et al.*, 2000). This is modeled by a connection from dendritic-projecting interneurons to somatic-projecting ones. The influence from neighboring or more distant populations was modeled by an excitatory input $p(t)$, which was assumed to be Gaussian white noise. The model output corresponds to the average post-synaptic activity of the pyramidal cells, which was considered to be the synthesized iEEG signals.

The detailed schematic representation of the neural mass model is shown in Fig. 1B. Each population is modeled by two blocks: 1) a sigmoid function $Sigm(v) = \frac{2e_0}{1+ e^{r(v_0-v)}}$ that converts the average postsynaptic membrane potential *v* into average pulse density of potentials fired by the population and 2) a transfer function that converts the average pulse density of afferent action potential into an average excitatory or slow/fast inhibitory postsynaptic membrane potential (with respective impulse response $h_e(t) = Aate^{-at}$, $h_b(t) = Bbte^{-bt}$ or $h_g(t) = Ggte^{-gt}$ (t $\geq$ 0)).

All the parameters in the model have physiological meanings. Their standard values were previously established (Jansen & Rit, 1995; Wendling *et al.*, 2002; Kerem & Geva, 2005). Their interpretation and standard values are listed in Table 2. All parameters were set to these standard values except the average synaptic gains (i.e. the average excitatory synaptic gain of the main population A, as well as the average inhibitory gains of the slow and fast inhibitory interneuron populations, respectively B and G) that can vary, as previously proposed (Wendling *et al.*, 2005; Lopez-Cuevas, 2015; Kameneva, 2017).

The average synaptic gains therefore need to be identified. We employed a window-by-window approach to search the parameter space exhaustively, as illustrated in Fig. 2. The pre-processing process includes two filtering approach. The clinical data were first filtered below 0.16 Hz and above 65 Hz to remove slow baseline drift and electronic noise. Second, power line noise was removed using a 50 Hz notch filter. After pre-processing, the clinical data was segmented using a 2 s sliding window with a step of 0.1s. For each window, the key parameters were identified by minimizing an error function, which was established as the Euclidean distance between the feature vectors estimated from the synthesized and recorded signal, respectively, i.e. $\widehat{F_s}(A, B, G)$ and $\widehat{F_r}$ in Fig. 2. The feature vector was constructed based on both spectral and morphographic properties of the signal. It contains seven temporal features and seven spectral features. For temporal features, the absolute signal amplitude was obtained first and the range was divided into seven equally sized bins. The ratios of sample numbers in each bin to the total sample number were retained as temporal features. The relative power within seven specific frequency bands (i.e. 0.5 - 1.5 Hz, 1.5 - 2.5 Hz, 2.5 - 4.5 Hz, 4.5 - 8.5 Hz, 8.5 - 16.5 Hz, 16.5 - 32.5 Hz and 32.5 - 65 Hz) were computed as spectral features. See (Fan *et al.*, 2018) for more details about the parameter identification procedure.

The distribution of key parameters in the parameter space and their temporal evolution were therefore obtained and the path through synaptic gain space could be analyzed. We made the proposed methodology available in a toolbox [1] integrated in the Statistical Parametric Mapping (SPM) software package[2], which is widely used in the neuroscience community for the analysis of brain imaging data sequences, such as EEG/MEG, fMRI and PET etc. (Friston *et al.*, 2003; Henson *et al.*, 2011; Ashburner, 2012).

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[1] http://beams.ulb.ac.be/research-projects/synaptic-gains-tracking-toolbox
[2] http://www.fil.ion.ucl.ac.uk/spm/

Distribution of identified parameters in the parameter space

To better understand the synaptic gain evolution before, during and after a seizure, we focused on the EEG epoch from four minutes before seizure onset to four minutes after seizure offset. Three recordings (#6, 10 and 13) were therefore excluded because of signal length shortage, resulting in 27 seizures for this analysis. Four periods of interest were defined, as illustrated in Fig. 3:

-- *IntIctal*, from 4 minutes before the onset to 2 minutes before onset,

-- *PreOnset*, from 2 minutes before the onset to the onset,

-- *Sz*, from marked onset to offset, and

-- *PostIctal*, from marked offset to 4 minutes after.

