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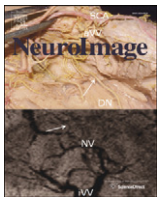

Self-organised transients in a neural mass model of epileptogenic tissue dynamics

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ABSTRACT

Stimulation of human epileptic tissue can induce rhythmic, self-terminating responses on the EEG or ECoG. These responses play a potentially important role in localising tissue involved in the generation of seizure activity, yet the underlying mechanisms are unknown. However, in vitro evidence suggests that self-terminating oscillations in nervous tissue are underpinned by non-trivial spatio-temporal dynamics in an excitable medium. In this study, we investigate this hypothesis in spatial extensions to a neural mass model for epileptiform dynamics.

We demonstrate that spatial extensions to this model in one and two dimensions display propagating travelling waves but also more complex transient dynamics in response to local perturbations. The neural mass formulation with local excitatory and inhibitory circuits, allows the direct incorporation of spatially distributed, functional heterogeneities into the model. We show that such heterogeneities can lead to prolonged reverberating responses to a single pulse perturbation, depending upon the location at which the stimulus is delivered.

This leads to the hypothesis that prolonged rhythmic responses to local stimulation in epileptogenic tissue result from repeated self-excitation of regions of tissue with diminished inhibitory capabilities. Combined with previous models of the dynamics of focal seizures this macroscopic framework is a first step towards an explicit spatial formulation of the concept of the epileptogenic zone. Ultimately, an improved understanding of the pathophysiologic mechanisms of the epileptogenic zone will help to improve diagnostic and therapeutic measures for treating epilepsy.

1. Introduction

The epileptic brain is capable of producing complex stimulus responses such as after-discharges due to prolonged stimulation (Blume et al., 2004; Lesser et al., 1999, 2008; Penfield and Jasper, 1954), and repetitive responses due to single perturbations (Flanagan et al., 2009; Valentín et al., 2002, 2005). Such "abnormal" responses to stimulation are currently of great interest due to their putative ability to localise epileptic tissue (Flanagan et al., 2009; Jacobs et al., 2010; Valentín et al., 2005). Although an imbalance between excitatory and inhibitory processes is expected to contribute to the excitability of epileptic cortex, and thereby convey an ability to display abnormal responses (Valentín et al., 2002), the mechanisms underlying these responses are currently unknown.

Insight into the excitability of epileptic tissue has been provided by electrical recordings from in vitro slice models of partially disinhibited cortex (Chervin et al., 1988; Pinto et al., 2005) as well as the imaging of spatio-temporal patterns of voltage sensitive dyes (Bai et al., 2006; Wu et al., 2008). It has been shown in these in vitro models that stimulation can induce the propagation of simple or more complex wave patterns, with propagation found to be mediated by synaptic excitation (Pinto et al., 2005). Such mechanisms have also been proposed for the spreading of epileptiform activity via depolarising potentials in excitatory pathways between pyramidal neurons (Elger and Speckmann, 1985). Along these lines, it has been suggested that sustained transient responses to single pulse perturbation in human epileptic tissue could be due to a re-entry of excitatory activity post-stimulus (Valentín et al., 2005). Thus, from the dynamical systems perspective, one can hypothesise that abnormal responses are due to a space-dependent induction of self-terminating, spatio-temporal transients by brief perturbation in an excitable medium. Here, excitability refers to the presence of a threshold beyond which stimulation can cause a large deviation from ongoing dynamics.

Macroscopic epileptic activity has previously been modelled in the neural mass framework of Jansen and Rit (1995) (see for instance Wendling et al. (2000); Labyt et al. (2006); Goodfellow et al. (2011), and references therein). That an epileptic neural mass displays features of excitability has been implicit in its use to generate inter-ictal spiking activity in a single compartment in response to random input (Wendling et al., 2000, 2002). Although studies have shown that spiking activity can be conferred between compartments in small systems of two and three coupled compartments (Wendling et al., 2000, 2001), the

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dynamics of connected systems of spiking neural mass models (as introduced by Jansen and Rit (1995)), and their response to perturbation in the context of epilepsy has not been explored.

