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Temporally correlated fluctuations drive epileptiform dynamics

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ABSTRACT

Macroscopic models of brain networks typically incorporate assumptions regarding the characteristics of afferent noise, which is used to represent input from distal brain regions or ongoing fluctuations in non-modelled parts of the brain. Such inputs are often modelled by Gaussian white noise which has a flat power spectrum. In contrast, macroscopic fluctuations in the brain typically follow a $1/f^b$ spectrum. It is therefore important to understand the effect on brain dynamics of deviations from the assumption of white noise. In particular, we wish to understand the role that noise might play in eliciting aberrant rhythms in the epileptic brain.

To address this question we study the response of a neural mass model to driving by stochastic, temporally correlated input. We characterise the model in terms of whether it generates "healthy" or "epileptiform" dynamics and observe which of these dynamics predominate under different choices of temporal correlation and amplitude of an Ornstein-Uhlenbeck process. We find that certain temporal correlations are prone to eliciting epileptiform dynamics, and that these correlations produce noise with maximal power in the δ and θ bands. Crucially, these are rhythms that are found to be enhanced prior to seizures in humans and animal models of epilepsy. In order to understand why these rhythms can generate epileptiform dynamics, we analyse the response of the model to sinusoidal driving and explain how the bifurcation structure of the model gives rise to these findings. Our results provide insight into how ongoing fluctuations in brain dynamics can facilitate the onset and propagation of epileptiform rhythms in brain networks. Furthermore, we highlight the need to combine large-scale models with noise of a variety of different types in order to understand brain (dys-)function.

1. Introduction

Epilepsy is a prevalent neurological disorder characterised by the recurrence of spontaneous seizures. Seizures predominantly arise amidst a backdrop of otherwise healthy brain activity and are often accompanied by salient changes in electrographic activity as measured, for example, on the electroencephalogram (EEG). There is much we do not understand about why seizures occur, and contributing factors exist across multiple temporal and spatial scales (Lytton, 2008; Wendling et al., 2015). Here we focus upon a large spatial scale of interconnected brain regions since this is the scale at which clinical signs and symptoms emerge, and clinical data are most often recorded. At this scale, deficits can be observed both in the dynamics of brain regions (Valentín et al., 2005; Iannotti et al., 2016) and the connections between brain regions (O'Muircheartaigh et al., 2012). Thus recent focus has been placed on the role that large-scale brain networks play in epilepsy (Spencer, 2002; Kramer and Cash, 2012; Richardson, 2012; van Diessen et al., 2013). A fundamental, unanswered question in this context is how seizures emerge and spread in such networks (Goodfellow et al., 2011; Terry et al., 2012; Petkov et al., 2014; Goodfellow, 2016; Aksenova et al., 2007; Villa and Tetko, 2010).

Understanding seizures as emergent dynamics in brain networks is a challenging endeavour. However, mathematical models of brain dynamics can be used to study the mechanisms underlying the generation of seizures (Suffczynski et al., 2006; Lytton, 2008; Wendling et al., 2015). Previous work has focused on the types of dynamics that could underpin transitions from healthy EEG to seizure EEG, such as changes in model parameters (bifurcations), co-existence of healthy and abnormal states (bistability) or more complex spatio-temporal dynamics (Wendling et al., 2002; Lopes da Silva et al., 2003; Breakspear et al., 2006; Goodfellow et al., 2011; Rothkegel and Lehnertz, 2011; Baier et al., 2012; Goodfellow and Glendinning,

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2013). The bifurcation route into seizures relies on a (relatively) slow time scale change in the brain that drives it into an alternate (pathological) state, whereas the bistability paradigm relies on a (fast) perturbation-induced transition from the healthy to pathological state. However, any of these scenarios can be assumed to occur amidst a backdrop of ongoing brain dynamics, which could additionally influence transitions into seizures.

Modelling studies of seizure onset typically lump the "background" dynamics of the brain into stochastic fluctuations. These fluctuations have most often been assumed to have a flat power spectrum (i.e. Gaussian white noise) (Lopes da Silva et al., 1974; Pons et al., 2010; Victor et al., 2011; Roberts and Robinson, 2012; Touboul et al., 2011; Petkov et al., 2014; Garnier et al., 2015), which can be motivated by the assumption that ongoing activity of the brain is so complex that no single frequency dominates. However, analysis of spectra of brain signals (for example scalp EEG) reveals ongoing brain dynamics to be characterised by a $1/f^b$ relationship (Buzsáki and Draguhn, 2004), with prominent frequencies appearing concomitantly with different brain states (Niedermeyer and LopesdaSilva, 2005; Buzsáki and Draguhn, 2004; Freeman et al., 2000). In the epileptic brain, abnormal ("epileptiform") rhythms such as spikes or slow waves can also be present, even during interictal periods (Valentín et al., 2014; Karoly et al., 2016). In particular, in humans an increase of power in the delta band has been observed in MEG (Gupta et al., 2011) and EEG (Sadleir et al., 2011) recordings preceding absence seizures and pathological slow rhythms can be observed in interictal or preictal periods associated with focal epilepsies (Valentín et al., 2014; Tao et al., 2011; Lee et al., 2000). In animal models of epilepsy, electrophysiological recordings performed in the preictal phase have revealed an increase of power in the delta (Sitnikova and van Luijtelaar, 2009), and delta and theta (Van Luijtelaar et al., 2011) bands.