For each recording, principal component analysis (PCA) was conducted separately on identified synaptic gains during different periods of interest and the contribution ratio of the first two principal components was obtained. Kruskal-Wallis test followed by pairwise multiple comparison tests were performed for determining whether the contribution ratio has equal means for different periods of interest. The significance level was set to 0.05.

Path through synaptic gain parameter space and clustering

Clustering approach

To obtain the path through synaptic gain parameter space and analyze the global trends of synaptic gains during interictal to ictal transition, a 10 s moving average window was first applied to the identified synaptic gains. Clustering analysis was performed on paths from seizure onset to offset to evaluate the consistency of paths across seizures. Clustering is a technique for data mining. It is a useful approach for exploratory data analysis as it finds structures in an unlabeled dataset by organizing data into similar groups (clusters) based on similarity. The objective here is to discover the patterns in paths through synaptic gain parameter space during seizures. More specifically, it will be used to know if paths through

synaptic gain parameter space show consistent trends within individual patients and distinct trends across different patients.

Spectral clustering (Luxburg, 2007; Tucci & Raugi, 2011) was chosen for clustering the paths through synaptic gain parameter space (excitatory, slow and fast inhibitory), since it is best suited for multivariate time series. One major advantage is that it only requires the pairwise similarities of the seizure paths. Centroids of clusters, which are difficult to define for time series, are not required.

Dynamic time warping (DTW) based distance was chosen as the similarity measure, as it is commonly the case in time series clustering (Aghabozorgi *et al.*, 2015). The analysis was performed on epochs ranging from seizure onset to offset that were normalized to have the same length, as in (Blenkinsop *et al.*, 2012). Amplitude normalization (unity-based normalization) was also performed.

Determining the number of clusters and cluster initiation

To determine the most appropriate cluster number, the silhouette coefficient (Rousseeuw, 1987) was used to evaluate the resulting cluster structure. The silhouette coefficient is a commonly used metric to evaluate the clustering structure when the ground truth is unknown. It examines how well the clusters are separated and how compact the clusters are (Han *et al.*, 2012).

For a data set D of n objects, suppose D is partitioned into k clusters, $C_1, \dots C_k$. For each object o $\in$ D, the silhouette coefficient $s(o)$ varies between -1 and 1. When $s(o)$ approaches 1, the cluster containing o is compact, and o is far away from other clusters, which is the preferable case. The average silhouette coefficient value of all objects in the data set gives a good indication of clustering appropriateness, i.e. large values of average silhouette indicates high evidence of cluster structure (Rousseeuw, 1987).

We set the number of clusters to 2, 3, 4 and 5, successively. Since the clustering structure depends to some extent on the initiation that is chosen randomly, the clustering approach was repeated 100 times for each condition. Therefore, 400 times of clustering were performed. The cluster structure with the highest average silhouette coefficient was determined as the most plausible.

Evaluating clustering results by comparing seizure path pairs against random path pairs

To further address the statistical significance of the similarity between path pairs from an individual patient and evaluate the difference between path pairs from two different patients, a bootstrapping test was performed. This was achieved by comparing the DTW distance of seizure path pairs with those of randomly generated paths, as proposed previously (Blenkinsop *et al.*, 2012; Nevado-Holgado *et al.*, 2012). Since the paths are multivariate (i.e. constituted of the three variables A, B and G), three vectors were generated randomly with uniform probability within the specific ranges defined for the real seizure paths. Subsequently, they were treated as if they were real seizure paths inferred from clinical data. We computed the DTW between two random paths (dtw_r) and repeated these calculations 500,000 times.