Here we investigate spatially extended systems composed of coupled neural mass models and demonstrate that these systems are excitable. We show that a stimulus to these systems can confer spreading of activity and is able to produce self-organised responses as dynamic transients (in the mathematical sense). The spatially extended neural mass formulation with local excitatory and inhibitory circuits allows us to investigate the effect of local functional heterogeneities which are considered crucial for the mechanisms of epilepsy (Rosenow and Lüders, 2001). We thereby specifically demonstrate nontrivial consequences of localised heterogeneities in cortical tissue on the post-stimulus dynamics. Thus, we propose an explicit hypothesis for the generation of macroscopic stimulus responses in the epileptic brain, namely that local (focal) regions of diminished inhibition can cause a repetitive, self-terminating re-activation of tissue. In addition we demonstrate that the complexity of these transient responses depends upon the spatial location of stimulation, relative to functional abnormalities, as observed in epileptic tissue (Valentín et al., 2005). We therefore introduce a new framework with which to explore the macroscopic dynamics and pathophysiology of the epileptogenic zone. This is a crucial step towards improved diagnostic and therapeutic measures for treating epilepsy.

2. Methods

We use the model of cortical neural mass activity of Jansen (Jansen et al., 1993; Jansen and Rit, 1995). For a detailed description, a schematic of the structure of this model, and the physiological interpretation of output variables we refer the reader to the main text and Fig. 1 of Jansen and Rit (1995) and, for example, the detailed description of Wendling et al. (2002). In brief, the model in its original form captures, in three coupled impulse response equations (six differential equations), a feedback network between principal neurons, inhibitory interneurons and excitatory interneurons within a local cortical mass, i.e. at the macroscopic scale.

The model has been researched extensively in studies of evoked EEG responses (David et al., 2005; Zavaglia et al., 2006), functional connectivity (David et al., 2004; Wendling et al., 2001 and whole brain dynamics (Babajani-Feremi and Soltanian-Zadeh, 2010; Sotero et al., 2007). It has also been extensively applied to the investigation of focal epilepsies (Cosandier-Rimélé et al., 2008; Labyt et al., 2006; Wendling et al., 2002). In the current study we incorporate N interacting local populations of neurons with model connectivity given according to the original work of Jansen (Jansen and Rit, 1995), whereby populations communicate via excitatory input from other principal neurons. However, explicit time delays are neglected as we restrict the model here to interacting *local* populations. Each population, defined by superscript i, is modelled by a system of six differential equations representing the interaction of excitatory and inhibitory cortical processes (Jansen et al., 1993; Jansen and Rit, 1995), with model equations given by:

$$\begin{aligned}
\dot{y}_0^i(t) &= y_3^i(t)\\
\dot{y}_3^i(t) &= Aa\left\{S\left[y_1^i(t)-y_2^i(t)\right]\right\}-2ay_3^i(t)-a^2y_0^i(t)\\
\dot{y}_1^i(t) &= y_4^i(t)\\
\dot{y}_4^i(t) &= Aa\left\{I+P^i+C_2S\left[C_1y_0^i(t)\right]\right\}-2ay_4^i(t)-a^2y_1^i(t)\\
\dot{y}_2^i(t) &= y_5^i(t)\\
\dot{y}_5^i(t) &= Bb\left\{C_4S\left[C_3y_0^i(t)\right]\right\}-2by_5^i(t)-b^2y_2^i(t)
\end{aligned}$$

Inter-compartment connectivity is defined by a homogeneous connectivity constant, R, representing coupling between different local populations. Previous neural mass models have employed nearest neighbour (David et al., 2005; Wendling et al., 2000, 2001) or distance dependent connectivity (Babajani-Feremi and Soltanian-Zadeh, 2010; Sotero et al., 2007), whereas neural field models couple via diffusion terms (Kim et al., 2009) or by distance dependent integration over the output of a spatially extended continuum (Kramer et al., 2005; Shusterman and Troy, 2008). Here we opt for a nearest neighbour connectivity scheme and so form larger systems as open ended chains in 1-d, and ultimately an open ended sheet in 2-d. In addition, we study an alternative connection scheme and, briefly, the impact of long-range connections on the dynamics but leave considerations of inhibitory coupling, more complex connection topology and the effect of different boundary conditions for future studies. The input to each population, P^i ($i=1,..,N$) is given by the weighted contribution of nearest neighbours, as shown below, where R indicates the strength of connectivity and δ_{ij} indicates the presence of connections:

$$P^i=\sum_{j=1}^{N}\delta_{ij}RS\left[y_1^j-y_2^j\right]$$

Model output for the i_{th} compartment is given by the net PSP on principal neurons in that compartment ($y_1^i-y_2^i$). Within the model a net post-synaptic potential (PSP) is transformed via the sigmoidal activation function $S[v]$ (Marreiros et al., 2008) into neuronal activity or firing rate:

