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Title: Dynamics underlying interictal to ictal transition in temporal lobe epilepsy: insights from a Neural Mass Model

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Abstract

We propose an approach that combines a neural mass model and clinical intracranial electroencephalographic (iEEG) recordings to explore the potential pathophysiological mechanisms (at the neuronal population level) of ictogenesis. Thirty iEEG recordings from ten temporal lobe epilepsy (TLE) patients around seizure onset were investigated. Physiologically meaningful parameters (average excitatory [Ae], slow [B] and fast [G] inhibitory synaptic gain) were identified during interictal to ictal transition. Four ratios (Ae/G, Ae/B, Ae/(B+G) and B/G)

were derived from these parameters and their evolution over time were analyzed. The excitation/inhibition ratio increased around seizure onset and decreased before seizure offset, indicating the impairment and re-emergence of excitation/inhibition balance around seizure onset and before seizure offset, respectively. Moreover, the slow inhibition may have an earlier effect on excitation/inhibition imbalance. We confirm the decrease of excitation/inhibition ratio upon seizure termination in human temporal lobe epilepsy, as revealed by optogenetic approaches both in vivo in animal models and in vitro. The increase of excitation/inhibition ratio around seizure occurrence could be an indicator to detect seizures.

Introduction

Epilepsy is one of the most common neurologic conditions and is characterized by repeated transient seizures separated by interictal periods (Blauwblomme *et al.*, 2014). Seizures are thought to be caused by a sudden abnormal excessive or synchronous neuronal activity in the brain and can cause notable deterioration of the patients' quality of life. However, mechanisms of interictal to ictal transition remains poorly understood and may vary between conditions and syndromes.

Experimental works have established an excitation/inhibition imbalance as the leading mechanism of ictogenesis (Scharfman, 2007; Naylor, 2010). The mechanistic role of γ-aminobutyric acid (GABA) in both seizure initiation and termination is increasingly being recognized. Gamma oscillations, one of the most characteristic electrophysiological patterns in focal epileptic seizures, can be induced by optogenetic activation of fast-spiking inhibitory interneurons in vivo (Cardin *et al.*, 2009). Functional upregulation of a portion of GABAergic inhibitory neurons was upon seizure termination in ex vivo model of temporal lobe epilepsy

(Wen *et al.*, 2014). Further, both optogenetic inhibition of excitatory principal cells and activation of a sub-population of GABAergic cells can readily stop temporal lobe seizures induced in mice (Krook-Magnuson *et al.*, 2013). Experiments in vitro confirmed the effectiveness of activating GABAergic inhibitory interneuron populations for seizure control, more specifically when using global optogenetic activation of mixed interneuron populations (Ledri *et al.*, 2014).

Computational modeling is now considered an efficient method to gain new insights into the mechanisms of brain disorders, including epilepsy. It can relate depth-EEG activities recorded during interictal to ictal transition to mechanisms of ictogenesis. The transition from interictal to ictal could be caused by either a random perturbation in bistable state (Lopes da Silva *et al.*, 2003; Baier *et al.*, 2012; Taylor *et al.*, 2014), the gradual change of underlying parameters (Wendling *et al.*, 2002; Wendling *et al.*, 2005; Breakspear *et al.*, 2006), or a combination of both (Lopes da Silva *et al.*, 2003; Wang *et al.*, 2014). A typical example of the first scenario is the absence seizure (Lopes da Silva *et al.*, 2003; Taylor *et al.*, 2014). Temporal lobe seizures, on the other hand, may be preceded by a gradual change in dynamics (Wendling *et al.*, 2002; Lopes da Silva *et al.*, 2003; Wendling *et al.*, 2005) and studying the temporal evolution of underlying parameters could reveal the mechanisms underlying the interictal to ictal transition. One strategy is to use coarse-grained cortical units as models of cortical tissue (Coombes, 2010). In these models, the average behavior of a large number of neurons is described to capture the dynamics of a neuronal population and study the interactions among different populations. The benefits are twofold. First, the dimensionalities of both parameters and variables are dramatically reduced compared to fine-grained models, contributing to a much lower computational load. Second,

experimental data required to construct such models are already available since no detailed knowledge at the neuron scale is needed.