Both real seizure paths and randomly generated paths were normalized to have the same length, arbitrarily chosen of 1000 samples (Blenkinsop *et al.*, 2012). For each seizure path pair o_i and o_j, the bootstrap value was calculated as the percentage of random path pairs that are equally close or closer than the real seizure path pairs (Nevado-Holgado *et al.*, 2012). A small bootstrap value indicates high consistency between two paths o_i and o_j. If the bootstrap value is smaller than 0.05, i.e. less than 5% of random path pairs show a DTW smaller than the one of the seizure path pair o_i and o_j, the consistency between o_i and o_j was considered significant.

Results

Distribution of identified synaptic gains in the parameter space

The distribution of synaptic gains in the parameter space is demonstrated in Fig. 4. It shows the synaptic gains collected from the recordings of all patients. Each subfigure corresponds to one period of interest. Visual inspection showed that the synaptic gains locate roughly on one plane during *IntIctal*, *PreOnset* and *PostIctal* (see the planes in Fig. 4A, B and D). During *Sz* however, they diffuse mostly to regions in the synaptic gain parameter space where the excitatory/inhibitory synaptic gain ratios increase (see the arrows in Fig. 4C). It is consistent with previous work from our group (Hocepied *et al.*, 2013; Fan *et al.*, 2018), showing that the excitation/inhibition ratios increase around seizure onset and decrease before/around seizure offset.

Principal component analysis was used to confirm this visual impression. Figure 5 shows that the synaptic gains identified during *IntIctal*, *PreOnset* and *PostIctal* can be better explained by the first two principal components (contribution ratios are 0.979 ± 0.022, 0.975 ± 0.031, and 0.992 ± 0.009, respectively), compared to those identified during *Sz* (contribution ratio is 0.791 ± 0.045) (pairwise multiple comparison after Kruskal-Wallis test: $p < 0.001$).

Consistency of paths through synaptic gain parameter space during seizure evolution

The highest average silhouette coefficient was 0.93, 0.88, 0.72, 0.73, when the cluster number was set to 2, 3, 4 and 5, respectively. The cluster results and corresponding silhouette coefficients are illustrated in Fig. 6. It can be seen that, for all cases, four seizures (seizure # 6 from patient B, seizure # 18 from patient E and seizures #29&30 from patient J), were isolated from the others. These seizures were of short duration (less than 30s) compared to the others (130s on average). These two reasons motivated us to consider them as outliers and re-performed the cluster analysis on the remaining 26 seizures.

When the four outliers were ruled out, the highest average silhouette coefficient was 0.80, 0.63, 0.57 and 0.53, when the number of clusters was 2, 3, 4, and 5, respectively, suggesting strong evidence of 2 clusters (Rousseeuw, 1987). The resulting cluster structure is shown in Fig. 7. We show the results with the original seizure numbering from Table 1 for clarity. The seizures from individual patients were grouped together except seizure 27 from patient I, indicating a consistent seizure evolution for individual patients for all patients but one. Of note, this clustering result (two clusters, shown in Fig. 7) is strikingly consistent with the one with four clusters (in Fig. 6D), except that the four outliers were ruled out, suggesting the robustness of this result.

Figure 8 gives an example of paths through synaptic gain parameter space, of two seizures from a given patient, grouped in cluster 1 (seizures # 4 and 5 from patient B). Visually inspection revealed a counterclockwise pattern in the B-G plane (B and G are average slow and fast inhibitory gain, respectively) for seizures in cluster 1 (see the last column in Fig. 8). This reflects the interaction between slow and fast inhibitory interneuron population. For instance, in Fig. 8C and F, at the beginning of the seizures (in red), a decrease in B (average slow inhibitory synaptic gain) can be first observed while G (average fast inhibitory synaptic gain) increases or stays constant. Then a period where B increases and G decreases (either together e.g. in Fig. 8F or one after the other, e.g. in Fig. 8C) is seen. Finally, G increases again and the seizure stops.