$$S[v]=2e_0/(1+exp(r(v_0-v)));$$

The dynamics of a single mass in the standard parameter set suggested by Jansen and Rit (1995), has been previously explored (Grimbert and Faugeras, 2006; Jansen and Rit, 1995; Spiegler et al., 2010) and has a structure of particular interest for the study of epilepsy (Wendling et al., 2000), which we briefly review here. The bifurcation structure for changes in the input parameter, I, presents two branches, a lower branch, corresponding to relative quiescence (low firing output of principal cells) and an upper branch, corresponding to increased activity (high output of principal cells and oscillatory activity). When starting at the lower branch and increasing I, there is a saddle node on invariant circle bifurcation which eliminates the stable fixed point on the bottom branch. This bifurcation reveals a high amplitude limit cycle which has previously been used to model epileptic EEG spiking (Wendling et al., 2000). The upper branch is a saturated high output fixed point for high I and undergoes a Hopf bifurcation into a small-amplitude oscillation when I decreases. For intermediate I there is a region of bistability between the large limit cycle and the Hopf oscillation. Although the small-amplitude oscillation generated via Hopf bifurcations was originally used to represent the (background) alpha rhythm, we follow previous mass modelling studies of epileptic transitions (Breakspear et al., 2006; Marten et al., 2009; Wendling et al., 2000, 2002) and suggest the lower branch fixed point as a model for background activity. Therefore, in this framework, and with the connectivity structure defined above, we can study the spreading of epileptiform activity due to coupling in a spatially extended system.

In order to simplify the dynamics, we reduce the extent of bistability in the model by slightly increasing the internal connectivity parameter, C, from 135 to 140 (Grimbert and Faugeras, 2006). In this configuration, $I=50$ is chosen to represent the lower branch fixed point dynamics (henceforth referred to as "fixed point"). We summarise the values for system parameters in Table 1. The reader is referred to Grimbert and Faugeras (2006) and Spiegler et al. (2010) for a detailed examination of the single compartment model.

The presence of oscillations in large systems was determined by calculating the variance over time for the mean output over all compartments. A threshold of variance ≤ 0.0001 was found adequate to reliably distinguish fixed point from out of phase oscillations. The

length of transient responses to perturbation was found by comparing the mean output over all compartments 1 s before stimulus to the mean post stimulus. The length was given by the time taken to return to within 0.001 of the pre-stimulus mean value.

Two dimensional figures and corresponding supplementary movies are colour coded by amplitude on a blue to red scale, with deep blue representing the lowest amplitude. The resolution of these figures was improved by inserting additional compartments and interpolating over their values.

2.1. Model perturbations

The effect of stimulation was investigated by delivering a short, rectangular pulse in the input, I, to the EPSP input (of the principle neuron population) of a single compartment either at the centre of the system, or at different locations. Square wave pulses of duration 0.1 s were considered in this study, though the amplitude was varied. This follows previous investigations of the effects of stimulation on the dynamics of neural masses in the context of epilepsy (Adhikari et al., 2009; Suffczynski et al., 2004), and provides an abstract notion of the fact that stimulation introduces a local excitatory perturbation to the system. However, we note that, in experimental settings, bipolar stimulation is delivered via implanted electrodes (Valentín et al., 2002), with current flowing between anode and cathode and with strongest impact (highest current density) at the tip of an electrode. In addition, the action of direct stimulation is complex, and not completely understood, with excitation probably targeting axons rather than dendrites, remote effects (David et al., 2010) and also the possible activation of inhibitory neuronal populations. Thus, future studies will need to account for greater bio-physical detail of nervous tissue stimulation, for example as implemented in the models of Anderson et al. (2007, 2009). However, in the current study we focus on the macroscopic propagating activity due to a short time dependent "activation". In future, this principle might therefore extend to localised pharmacological stimulation, where the details of an applied electrical field would not need to be considered.

Propagation of activity to the extremes of a system was detected by whether the maximum of the EEG output variable in one of the compartments at the edge of the system exceeded a value of 2, which is above the range of output seen in non-oscillating compartments. The threshold stimuli to elicit such a response was found by sequentially incrementing the stimulus strength in successive simulations proceeding from the background fixed point.