One of the best-known neural mass models is proposed by Jansen and Rit (Jansen & Rit, 1995) based on the original work of Lopes da Silva et al. (Lopes da Silva *et al.*, 1974) and was further studied by Wendling et al. (Wendling *et al.*, 2002) in the framework of the analysis of temporal lobe epileptic signals. It has been proposed that seizures are oscillatory attractors that can be reached through underlying parameter change, or bifurcation (Wendling *et al.*, 2002). The interictal to ictal transition in human temporal lobe epilepsy was studied in this framework by fitting a neural mass model to temporally broad segments of intracranial EEG (iEEG) signals (Wendling *et al.*, 2005). Further, a time-optimized identification procedure to process long duration signals (over a sliding window) was used and a path through parameter space was illustrated to explain the changing features of EEG waveform in absence seizure evolution (Nevado-Holgado *et al.*, 2012).

In this paper, a neural mass model (Wendling *et al.*, 2002) that consists of four neural populations (main population, excitatory interneurons, slow dendritic-projecting inhibitory interneurons and fast somatic-projecting inhibitory interneurons) is implemented and automatically fitted to 30 SEEG signals recorded from 10 temporal lobe epilepsy (TLE) patients during interictal to ictal transitions. The recordings are processed within a sliding window and physiologically meaningful parameters, namely average excitatory Ae, slow B and fast G inhibitory (related to $GABA_A$ kinetics) synaptic gains are identified within each window to reproduce those recordings. The temporal evolution of excitation/inhibition ratios (Ae/G, Ae/B and Ae/(B+G)), and slow/fast inhibition ratio (B/G) was obtained and the global trend was analyzed to reveal dynamics underlying interictal to ictal transition. Compared to previous

studies, our approach therefore allows a systematic analysis on clinical data with both fine temporal resolution and global trend analysis to better link computational research with experimental findings.

Materials and Methods

The Neural Mass Model

The model implemented in our study was detailed previously (Wendling et al., 2002). The neural mass model macroscopically reflects the interactions between four subsets of neurons (see Fig. 1A). The main population is composed of the principal cells (i.e. pyramidal cells). It projects to and receives feedback from three other populations of local interneurons, one excitatory, two inhibitory. The two subsets of inhibitory interneurons are dendritic-projecting interneurons with slow synaptic kinetics ($GABA_{A,\ slow}$) and somatic-projecting interneurons with faster synaptic kinetics ($GABA_{A,\ fast}$), respectively. Somatic-projecting interneurons received feedback from the other inhibitory interneurons.

The detailed schematic representation of the neural mass model is shown in Fig. 1B. Each subset is modeled by two blocks, an asymmetric sigmoid function $Sigm(v)$ that converts the average postsynaptic membrane potential v into average pulse density of potentials fired by the population, and a transfer function that transfers the average pulse density of afferent action potential into an average excitatory or fast/slow inhibitory postsynaptic membrane potential with respective impulse response $h_e(t)$, $h_b(t)$ or $h_g(t)$, as shown in Eq. (1) and Eq. (2) respectively.

$$Sigm(v) = \frac{2e_0}{1+ e^{r(v_0 - v)}} \tag{1}$$

Where e_0 determines the maximum firing rate of the population, v_0 denotes the postsynaptic potential when a 50% of firing rate is achieved, and r is the steepness of the sigmoid function.

$$h_e(t) = A_e\, a_e t e^{-a_e t},\ h_b(t) = B\, b t e^{-bt},\ h_g(t) = G\, g t e^{-gt} \qquad (t \geq 0) \tag{2}$$

Here A_e , B and G respectively represent the average excitatory, slow and fast inhibitory synaptic gain. a_e, b and g respectively stand for the average time constant in the feedback excitatory, slow and fast inhibitory loop.

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 constants C_i in Fig. 1B refer to the average number of synaptic contacts in the feedback loops. The model outputs the summed average postsynaptic potentials in principal cells, which was considered to be the synthesized iEEG signals. The model can be represented by a set of first order differential equations (Wendling *et al.*, 2002).

All the parameters in the model have physiological meanings. The average synaptic gains (i.e. the average excitatory synaptic gain of the main population A_e , as well as the average inhibitory gains of the slow and fast inhibitory interneuron populations, respectively B and G) were granted a degree of freedom. Other parameters were set to the standard values reported earlier (Wendling et al., 2005). We chose to estimate the 3 parameters, A_e , B and G, (average excitatory, slow and fast inhibitory synaptic gain) as previously proposed (Wendling *et al.*, 2005; Blenkinsop *et al.*, 2012; Hocepied *et al.*, 2013; Armando *et al.*, 2015; Kameneva *et al.*, 2017) since they play central roles in the transition between background EEG activity and seizures (Wendling *et al.*, 2002).