Seizures in cluster 2 demonstrated a distinct path through synaptic gain parameter space. Figure 9 gives an example for three seizures from a given patient grouped in cluster 2 (seizures # 21-23 from patient G). A regular pattern in the A-B plane (A and B are average excitatory and slow inhibitory synaptic gain respectively) was observed, with an increase in A while B decreases or stays constant (see first column in Fig. 9). Then A decreases while B increases or stays constant. For some patients of cluster 2, as it is the case for the seizures

illustrated in Fig. 9, a pattern was also observed in the A-G plane (see middle column in Fig. 9). At the start of these seizures (in red), A increases and G stays constant. Then A decreases and G first decreases and then increases. It seems that, for this particular patient, the first two columns, i.e. paths in A-B and A-G plane, show consistency whereas the last column, i.e. paths in B-G plane, are less consistent. However, if we look into the last column in Fig. 9 closely, we can see some consistency among them. All seizures involved decreased B and constant G at the beginning of the seizure (red arrow). Afterwards B started to increase while G decreased (black arrow), followed by co-increase (yellow arrow) and then co-decrease (blue arrow). Finally, both B and G increased (gray arrow) at the end of the seizure. Therefore, these seizures share global trend, despite transient fluctuations.

We further applied a bootstrapping test to validate the clustering results. This was achieved by comparing the DTW distance between intra-patient/inter-patient/intra-cluster/inter-cluster seizure path pairs and random path pairs (see Methods).

We computed the bootstrap value for seizure path pairs o_i and o_j from five groups:

- *Intra-patient path pairs:* All possible pairs of seizure paths from individual patients, i.e. o_i and o_j are from an individual patient (33 pairs in total);

- *Inter-patient path pairs:* All possible pairs of seizure paths from different patients, i.e. o_i and o_j are from two different patients (402 pairs in total);

- *Cluster 1 path pairs:* All possible pairs of seizure paths from patients in cluster 1, i.e. o_i and o_j are from seizures in cluster 1 (36 pairs in total);

- *Cluster 2 path pairs:* All possible pairs of seizure paths from patients in cluster 2, i.e. o_i and o_j are from seizures in cluster 2 (136 pairs in total);

- *Inter-cluster path pairs:* All possible pairs of seizure paths from different clusters, i.e. o_i is a seizure in cluster 1 and o_j is a seizure in cluster 2 or vice versa (153 pairs in total).

Figure 10 illustrates the boxplots of bootstrap values (%) for seizure path pairs from the five groups. The percentage of consistent seizure path pairs for each group is shown in Table 3 (the bootstrap value < 5% is considered significantly consistent). The median of bootstrap value for each group is also provided. As a supplement, Wilcoxon rank sum tests were performed between any two groups, offering a statistical comparison of bootstrap value between groups. The significance level was set to 0.05 and indicated by * in Table 3.

In total, 66.7% intra-patient path pairs showed significant consistency, indicating similar seizure evolution across seizures from individual patients. Path pairs involving the four outliers identified by cluster analysis (seizures #6, 18, 29 and 30), showed extremely large bootstrap values (i.e. they were significantly different from other seizures from the same patient). These seizures were therefore again excluded from the analysis.

After ruling out these outliers, 78.6% intra-patient path pairs were consistent, compared to only 34.3% for path pairs in inter-patient group. If we further elevate the significance level to 0.1, this percentage for intra-patient path pairs elevated to 89.3%. These results suggest consistency in seizure evolution within individual patients. Intra-patient path pairs demonstrate a significant lower bootstrap value, compared to inter-patient ones (Wilcoxon rank sum test: p < 0.001). This confirms the consistency across seizures within individual patients and also suggests diversity across seizures from different patients.

Cluster 1 showed intra-cluster path pair consistency (77.8%) comparable to the one of intra-patient (78.6%). Consistency across seizures in cluster 1 was validated (Wilcoxon rank sum test: p > 0.05). Cluster 2 showed a path pair consistency (39.7%) lower than the one of intra-patient (78.6%), yet just above the one of inter-patient (34.3%). Statistically, the bootstrap value for cluster 2 path pairs was significantly larger than the one of intra-patient path pairs and of cluster 1 path pairs (Wilcoxon rank sum test: p < 0.001), but significantly smaller than the one of inter-patient path pairs (Wilcoxon rank sum test: p = 0.0012). This

suggests that cluster 2 path pairs were less consistent than intra-patient ones, yet more consistent than inter-patient ones. Therefore, although the seizures in cluster 2 showed less consistent evolution compared to cluster 1, it is still meaningful to group seizures of cluster 2 together. This is further reflected by the bootstrap value for inter-cluster path pairs that was significantly larger than for any other category, showing that the path pairs among the two clusters differed the most.