3. Results

We explore the transition from background activity to abnormal spiking in progressively larger systems, beginning with two coupled compartments and moving onto one and two-dimensional spatially extended systems. In the penultimate subsection we investigate the effect of adding a spatial heterogeneity to a two dimensional system, simulating a patch of abnormal tissue in the epileptic brain. In the final subsection we relax the assumption of strict nearest-neighbour coupling and show how the current scheme can be extended to include long range connections.

Table 1
Parameter values used for all model output in this study.

Parameter	Description	Value
A	Average excitatory gain	3.25 mV (is varied)
B	Average fast inhibitory gain	22 mV (is varied)
a	Average excitatory time constant	$100\ s^{-1}$?
b	Average fast inhibitory time constant	$50\ s^{-1}$?
C, C_1, C_2 C_3, C_4	Connectivity constants	$C=140$, $C_1=C, C_2=0.8C$ $C3=C4=0.25C$
I	External input to pyramidal neurons	$I=50$
R	Matrix of connectivity constants	R is varied though is homogeneous.
v_0	Parameters of the sigmoid function	$v_0=6mV$
e_0, r		$e_0=2.5s^{-1}, r=0.56mV^{-1}$

3.1. Bifurcations and excitability in two coupled compartments

Each model compartment is representative of a salient cortical circuit with excitatory and inhibitory influences at the level of populations of neurons (for example a cortical column (Jansen and Rit, 1995; Mountcastle, 1997)) and is referred to as a neural mass. Thus the effect of excitatory connectivity between neural masses can be explored by connecting compartments in the model framework described in Methods. This introduces an additional parameter into the model, R, which represents the strength of excitatory influence between one neural mass and another. The effect of changes in this parameter on the model dynamics are explored in the bifurcation diagram of Fig. 1 (a) (for details on bifurcations in neural mass models see e.g. (Breakspear and Jirsa, 2007; Grimbert and Faugeras, 2006; Spiegler et al., 2010)).

The system of two coupled compartments shows fixed point behaviour for values up to $R=135$, which is characterised by a low (resting) activity of the neural mass. Between $R\approx135$ and $R\approx147$, there is a window of oscillatory activity which resembles the periodic spiking of a single compartment (see example time series in Fig. 1 (b)). The spiking frequency is variable and depends on the coupling strength; for $R=139$ it is around 1/s, but by $R=143$ the oscillation has a faster frequency of around 6/s and a slightly smaller amplitude (see example time series in Fig. 1 (c)). Beyond $R=148$, the system settles into a fixed point with permanent high activity of principal neurons in the neural mass.

In Fig. 1 (d) we demonstrate the excitability of this system of two coupled compartments by delivering a sub- or supra-threshold pulse stimulus to both compartments. This threshold response to stimulus defines excitability and it can be seen in the coupled compartment model over a large range of coupling strength, R. Interestingly, certain stimuli could also lead to a prolonged response in both compartments mediated by faster oscillations. An example of this behaviour is shown in Fig. 1 (e). The initial excitation is followed by a number of oscillations with small amplitude, but at an elevated level of excitation, before the return to basal activity. This indicates that the coupling of compartments creates complex transients due to the mixing of the two oscillatory modes present in the uncoupled system (c.f. the description in Methods).

3.2. Simple and complex propagating activity in one-dimension

The consequences of excitatory connectivity in larger systems of interacting neural masses, and its impact on the model's excitability, were explored by connecting 21 compartments in a nearest neighbour coupled chain. This provides a one-dimensional approximation to an extended region of cortical tissue. As in the previous section, the effect of varying strengths of connectivity between masses was examined as a function of the coupling strength, R. These results were additionally tested for stability by introducing a small heterogeneity (random distribution around the value given in Table 1) in each of the parameters in the first two compartments.

In this spatially extended system with $N=21$, the coupling strength required to produce sustained oscillatory activity is lower than in the two compartment case, as can be seen in the bifurcation diagram of Fig. 2 (a). In this case, the onset of oscillatory activity is at $R\approx68$, initially as regular propagating spikes, similar to those observed in Fig. 1 (b). For a small region, approximately $68\leq R\leq68.7$, this spiking solution is bistable with the background steady state.