Clinical data

After approval from the Ethics Committee of Hôpital Erasme, 30 iEEG recordings recorded from ten patients diagnosed with temporal lobe epilepsy (TLE) were retrospectively selected from our EEG database. The detailed information about the patients can be found in Table 1. All patients underwent stereo-electroencephalography (SEEG) with 500 Hz sampling frequency and

16-bit resolution. For the analysis, an epoch of iEEG comprising the seizure was selected on visual inspection by an expert neurophysiologist in the channel that showed the first implication during the seizure. The expert also marked the onset and offset of each seizure.

Identification of key parameters

The schematic illustration of the algorithm is shown in Fig. 2. The recordings were first filtered below 0.16 Hz and above 65 Hz to remove slow baseline drift and electronic noise. 50 Hz notch filter was used to remove power line noise. After pre-processing, the recordings were segmented using a 2 s moving window with a step of 0.1 s. For each window, the model parameters were identified to generate the corresponding EEG segment. The window size (2 s) was chosen short enough to obtain quasi-stationary EEG segments and yet long enough to achieve proper parameter identification. The window step size (0.1 s) was chosen small enough to track parameters changes with a high temporal resolution.

To find the parameters (A_e, B and G) that enable the model to generate a signal similar to the recorded EEG, we established an error function $\varepsilon(\widehat{F_r}, \widehat{F_s}(A_e, B, G))$, where $\widehat{F_r}$ and $\widehat{F_s}$ are the feature vectors estimated from the recorded signal and synthesized signals, respectively. It evaluates the dissimilarity between two signals and is defined as the Euclidean Distance between their feature vectors. A small error indicates high similarity between two signals. By minimizing the error function, the parameters can be identified.

The feature vector was constructed based on both spectral and morphographic properties of the signal. It contains seven temporal features and seven spectral features. Specifically, the relative power within seven specific frequency bands 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 retained as 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.

Searching the parameter space is a commonly used approach to find the optimal parameter set. In this study, we employed an exhaustive grid searching with a constant step. We computed the error function between clinical data and the synthesized signals generated from all possible combinations of parameters in the parameter space. The grid searching space has a resolution of 0.5 mV in slow (B)/fast (G) inhibition and 0.125 mV in excitation (Ae). Wendling et al. employed a similar grid to map the key parameters with the different EEG patterns that the model was able to generate (Wendling *et al.*, 2002). The key parameters (Ae, B and G) were bounded within specific ranges around standard values (Jansen & Rit, 1995; Wendling *et al.*, 2002). Specifically, Ae (excitatory) was varied from 3 to 7 mV, B (slow inhibitory) and G (fast inhibitory) were varied from 0.5 to 50 mV.

Since the excitation input *p(t)* is modeled with white Gaussian noise, the synthesized EEG depends on the realization of the model input excitation. Therefore, we repeated simulations 15 times for each possible triplet to generate 15 synthesized EEG segments, from which the averaged features were obtained. To evaluate potential bimodality (i.e. the existence of two peaks in the probability density function) of feature values, the bimodality coefficient was calculated (Jonathan B. Freeman & Dale, 2013; Pfister *et al.*, 2013), showing that large majority of the feature values (95.86%) can be considered unimodal (bimodality coefficient below 0.555). Therefore, this averaging is meaningful because features show high unimodality for nearly all points in parameter space.

The algorithm finds a family of potential solutions, instead of looking for one “best” triplet. The errors calculated during exhaustive grid searching for each 2-s segment were sorted in

ascending order. The top fifty fits (0.15‰) with the lowest values of the error function were selected as potential solutions. We assume that the parameters with similar values (close in the parameter space) enable the model to generate similar signals (unless it's a bifurcation point). This is supported by various studies (Wendling *et al.*, 2002; Blenkinsop *et al.*, 2012). We then employed density-based spatial clustering of applications with noise (DBSCAN) (Sander *et al.*, 1998), to further select the solutions. In DBSCAN, points with many nearby neighbors are grouped while points lying alone in low-density regions are marked as outliers. These outliers were discarded from the family of potential solutions. Finally, the cluster center calculated from the cluster with smallest average error was taken as the optimum and assumed to be a good representative fit, as previously shown (Nevado-Holgado *et al.*, 2012). In this sense, our algorithm does not seek the "best" set of parameters (i.e. the one minimizing the cost function) but the one that is most representative of the model behavior.