We therefore need to better understand the response of neuronal populations to afferent rhythms and stochastic fluctuations with a variety of dynamics, including those that can be approximated by noise yielding a realistic $1/f^b$ power spectrum, and those that contain dominant rhythms observed in the epileptic brain. A natural choice for the generation of such noise is the Ornstein-Uhlenbeck (OU) process, which exhibits a Lorentzian power spectrum. The spectral distribution in the OU process can be tuned through temporal correlations (i.e. "colour") of the resulting noise, therefore modelling alternative spectral compositions. OU noise has also been associated with the integration of background synaptic activity acting upon a neuron (Destexhe and Rudolph, 2004). Recent studies of OU processes driving neural models have investigated the effects of coloured noise on temporal distributions of neuronal spiking (Braun et al., 2015; da Silva and Vilela, 2015) and the generation of multimodal patterns of alpha activity (Freyer et al., 2011). In addition, networks of spiking neurons (Sancristóbal et al., 2013) and of neuronal populations (Jedynak et al., 2015) have been shown to generate realistic $1/f^b$ – like spectra when driven by OU noise, or more complex dynamics when subjected to driving at specific frequencies (Spiegler et al., 2011; Malagarriga et al., 2015). However, we lack an understanding of the ways in which non-white noise or rhythmic perturbations interact with neuronal populations to produce epileptiform dynamics.

Here, we study the effect of temporally correlated noise and rhythmic driving on the generation of epileptiform dynamics. Our starting point is a neural mass model that represents canonical interactions between populations of neurons in a region of brain tissue. Such models have been shown to be capable of generating pathological spiking dynamics reminiscent of seizure activity (Jansen et al., 1993; Jansen and Rit, 1995; Wendling et al., 2000; Grimbert and Faugeras, 2006). We classify the dynamics of this model by assessing variations of the signal around its time-averaged value, thus distinguishing between "healthy" and epileptiform dynamics. We then study the response of the system to prototypical coloured noise (an OU process) and identify an interval of temporal correlations for which noise can more readily elicit epileptiform dynamics. We show that this region is bounded on the one hand by noise intensity being insufficient to generate spikes, and on the other by bursting and transitions to an alternative rhythmic state, previously used to model healthy dynamics (the alpha rhythm). Analysing the spectrum of noise in this interval reveals it to contain high power in low (2–8 Hz) frequencies. In order to understand why such frequencies can drive epileptiform rhythms, we study periodic perturbations in a deterministic version of the model. Our analysis shows that driving the deterministic model using frequencies in this band causes epileptiform dynamics to predominate. We show how consideration of the bifurcation structure of the model can shed light on these observations, which in turn highlight the need to consider a fuller analysis of the repertoire of dynamics in the model beyond the genesis of epileptiform rhythms. Our findings elucidate potential mechanisms by which healthy or epileptiform rhythms present in certain regions of the brain can cause the onset of aberrant dynamics in connected regions.

2. Materials and methods

2.1. Jansen and Rit model

In order to study the dynamics of regions of brain tissue, we use a neural mass model of a canonical circuit of interacting neuronal populations (Jansen et al., 1993; Jansen and Rit, 1995). The populations considered are pyramidal neurons, excitatory interneurons and inhibitory interneurons. The dynamics of these populations is governed by a linear transformation that converts presynaptic spiking activity to changes in postsynaptic membrane potential (PSP) and a nonlinear transformation of net membrane potential to an efferent firing rate.

The linear transformation is given by the following convolution:

$$y(t) = \int_0^\infty h(t')s_{\text{in}}(t - t')\mathrm{d}t', \tag{1}$$

where $s_{\text{in}}(t)$ is the spike rate of activity afferent to the population, $y(t)$ gives the dynamics of the PSP, and $h(t)$ describes the way in which membrane potentials respond to an activating impulse. $h(t)$ equals zero for $t < 0$ and otherwise is given for excitatory and inhibitory connections with the following equations:

$$h_e(t) = Aate^{-at}, \tag{2}$$

$$h_i(t) = Bbte^{-bt}, \tag{3}$$

where A and B are the maximum excitatory and inhibitory PSPs, respectively, and a and b are time constants of these responses. They follow from lumped contributions of all dilatory effects that include synaptic kinetics, dendritic signal propagation and leak currents (Wilson and Cowan, 1972; Freeman, 1972; Amari, 1974; Nunez, 1974; Lopes da Silva et al., 1974).

Eq. (1) can be rewritten, using Eq. (2), as a second order ordinary differential equation (ODE):

$$\frac{d^2y(t)}{dt^2} + 2a\frac{dy(t)}{dt} + a^2y(t) = Aa \cdot s_{\text{in}}(t), \tag{4}$$

Similarly, by using Eq. (3) one can find a corresponding representation for inhibitory population dynamics.

Conversion of net membrane potential to efferent spiking is given by the following sigmoid function:

$$s_{\text{out}}(y) = \text{Sigm}(y) = \frac{2e_0}{1 + e^{r(v_0 - y)}}, \tag{5}$$

where $s_{\text{out}}(y)$ is a firing rate of a spike train outgoing from the population, y is its momentary total PSP (in general, time dependent), $2e_0$ is the maximum firing rate, v_0 is the PSP for which half maximum of the firing rate is reached, and r determines steepness (and thus nonlinearity) of this transformation.