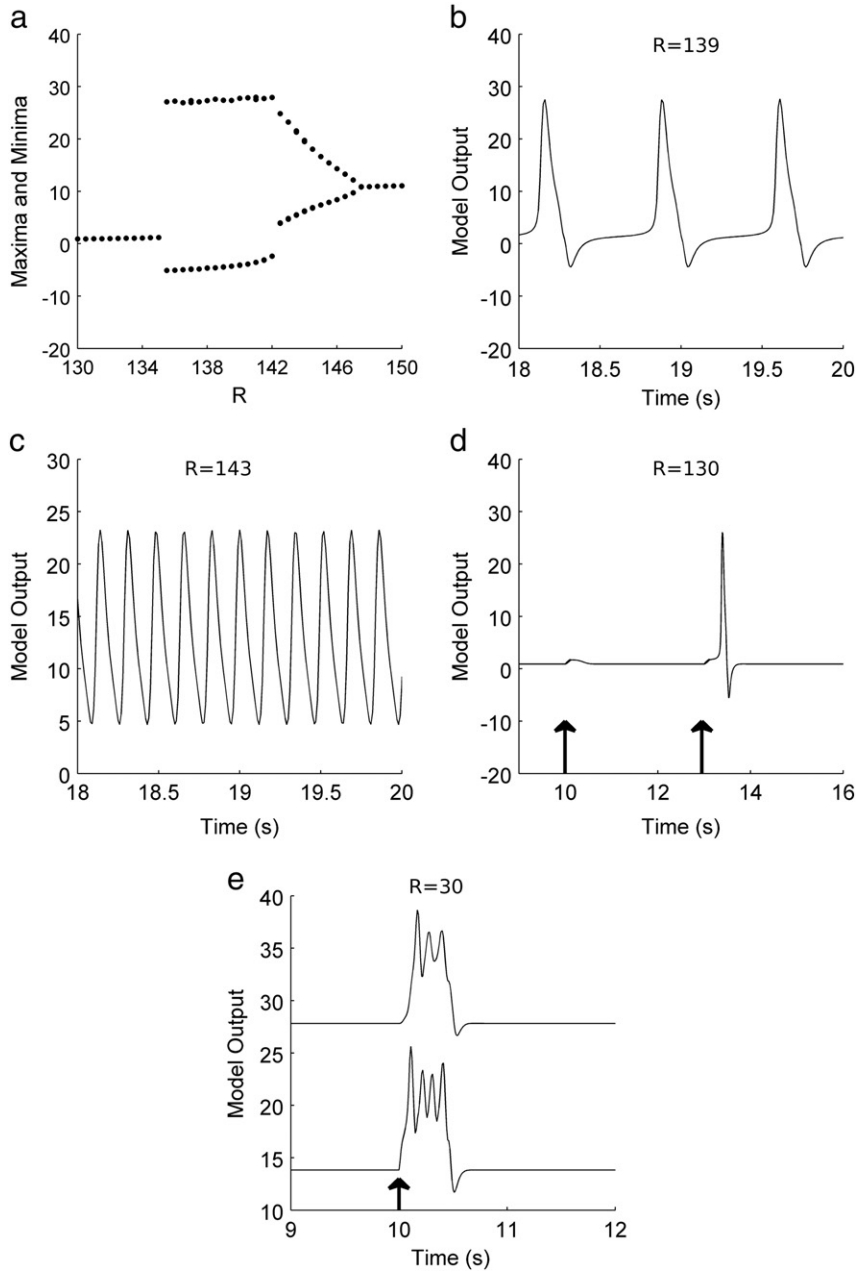

Fig. 1. Dynamics of two coupled compartments under changing connectivity strength. a) Bifurcation diagram for changing R. Maxima and minima for compartment 1 are shown. The dynamics of compartment 2 are equivalent. b) Spiking solution, $R=139$, c) faster oscillations, $R=143$, d) response to perturbation with $R=130$. Stimulus strength at t = 10 s is 62 and at t = 13 s is 62.5. e) Response to stimulus of strength 150 at t = 10 s, $R=30$. Timeseries in e) are plotted with an offset on the vertical axis. Arrows indicate stimulus times.

The simple spiking solution is replaced by complex oscillations for $70 \leq R \leq 74$, with reverberating activity across the range. An example of complex oscillations (henceforth referred to as "mixed oscillations") is shown in Fig. 2 (b).