Data analysis

Calculation of ratios

Epileptic seizures are classically considered as hyperexcitable phenomena. Previous studies have shown that interictal and ictal epileptiform discharges cannot be explained simply by enhanced excitation and/or decreased inhibition (Engel, 1996; Nusser *et al.*, 1998). The role of excitation, inhibition and the relationship between them in epileptogenesis have long been discussed (Dichter, 1997; Dalby & Mody, 2001). Epileptic seizures are assumed to reflect an imbalance between neuronal excitation and inhibition (Engel *et al.*, 2003; Dehghani *et al.*, 2016). Therefore, we analyzed the ratios calculated from the key parameters (average excitatory Ae, slow B and fast G inhibitory synaptic gains).

Four ratios were calculated for each 2-second segment: 1) Ae/G: the ratio between excitation and fast inhibition; 2) Ae/B: the ratio of excitation to slow inhibition; 3) Ae/(B+G)): the ratio between excitation and the sum of slow and fast inhibition; and 4) B/G: the ratio of slow to fast inhibition.

Analysis of time evolution of ratios

A moving average filter was applied using a 30s window to smooth the time series of each ratio and analyze global trends. We expected ratios to show an increase around seizure onset and decrease around seizure offset (Wendling *et al.*, 2005). Thus, we defined two points of interest to identify the rise and fall of a ratio (see Fig. 3 for illustration). The first (called I_{rise}) indicates the point when the ratio starts to increase and the second one (called I_{fall}) reveals the point when it returns back to I_{rise} value . I_{rise} (red dot in Fig. 3B) is defined as the first point in the sample where the ratio crosses one standard deviation (SD) above the mean (horizontal solid blue line in Fig. 3B) while continuing to increase to at least two SD (horizontal dashed blue line in Fig. 3B). I_{fall} (green circle in Fig. 3B) was identified as the point following $I_{rise}$where the ratio falls below one SD above the mean.

We related I_{rise} and I_{fall} with seizure onset and offset, respectively. Changes in excitation, slow and fast inhibition were found a few tens of seconds before the seizure, which was considered as pre-onset period (Wendling *et al.*, 2005). Recent EEG-based algorithms are able to detect seizures 10s (F. Fürbass *et al.*, 2017) to even 1 min (Hocepied *et al.*, 2013) before their onset. Therefore, we relate I_{rise} to the seizure onset if I_{rise} locates within the period from 30s before onset to offset (i.e. between the first vertical solid line and the second vertical dashed line in Fig. 3B). Similarly, I_{fall} was related to seizure offset if it locates within the period from onset to 30s after offset (i.e. between the first vertical dashed line and second vertical solid line in Fig.

3B). For each ratio, the time delay to onset is calculated as $T_{I_{rise}} - T_{onset}$, while the time delay to offset is $T_{I_{fall}} - T_{offset}$. Of note, I_{rise} and I_{fall} are obtained for each ratio.

We further analyzed the recordings for which both I_{rise} and I_{fall} of Ae/B (excitation/slow inhibition) and Ae/G (excitation/fast inhibition) could be related to the seizure. More specifically, we compared the time delay to seizure onset/offset calculated from these two ratios (excitation/slow inhibition Ae/B and excitation/fast inhibition Ae/G).

Sensitivity analysis of ad hoc parameters

There are several ad hoc parameters in this study, i.e. size (2 s) and step (0.1 s) of the sliding window, number of potential solutions (50) and moving average window length (30 s). Their values were chosen empirically and may vary from one study to another.

Processing EEG with a sliding window is a widely used approach in epileptic EEG analysis. Different values have been proposed previously, for instance, 1-s window size with 0.5-s step (Sinha et al., 2017), 1-s window with 1-s step (Chiu et al., 2011), 1.7-s window size with 0.1-s step (Rogowski et al., 1981), 3-s window size with 1.8-s step (Dadok *et al.*, 2015), 10 s window size with 10-s step (Aarabi & He, 2014), etc. Similarly, different moving average window lengths have been chosen in previous studies. For instance, spike rate was smoothed using a 30-s moving average filter for seizure prediction (Li *et al.*, 2013). More recently, a moving average filter with a window length of 150 s was applied on EEG features for seizure detection (Bhattacharyya & Pachori, 2017). In a model-based seizure detection approach, the authors applied a moving average filter with a 5-min window to smooth identified model parameters and detected seizures by investigating changes in the parameters prior to seizures (Gadhoumi *et al.*, 2016).