Discussion and conclusion

In this paper, we have explored the potential mechanisms underlying the occurrence of a seizure by analyzing the temporal evolution of synaptic gains using a generative model of intracranial EEG recordings. Synaptic gain values located roughly on a plane before seizure onset, dispersed during seizure and returned to the plane when seizure terminated. Seizure clustering allowed to separate all patients, except one, into two groups, each one corresponding to a specific synaptic gain evolution in the parameter space during a seizure. The existence of the two clusters has been validated by a bootstrapping test based on comparison with random path pairs. Different paths through synaptic gain parameter space have been observed, corresponding to the different clusters, and these paths are highly consistent across different seizures within individual patients.

The low voltage fast activity (LVFA) is recognized as the most common pattern at seizure onset during iEEG recordings (Perucca *et al.*, 2014; Singh, 2015; Lagarde *et al.*, 2016). In this study, low-voltage fast activity has been recognized at the onset for all seizures, yet our approach identified two classes of synaptic gain evolution pattern. Our results suggest that seizures initiate with identical EEG changes do not necessarily progress the same way, possibly driven by distinct subtle physiological changes that are challenging to identify directly from the EEG waveforms. It has to be noted that no hints can be derived, from this study, on whether the differences in the two groups may be related to etiology of epilepsy. To

address this issue, a follow-up study in a large-scale clinical database is needed, where associations between EEG dynamics and pathologies can be investigated. Interpreting EEG in clinical practice can be subjective and the inter-rater agreement is unsatisfactory (Grant *et al.*, 2014). The temporal evolution of synaptic gains revealed by our approach may provide a more objective way for interpreting EEG in clinical practice, and thus may supplement expert interpretation of EEG dynamics. A follow-up study in a large-scale clinical database can also explore this hypothesis, where the relationship between EEG dynamics, pathology, diagnosis, and prognosis can be more systematically investigated.

Patients in cluster 2 have seizure onset at the left side (except that patient D has bilateral hippocampal seizure onset) while patients in cluster 1 mostly have seizure onset at the right side (except patient H who has left hippocampal onset and patient B has bilateral temporal lobe onset) (see Table 1), even though the analysis did not use any a priori regarding the side of the seizure (only one derivation was considered for analysis). This could suggest a link between the synaptic gain path during a seizure and the side of the seizure. The anatomical (Watkins, 2001) and functional (Cohen *et al.*, 1968) asymmetry of the two hemispheres has long been recognized (Hugdahi, 2005). Patients with left MTLE have been reported to perform worse in memory tasks (Zhao *et al.*, 2014; de Campos, 2016) and have distinct structural damage of cerebral gray and white matter than patients with right MTLE (Keller *et al.*, 2002; Besson *et al.*, 2014), suggesting that left and right MTLE could have different pathological mechanisms (Pustina *et al.*, 2015). A study of 16 patients has reported different dynamic network patterns in left and right TLE and suggested an ipsilateral predominance in left TLE but a more bilateral pattern in right TLE (Coito *et al.*, 2015). Interestingly, another study with a larger cohort reached a different conclusion and demonstrated that left MTLE has a more intricate bilateral dysfunction compared to right MTLE (de Campos, 2016).

Different MRI lesions are involved in cluster 2, i.e. mesial temporal sclerosis (patient F) and periventricular nodular heterotopia (patient C and D). This could explain the lower consistency of seizure paths in cluster 2, compared to cluster 1.