It can be seen that activity is heterogeneous across the range apart from a brief refractory period which is conserved across all compartments. As R is increased within the region of mixed oscillations, these global refractory periods become more sparse. An important feature of this complex dynamic regime is that the spatial symmetry of the model is broken and a given variable varies in amplitude and phase at different locations for any given time point. Note that the spatially symmetric oscillatory state still exists as a solution when initiated in a spatially symmetric state (i.e. when all compartment and coupling parameters are identical). However, this solution is unstable and would therefore be unobservable under physiological conditions, where fluctuations are unavoidable.

As R increases beyond 70, the amplitude of oscillatory activity at the centre of the system becomes smaller until it appears saturated at high output, though until $R \approx 85$ there are oscillations at the periphery of the system, as can be seen in Fig. 2 (a). The region of bistability apparent in Fig. 2 (a) around $R=75$ is mediated by the amplitude of oscillations at the periphery. For $R \leq 72$ the periphery oscillates with spiking dynamics of variable amplitude. For $72 \leq R \leq 77$, the peripheral compartments are either both oscillating with high amplitude spikes, or one of them is oscillating at the smaller amplitude, faster oscillations, which give the lower amplitude maxima and minima seen in Fig. 2 (a). In the region $74 \leq R \leq 77$, the maxima and minima of oscillations at the periphery fluctuate less. An example of this activity is given in Fig. 2 (c), for $R=75$.

If the one dimensional system is set in the fixed point state a single stimulus to the model elicits a single propagating wave of activity, as shown in Fig. 2 (d), where the elicited spike propagates uniformly