Sensitivity analysis was conducted on all patients and for all ratios (when the ratios could be related to the seizure) to evaluate the effect on results if different values were set. This was done by a one-at-a-time approach (Murphy *et al.*, 2004), i.e. changing the value of one parameter while keeping the others constant.

Results

Global trend of calculated ratios

We show the illustration of results for two seizures in Fig. 4 and Fig. 5, respectively. The four ratios (Fig. 4 or Fig. 5 B, C, D, E) are aligned with the iEEG recording (Fig. 4 or Fig. 5 A) at marked seizure onset. As shown in Fig. 4 and Fig. 5, some ratios (Ae/B, Ae/G and Ae/(B+G) in Fig .4 and all ratios in Fig. 5) increased above one SD above the mean around seizure onset and decreased (below one SD above the mean) around seizure offset, i.e. the interactions among neuronal populations were disturbed with seizure onset and recovered when seizure ends.

Each recording was individually analyzed to assess which ratio(s) showed such variations during the occurrence of a seizure (increased around seizure onset and decreased around/before seizure offset). Fig. 6 gives an insight on how I_{rise}, the rise of a ratio to one SD above the mean, is positioned in time compared to the onset of a seizure. It shows, for each seizure and each ratio, the delay between the rise of a given ratio and the onset of a given seizure (i.e. $T_{I_{rise}} - T_{onset}$). It equals zero when the ratio exceeds one SD above the mean exactly at seizure onset. It is negative when it precedes seizure onset and positive when it follows it. We relate I_{rise} with seizure onset when it locates between 30s before seizure onset and seizure offset, i.e., as illustrated in Fig. 6, when a ratio lies between the solid red line (that indicates 30s before seizure onset) and the dashed green line (that indicates the seizure offset).

Similarly, Fig. 7 shows the delay between the decrease of a given ratio (below one SD above the mean) and the offset of a given seizure. We relate I_{fall} with seizure offset when it locates between seizure onset (solid red line in Fig. 7) and 30s after seizure offset (dashed green line in Fig. 7).

Results showed that for most seizures, the ratios increased to one SD above the mean around seizure onset and decreased below one SD above the mean around/before seizure offset. More specifically, among 30 seizures, 25 (83.3%), 28 (93.3%), 24 (80.0%) and 18 (60.0%) showed this pattern for Ae/(B+G) (excitation/(slow + fast inhibition)), Ae/B (excitation/slow inhibition), Ae/G (excitation/fast inhibition) and B/G (slow/fast inhibition) respectively (indicated by the markers located between the solid red line and dashed green line in Fig.6 and Fig. 7). Further analysis showed that these ratios restored before seizure offset (negative time delay to seizure offset) for most seizures (25/25 for Ae/(B+G), 24/28 for Ae/B, 24/24 for Ae/G and 17/18 for B/G). We next considered the 22 seizures for which both Ae/B (excitation/slow inhibition) and Ae/G (excitation/fast inhibition) could be related to I_{rise} and I_{fall} (i.e. increased around seizure onset and decreased around/before seizure offset). Among them, Ae/B increased and restored earlier than Ae/G for 17 (77.3%), 18 (81.8%) seizures, respectively (blue triangles are below corresponding dark circles for most seizures in Fig.6 and Fig. 7). Therefore we concluded that excitation/slow inhibition rises and restores earlier, compared to excitation/fast inhibition for most seizures. Visual examination seems to show a transient low value in Ae/G at seizure onset in many seizures (see the low value of the light blue trace in Fig.4B just after seizure onset). In addition, 11 (50%) seizures showed longer Ae/B disturbance, while the other 11 (50%) showed longer Ae/G disturbance.

Sensitivity analysis of ad hoc parameters

To evaluate the robustness of our conclusions to the choice of the values of ad hoc parameters, a sensitivity analysis was conducted. This was done by a one-at-a-time approach (Murphy *et al.*, 2004).