Seizure clustering allowed to separate all patients into two groups, corresponding to two specific synaptic gain evolutions in the parameter space during a seizure, except for patient I. The three seizures recorded from patient I were separated among the two clusters. This should not be considered surprising given the complexity of epilepsy (Fisher *et al.*, 2005; Blenkinsop *et al.*, 2012). We note that patient I was diagnosed to have partial and secondary generalized seizures and seizure # 27 was clinically determined to spread quickly to a more generalized area (hippocampal, post-pole, insula and posterior cingulum). This may explain why it was grouped into a different cluster from the other two seizures of the same patient.

The consistency of seizure evolution within patients was previously reported, in focal-onset epilepsies (Blenkinsop *et al.*, 2012) and idiopathic generalized epilepsies (Nevado-Holgado *et al.*, 2012). Blenkinsop et al. subdivided each seizure recording into near-stationary epochs and mapped each epoch into an equivalent region of patameter space where the model output has similar features, resulting a path coded by these regions characterizing temporal seizure evolution. Correlations and Euclidean distances of each pair of seizure paths were compared against those of randomly generated pairs. Although their characterization of seizure evolution is crude, results suggest consistency of underlying mechanisms during seizures within the same individual. Nevado-Holgado et al. used a multi-objective genetic algorithm to fit parameters of a NMM from scalp EEG that was recorded from patients with idiopathic generalized epilepsies to capture changes in underlying parameters (Nevado-Holgado *et al.*, 2012). The absolute difference between the paths through parameter space was compared against random path pairs. Bootstrapping test demonstrated consistent trends in paths within individual patients. In our study, a similar approach based on parameter

identification procedure of a NMM was employed. However, besides the larger cohort and the fine temporal analysis, our approach offers two major benefits compared to these two previous ones. First, we performed cluster analysis, which allowed to explore diverse temporal evolution patterns underlying seizures. Results not only confirmed the significant consistency in synaptic gain evolution for independent seizures within an individual patient, but also identified distinct patterns of synaptic gain evolution across patients. Second, we analyzed all synaptic gains together, i.e. in a multivariate path, instead of analyzing the trend in different parameters independently. It allowed to characterize the seizure evolution in an integrated way by analyzing the interaction among different neuronal populations and better corresponds to a physiological behavior.

Our results also showed that the synaptic gains located roughly on a plane before the occurrence of a seizure, spread out during a seizure and returned to the plane after the seizure. This indicates that the average synaptic gains of excitatory, slow and fast inhibitory are interdependent and the excitation/inhibition balance is required to keep the brain non-ictal (Engel *et al.*, 2003; Dehghani, 2016; Fan *et al.*, 2018).

The NMM used in this study describes a local population of interacting neurons. Extended models that allow the investigation of coupling between populations or brain regions have also been developed in epilepsy studies (Cosandier-Rimele *et al.*, 2008; Richardson, 2012; Freestone *et al.*, 2014; Hassan *et al.*, 2017), based on the notion that epilepsy is a network disease (Engel *et al.*, 2013), even for focal epilepsy (Terry *et al.*, 2012; Lam, 2016). This can be achieved by coupling an ensample of NMMs into mesoscopic circuits and macroscopic systems. Thus both temporal and spatial dynamics are considered. Promising advances have been achieved with this perspective. A network model with NMM nodes was established to estimate brain network ictogenicity and predict the outcome from

epilepsy surgery, and even to suggest alternative resection regions (Goodfellow, 2016; Sinha, 2017). Further study could investigate the proposed approach in such an extended model.

In conclusion, we have explored the path through synaptic gain parameter space obtained by fitting a NMM to iEEGs recorded from thirty seizures from ten TLE patients. Seizure evolution was constant within individual patients. Synaptic gain values located roughly on a plane before seizure onset, dispersed during seizure and returned to the plane afterwards. Seizures were clustered, identifying this way two patient groups, corresponding to different synaptic gain path in the parameter space. This study may aid clinicians to classify patients into subgroups based on underlying mechanisms during seizures and potentially enable more robust decisions concerning treatment strategy.

Conflict of Interest Statement

None of the authors has any conflict of interest to disclose.