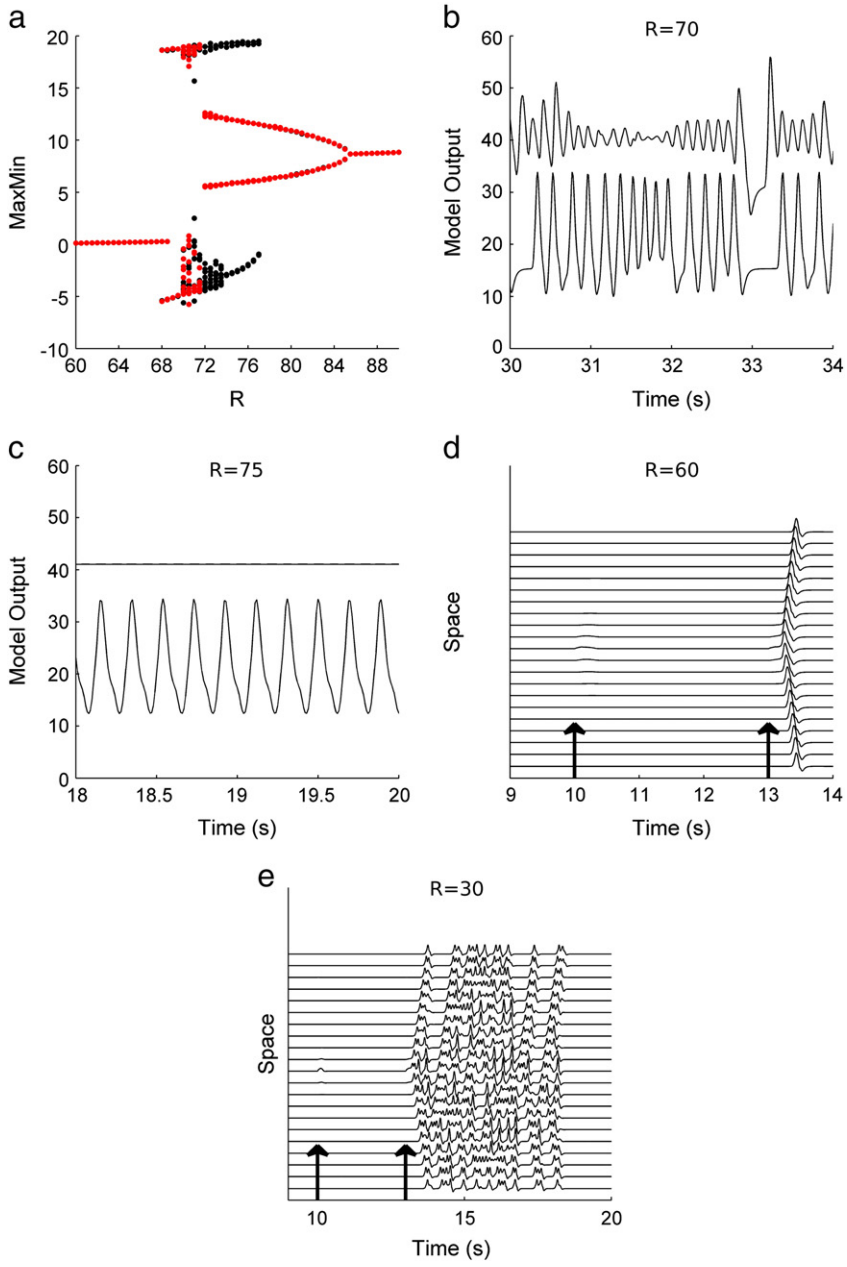

Fig. 2. Dynamics of 21 compartments coupled in a one dimensional chain. a) Bifurcation diagram for changing R (remaining parameters are default values as in Table 1). Maxima and minima are plotted for compartment 1 at the end of the chain. Forward scan is plotted in black, backwards scan is in red. b) Solution with mixed oscillations at $R=70$. Note the refractory period at t = 33. c) Solution with central saturation, $R=75$, d) response to perturbation with $R=60$, strength = 87 at t = 10 s and strength = 88 at t = 13 s, e) response to perturbation with $R=30$, strength = 120 at t = 10 s and strength = 121 at t = 13 s. In b and c, time series for the central compartment and a peripheral compartment (compartment 1) are plotted, with an offset on the vertical axis. Arrows indicate stimulus times.

from the central compartment to the periphery. If the system is prepared in the fixed point state near the onset of the periodically spiking solution, long initial transients of mixed oscillatory activity can be observed.

Over a large region of R (for example, $25 \leq R \leq 50$), a non-trivial response of the background, fixed point state to single perturbations was found for the system with $N=21$. An example of this behaviour is shown in Fig. 2 (e). The complexity is due to so-called "backfiring" (Bär et al., 1994) which occasionally sparks new propagating oscillations starting from locations other than the perturbed compartment.

As shown in Fig. 2 (d) and (e), propagation of activity depends upon the size of the stimulus to the central compartment, with an approximately all or none threshold for propagation. That is, the system can either show only a damped response with small amplitude in its neighbours, whilst leaving the periphery unaffected, or actively propagate high amplitude activity throughout the entire chain of compartments, with a sharp threshold for onset of propagation. Following previous in vitro experiments regarding the effect of changes in inhibitory and excitatory strength on propagation of activity in epileptic tissue (Pinto et al., 2005), we explored the effect of changes in excitation and inhibition on the stimulus threshold in our model. This was achieved by altering the gain parameters in the PSP equations, A and B, the results of which are documented in Fig. 3. It was found that, for fixed parameter B, decreased excitation leads to an increase in the stimulus intensity required to elicit a spreading response (Fig. (a)), whereas for constant A, decreasing inhibition has the reverse effect (Fig. 3 (b)). In the case of low inhibitory gain, propagation is of the form of the previously described complex transients as e.g. in

Fig. 2 (e), rather than simple wave propagation as e.g. in Fig. 2, (d). This latter result suggests that responses reminiscent of epileptic afterdischarges can be modelled in the spatially extended system with low inhibitory gain, whereas these reverberating responses to stimulus can be eliminated by increasing the inhibitory gain in the system.

Under the default parameter settings employed for the simulations in Fig. 2, increasing the size of the system causes the fixed point to become unstable and leads to permanent oscillations, due to reverberating, travelling activity. However, the lower steady state and the travelling wave response to stimulation can be recovered in larger systems by adjusting, for example, the inhibitory gain parameter, B. In the system with 21 compartments, increasing B shifts the onset of oscillatory activity to higher values of R (results not shown).

3.3. Propagating activity in two dimensional excitable media

The cortex can be approximated by a two-dimensional system of interacting neural masses if it is assumed that the vertical direction is redundant, as is the case when considering the local activity of neural masses (Mountcastle, 1997; Wilson and Cowan, 1973). This induces an additional spatial degree of freedom compared to the one-dimensional case, which must be investigated in model systems arranged in two-dimensions. Here, we examined these systems in a hexagonally arranged, nearest neighbour coupled scheme. The central compartments have 6 neighbours each, whereas the peripheral compartments have 3 neighbours.