The variations of $T_{I_{rise}}$ and $T_{I_{\text{fall}}}$ (the location of red dots and green circles in Fig. 4 and Fig. 5) due to parameters change have been assessed, as shown in Tab. 2. In summary, $T_{I_{rise}}$ and $T_{I_{fall}}$ varied on average less than 5% for all parameters, the only exception being the rise/fall of B/G (slow/fast inhibition) that is more sensitive to step size of the sliding window. This exception could be due to the variation of B/G that seems more complex (the increase around seizure onset and decrease around seizure offset is seen only for 60% seizures), indicating sophisticated interactions between fast and slow inhibitory interneurons. Therefore, small variations of these ad hoc parameters (i.e. size and step of the sliding window, number of pre-selected potential solutions and moving average window size) had minor effect on the global trends of ratios, thus would not change our conclusions.

Discussion

We have shown that a model-based approach can be used to explore potential mechanisms underlying the occurrence of a seizure by analyzing parameter shifts over time. We analyzed 30 seizures from 10 patients with a fine temporal resolution and inferred general trends. Increase of Ae/(B+G), i.e. excitation/(slow + fast inhibition), suggests excitation/inhibition imbalance underlying seizure onset, as reported earlier (Engel *et al.*, 2003; Dehghani *et al.*, 2016). In the same way, the decrease of this ratio indicates the re-emergence of the balance toward the end of the seizure (Dehghani *et al.*, 2016). Similar changes were found in Ae/B (excitation/slow

inhibition) and Ae/G (excitation/fast inhibition). Our results thus support a role for excitation/inhibition imbalance in seizure occurrence.

Furthermore, Ae/B increased earlier for most seizures, indicating an earlier break of excitation/slow inhibition balance around seizure onset, compared to excitation/fast inhibition balance. These results are in line with previous publications reporting that fast activity at the beginning of a seizure involves a significant participation of fast spiking inhibitory interneurons (Cardin *et al.*, 2009; De Curtis & Gnatkovsky, 2009; Jiruska *et al.*, 2013). Increase in fast inhibition at the onset of a seizure tends to reduce the value of the excitation/fast inhibition ratio, since the denominator increases, but does not have any impact on the excitation/slow inhibition ratio, since it is not related to it. Both ratios are also related to the excitation – i.e. the numerator – and so their exact value also depends on it. We can, however, still infer that the excitation/fast inhibition ratio will not increase as fast as the excitation/slow inhibition ratio as the seizure progresses from seizure onset. This is consistent with the delayed increase in excitation/fast inhibition at seizure onset, relative to excitation/slow inhibition, shown in our study.

Focusing only on the excitation/fast inhibition ratio, with the enhancement of fast inhibition at seizure onset, one could expect that the excitation/fast inhibition ratio would show a low value or a decrease. Visual examination seems to support this hypothesis in many seizures (e.g. see the low value of the light blue trace in Fig.4B just after seizure onset). However, this was not seen in the analysis of the general trend (e.g. see the low value of the dashed black trace in Fig.4B, at the same time), which was the focus of our study. This could be explained by the rather short period of time of activation of fast-spiking interneurons at the beginning of the seizure. Indeed, it was reported that the fast spiking interneuron firing rates were initially high, yet began to drop as pyramidal cell firing rates increased approximately 4 s later, in the pilocarpine freely moving rat

model of epilepsy (Grasse *et al.*, 2013). Therefore, the possible decrease of excitation/fast inhibition ratio at seizure initiation should be brief. This transient decrease in excitation/fast inhibition ratio at seizure onset cannot be seen when analyzing more general trends (please remind the 30s smoothing window).

The fast activity here refers to low voltage fast activity at seizure onset, usually between 20 - 30 Hz (Uva *et al.*, 2005; Gnatkovsky *et al.*, 2008; Trombin *et al.*, 2011; Wendling *et al.*, 2012). The exact frequency range for low amplitude fast activity at seizure onset is inconsistently defined between studies. In some studies, the fast activity at seizure initiation refers to activities in beta and low-gamma band (15 - 40 Hz) (De Curtis & Gnatkovsky, 2009; Wendling *et al.*, 2016). Other studies extend this range to higher frequency (Medvedev, 2001; Fisher *et al.*, 2014), but usually lower than ripples (>80 Hz) (Jiruska *et al.*, 2017). Here, activities faster than 65 Hz cannot be explained by identified parameters in this study since they were filtered. Further investigation could be undertaken to include activities in a higher frequency range.