Author Contributions

Xiaoya FAN designed the study, analyzed and interpreted the data and wrote the manuscript. The other coauthors made a critical revision of the manuscript. Nicolas GASPARD acquired and annotated the data, gave his medical expertise on interpretation and analysis of data. Benjamin LEGROS acquired and annotated the data, gave his medical expertise on interpretation and analysis of data. Federico LUCCHETTI and Rudy ERCEK provided advice on data analysis. Antoine NONCLERCQ designed and supervised the study.

Data Availability Statement

De-identified clinical data, as well as programming code from this study are stored in authors' local server. The authors confirm that all data is fully available without restriction and will be shared with the research community upon request.

Abbreviations

iEEG

Intracranial electroencephalography

SEEG

Stereoelectroencephalography

TLE

Temporal lobe epilepsy

DTW

Dynamic Time Warping

NMM

Neural Mass Model

Reference

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Figure legends:

Figure 1. (A) Illustration of the neural mass model (+/− represents excitatory/inhibitory); (B) Detailed schematic representation of the model (EPSP/IPSP denotes excitatory/inhibitory postsynaptic potential), cited from (Fan et al., 2018) and adapted from (Wendling et al., 2002).

Figure 2. Schematic illustration of parameter identification procedure (Fan et al., 2018)

Figure 3. Illustration of periods of interest

Figure 4. Distribution of identified synaptic gains in the parameter space. It shows the synaptic gains collected from the recordings of all patients. Each subfigure corresponds to one period of interest. The planes are identical and obtained by linear regression on data from IntIctal period.

Figure 5. The boxplot of contribution ratios of the first two principal components during the four periods of interest.

Figure 6. Clusters showing the highest average silhouette coefficient. (A), (B), (C) and (D) correspond to different number of clusters, i.e. 2, 3, 4, 5, respectively. For each of the four subfigures, the cluster structure is shown on the left and the silhouette coefficients on the right. In the cluster structure, each circle represents one seizure. Seizures recorded from different patients are separated by dashed lines and indicated by patient ID in subfigure (D) (from A to J). In the silhouette coefficients, values for all the seizures of the corresponding cluster structure are shown with horizontal bars (seizures grouped in the same cluster are shown together and clusters are separated).

Figure 7. Clusters showing the highest average silhouette coefficient (analysis over 26 seizures, after removing 4 outliers). (A) Cluster structure. Each circle represents one seizure. Seizures recorded from different patients are separated by dashed lines and indicated by patient ID (from A to J). (B) Silhouette coefficients of all seizures of the corresponding

cluster structure (seizures grouped in the same cluster are shown together and clusters are separated).

Figure 8. Illustration, for the patient B, of paths through synaptic gain parameter space in cluster 1. The three subfigures of each row represent one seizure. Each corresponds to a 2-D projection. Seizures start in red and end in blue.

Figure 9. Illustration, for the patient G, of paths through synaptic gain parameter space in cluster 2. The three subfigures of each row represent one seizure. Each corresponds to a 2-D projection. Seizures start in red and end in blue.

Figure 10. Boxplots of bootstrap values (%) for seizure path pairs from five groups, i.e. intra-patient path pairs, inter-patient path pairs, cluster 1 path pairs, cluster 2 path pairs and inter-cluster path pairs (obtained by the "boxplot" function in MATLAB). Bootstrap value < 5% indicates significant consistency between two paths. The whiskers extend to the most extreme data points not considered anomalies (approximately $+/-2.7\sigma$ and 99.3 percent coverage if the data are normally distributed) and the crosses in red represent anomalies.

Table 1. Basic information about the patients and cluster results. N/A, not available; NL, neuronal loss; NI, normal MRI; PNH, periventricular nodular heterotopia; HD, hippocampal dysplasia; MTS, mesial temporal sclerosis; LVFA, low-voltage fast activity.