$GABA_{A,\ slow}$ and $GABA_{A,\ fast}$ interneurons were found to be two different populations in region CA1 of the hippocampus and were responsible for theta and gamma rhythms generation (White *et al.*, 2000) which can be observed in EEG seizure signals. Integrated optogenetic and electrophysiology approaches suggest that $GABA_{A,\ fast}$ interneurons (e.g. fast-spiking parvalbumin positive interneurons) impose a brief but powerful suppression on nearby excitatory cells, whereas $GABA_{A,\ slow}$ interneurons (e.g. low-threshold spike somatostatin positive interneurons) may have a longer suppressive effect (Cardin, 2012; Kvitsiani *et al.*, 2013). Our results do not confirm this difference at a larger population level, as they showed comparable imbalance duration for Ae/B ($GABA_{A,\ slow}$ related) and Ae/G ($GABA_{A,\ fast}$ related).

Generally, seizure terminates automatically within a few minutes (Timofeev & Steriade, 2004; Lado & Moshé, 2008; Zubler *et al.*, 2014; Wang *et al.*, 2015). This self-termination is often related to an increase of GABAergic inhibition (Lado & Moshé, 2008). Functional upregulation of a portion of inhibitory neurons in the cortices where seizures are appearing the earliest was reported as a mechanism for seizure termination in ex vivo model of temporal lobe epilepsy (Wen *et al.*, 2014). Our results suggest that the excitation/inhabitation balance restores before seizure ends and may contribute to its termination.

Evidence showed that temporal lobe seizures induced in mice can be stopped rapidly either by optogenetic inhibition of excitatory principal cells, or by activation of a subpopulation of GABAergic cells (related to $GABA_{A,\ fast}$), in a spatially restricted manner (Krook-Magnuson *et al.*, 2013). It was also found that global optogenetic activation of mixed interneuron populations was more effective at seizure suppression in vitro, compared to targeting only one interneuron population, due to a more generalized GABA release (Ledri *et al.*, 2014). We found a decrease in both excitation/fast inhibition and excitation/slow inhibition ratios before seizure termination. It suggests that, besides being more effective at seizure suppression, a more generalized GABA release better corresponds to a physiological behavior. There is a clear methodological difference between our study, which analyzes the global trends of excitation, slow and fast inhibition in human data, and optogenetic studies, which manipulates the behavior of specific cell populations. However, both approaches yield similar results and confirm each other.

The implicit assumption underlying our approach is that the dynamics of ictogenesis can be captured by smooth variations of several system parameters. This is often illustrated as a path through parameter space (Blenkinsop *et al.*, 2012; Nevado-Holgado *et al.*, 2012). It has been proposed that the transition from background activity to epileptic rhythms can be caused either

by a perturbation in a bistable state without change in parameters (Lopes da Silva *et al.*, 2003; Baier *et al.*, 2012), as most often in absence seizures, or by a deformation of the attractor leading to a gradual evolution onto the ictal state (Wendling *et al.*, 2002; Wendling *et al.*, 2005; Blenkinsop *et al.*, 2012), for instance in temporal lobe epilepsy (Lopes da Silva *et al.*, 2003). Seizures may be undetectable in the first scenario when caused by a random perturbation (Lopes da Silva *et al.*, 2003). However, in the second scenario, addressed in this study, some seizures can be detected or even predicted by analyzing the gradual change in dynamics. Since Ae/B, Ae/G and Ae/(B+G) increase around seizure onset, they could be used as indicators to detect seizures in an early stage using the model-based approach proposed earlier by our group (Hocepied et al., 2013).

The feasibility of seizure prediction has been long questioned and debated. Our results suggest that Ae/B may be a potential indicator to predict seizures before onset in TLE patients using a similar model-based approach, as it increases to one deviation above the mean before onset for most seizures (26/28).

This study builds on previous work by others where electrophysiological patterns typically observed during interictal to ictal transition in mesial temporal lobe epilepsy were related to mechanisms of seizure generation through a neural mass model (Wendling et al., 2005). They defined four periods of interest (intICTAL, PreONSET, ONSET and ICTAL), each with a duration of 10 s. An evolutionary algorithm was employed, for each temporally broad segment, to search the parameter space and generate observed data. In this work, we used a time-optimized parameter identification procedure to process recordings of long duration. Thus global change of these parameters, underlying interictal to ictal transition, could be captured. Furthermore, using this approach, we do not rely on EEG segmentation that can be difficult to

label because of inter-seizure variability and inter-expert subjectivity. For instance, it has been argued that the use of terms “interictal”, “ictal” and “postical” can be confusing (Fisher & Engel, 2010) and their boundaries are often indistinct (Fisher *et al.*, 2014). Also, instead of analyzing excitation and inhibition separately, we analyzed the variation of excitation/inhibition ratios (excitation/slow inhibition Ae/B, excitation/fast inhibition Ae/G and excitation/(slow + fast inhibition) Ae/(B+G)), which is of significance, since epileptic seizure events are assumed to involve a chronic imbalance between neuronal excitation and inhibition (Engel *et al.*, 2003).