Patient	Sex	Age	Pathology	MRI	Surgical outcome	Onset side	Seizure #	Cluster #	SOP
A	M	40	N/A	NI	Engel 1a	L	1	2	LVFA
							2	2	LVFA
							3	2	LVFA
B	M	31	N/A	NI	No surgery	B	4	1	LVFA
							5	1	LVFA
							6	-	LVFA
C	F	30	N/A	PNH; HD	Engel 1a	L	7	2	LVFA
							8	2	LVFA
							9	2	LVFA
							10	2	LVFA
							11	2	LVFA
D	F	26	N/A	PNH	No surgery	B	12	2	LVFA
							13	2	LVFA
							14	2	LVFA
E	F	11	NL	HD	Engel 1b	R	15	1	LVFA
							16	1	LVFA
F	M	41	N/A	MTS	Engel 1a	L	17	2	LVFA
							18	-	LVFA
							19	2	LVFA
G	M	35	Normal	NI	Engel 1a	L	20	2	LVFA
							21	2	LVFA
							22	2	LVFA
H	M	38	N/A	NI	Engel 2	L	23	1	LVFA
							24	1	LVFA
							25	1	LVFA
I	F	26	N/A	NI	Engel 1a	R	26	1	LVFA
							27	2	LVFA
							28	1	LVFA
J	F	43	N/A	MTS	No surgery	R	29	-	LVFA
							30	-	LVFA

Table 2. Model parameters, their physiological meanings and standard values. The standard values were established in previous studies (Jansen & Rit, 1995; Wendling *et al.*, 2002; Wendling *et al.*, 2005).

Parameters	Physiological meaning	Standard value
A	Average excitatory synaptic gain	3.25 mV
B	Average slow inhibitory synaptic gain	22 mV
G	Average fast inhibitory synaptic gain	10 mV
$1/a$	Average time constant in the feedback excitatory loop	$1/100$ s
$1/b$	Average time constant in the feedback slow inhibitory loop (targeting dendrites of pyramidal cells)	$1/50$ s
$1/g$	Average time constant in the feedback fast inhibitory loop (targeting soma of pyramidal cells)	$1/350$ s
C_1, C_2	Average number of synaptic contacts in the feedback excitatory loop	$C_1 = C, C_2 = 0.8C$ $C = 135$
C_3, C_4	Average number of synaptic contacts in the feedback slow inhibitory loop	$C_3 = C_4 = 0.25C$
C_5, C_6	Average number of synaptic contacts in the feedback fast inhibitory loop	$C_5 = C_6 = 0.1C$
C_7	Average number of synaptic contacts between the fast and slow inhibitory interneurons	$C_7 = 0.8C$
e_0	Half of the maximum firing rate of the population	2.5 s^{-1}
r	Steepness of the nonlinear asymmetric sigmoid function	0.56 mV^{-1}
v_0	The postsynaptic potential when firing rate is e0	6 mV
p(t)	Excitatory input noise (Gaussian white noise)	$\mu = 90 \; pulses/s,$ $\sigma = 30 \; pulses/s$

Table 3. Results of the bootstrapping test to validate cluster results. The bootstrap value was computed as the percentage of random path pairs that are equally close or closer than real seizure evolution path pairs. Bootstrap value < 5% indicates significantly consistent path pairs. Wilcoxon rank sum tests were performed to compare the statistical difference in bootstrap values between groups and significance was indicated by * (p<0.05). N represents no significant difference between groups. The values in the parentheses in the last and second last columns were computed after ruling out the four outliers.

Groups	Intra-patient	Inter-patient	Cluster 1	Cluster 2	Inter-cluster	Median of bootstrap value %	% of consistent path pairs
Intra-patient	-	*	N	*	*	0.6 (0.30)	66.7 (78.6)
Inter-patient	*	-	*	*	*	47.5 (15.80)	25.6 (34.3)
Cluster 1	N	*	-	*	*	0.45	77.8
Cluster 2	*	*	*	-	*	8.00	39.7
Inter-cluster	*	*	*	*	-	41.19	26.8

(A) Cluster Result Silhouette coeficient: Mean = 0.92909

(B) Cluster Result Silhouette coeficient: Mean = 0.88073

(C) Cluster Result Silhouette coeficient: Mean = 0.71984

(D) Cluster Result Silhouette coeficient: Mean = 0.73302