Since the parameter space was searched exhaustively, i.e. scan was performed through all possible combinations of parameters, the algorithm avoids converging in local optima. Despite this, the computational load was tremendously reduced by pre-calculating the average feature vectors of the simulated data. It allowed to compute one minute of recording in half a minute on a personal laptop, and therefore could be used in real time. More sophisticated algorithms, e.g. Kalman filtering (Freestone et al., 2014), could be considered for further study.

Besides the single neural mass model described in this study, models of multiple coupled neural populations have also been developed to generate epileptiform EEG signals, which allow the investigation of coupling among populations (Wendling *et al.*, 2000; Cosandier-Rimele *et al.*, 2012). They can be viewed as an extension of neural mass models and represent the spatiotemporal dynamics of several circumscribed brain regions. In this study, a single neural mass model was implemented to analyze the dynamics underlying interictal to ictal transition. We believe it is a necessary step to validate our method on a relatively simple model (only three parameters need to be identified) before moving to a more complex model, which would be of most interest for further work. Apart from the neurophysiology-inspired models, mathematical models or phenomenological models have also been proposed to capture some dynamical

properties of neural systems, for instance the Epileptor (Jirsa *et al.*, 2014). Although it is difficult to relate mathematical models to measurable biophysical data, the advantage is that the system behavior is unambiguously defined by bifurcations.

It is worth mentioning that the results were obtained on TLE patients, the most common form of focal epilepsy. We chose this particular type of epilepsy also because the neural mass model was initially designed to simulate iEEG recorded from TLE patients (Wendling *et al.*, 2002). It would, however, be interesting to adapt this approach to other types of epilepsy.

In conclusion, efforts have been made to reveal potential mechanisms underlying temporal lobe seizure occurrence using a model-based approach. This was achieved by analyzing the temporal evolution of key physiological parameters identified from clinical recorded data. Our results suggest the collapse and restoration of excitation/inhibition balance around seizure onset and before seizure offset, respectively. They also show that excitation/slow inhibition imbalance starts before the breaking of excitation/fast inhibition balance around the seizure. The present approach could be applied to seizure detection. Future works will be oriented towards the use of Ae/G, Ae/B and Ae/(B+G) as indicators in a model-based early seizure detection algorithm.

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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

GABA

Gamma-Aminobutyric acid (γ-Aminobutyric acid)

iEEG

Intracranial electroencephalography

SD

Standard deviation

SEEG

Stereoelectroencephalography

TLE

Temporal lobe epilepsy

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Table 1. Information about patients

Patient ID	Gender	Age	Number of recordings
A	Male	40	3
B	Male	31	3
C	Female	30	5
D	Female	26	3
E	Female	11	2
F	Male	41	3
G	Female	26	3
H	Male	38	3
I	Female	26	3
J	Female	43	2

Table 2. Variations (%) of $T_{I_{rise}}$ and $T_{I_{fall}}$ by varying ad hoc parameter values. The sliding window size was set to 1 s, 2 s, 5 s and 10 s. The sliding window step was set to 0.1 s, 0.5 s, 1 s, 1.5 s and 2 s. The number of candidates varied from 50 to 200 with a step of 25. The moving average length varied from 15 s to 50 s with a step of 5 s.

Ad-hoc parameters	Ae/G		Ae/B		Ae/(B+G)		B/G	
	$T_{I_{rise}}$	$T_{I_{fall}}$	$T_{I_{rise}}$	$T_{I_{fall}}$	$T_{I_{rise}}$	$T_{I_{fall}}$	$T_{I_{rise}}$	$T_{I_{fall}}$
Sliding window size	1.79	1.79	4.93	4.49	1.09	1.61	4.84	4.54
Sliding window step	2.15	1.64	0.96	0.41	0.83	0.49	13.30	11.30
Number of candidates	2.22	2.39	0.58	0.61	0.33	0.25	1.61	1.76
Moving average window length	4.12	3.47	2.52	1.89	2.09	1.45	4.24	3.90