We start with a model of one central compartment surrounded by 6 symmetrically coupled compartments, which represents the simplest such 2 dimensional configuration (c.f. the arrangement of grey hexagons in Fig. 8). The dynamics of this model of 7 coupled compartments are characterised by the bifurcation diagram in Fig. 4 (a). It can be seen that these dynamics follow a similar structure to those of the one dimensional chain, in that the fixed points are interrupted by a region of oscillations. However, the critical value for onset of oscillations is lower (compare Fig. 2 (a)) due to each compartment communicating with more neighbours and therefore receiving an increased net contribution for equivalent R.

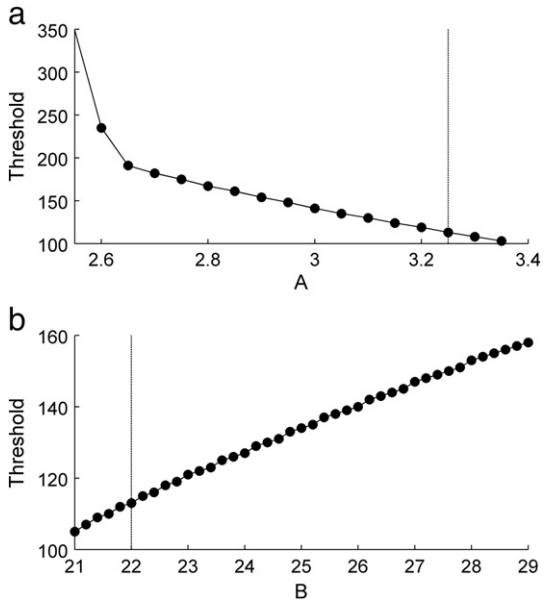

Fig. 3. Effect of changes in excitatory a) and inhibitory b) gain on the threshold required to propagate activity to the edge of the 21 compartment system. In a), $R=60$, $B=22$. In b), $R=60$, $A=3.25$. Vertical lines indicate previously used default values of these parameters (Jansen and Rit, 1995).

For $R\leq 32$ the fixed point background solution persists. At $R=32.5$, the system enters a region of bistability between fixed point and oscillatory dynamics. The oscillatory activity in this region is around 8 Hz, with phases distributed across the 7 compartments. Fig. 4 (b) shows that whilst the amplitude of the peripheral compartment can be relatively stable, the amplitudes in other compartments (here, the central compartment) may vary, leading to sub-harmonic components in the Fourier spectrum. Between $R=36$ and $R=40$, the system is in a region of bistability between large amplitude spiking activity, occurring at around 1 spike per second, and oscillations of smaller amplitude at around 8 Hz, with phases distributed across the 7 compartments. The dynamics of the former are shown in Fig. 4 (c), and the smaller amplitude oscillations are shown in Fig. 4 (d). The effect of increasing R beyond 40 was i) to bring into closer alignment the phases of the oscillations in the peripheral compartments, and ii) to produce an offset between the central compartment, which oscillated at a higher mean value, and the rest of the system, which oscillated around a lower mean.

A larger region of cortex was modelled by an extended two-dimensional sheet of connected model compartments. At the default value of $B=22$, low values of R in large two dimensional systems typically lead to sustained mixed oscillations. For example a 15×15 grid with $R=20$ outputs heterogeneous oscillations with apparent frequency components ranging from 5 to 10 per second and heterogeneous amplitudes and phases, somewhat reminiscent of mixed oscillations in the one dimensional case. As in the one dimensional case, these oscillations can be replaced by the fixed point solution if B is increased for a given coupling strength. In such a case, a stimulus applied to the system in the background fixed point can evoke a travelling wave, as shown in Fig. 5 (a) and (b). A movie of this response is given in supplementary file “SFigure5a.mp4”.

In contrast, at different values of coupling strength R, more complex responses can be observed, as seen in Fig. 5 (c) and (d). Here, the system is identical to that in Fig. 5 (a) and (b), but $R=35$, i.e. coupling is stronger. The initially induced wave activity evolves with a tail of higher amplitude compared to that observed for $R=20$, and causes the evolution of two subsequent travelling fronts. Collision of wave fronts then eliminates further activity leading to a total duration of around 1 s for this transient. A movie of this response is given in supplementary file "SFigure5c.mp4".

In addition to travelling waves, it is expected that a two dimensional excitable system can propagate spiral activity (see e.g. Winfree (2001)). Indeed, our two dimensional, excitable system is capable of generating complex spiral waveforms, as shown in Fig. 6 (a) and (b), for a $N=421$ square arrangement of hexagonally coupled compartments with $B=35$ and $R=50$. A movie of these dynamics is given in supplementary file “SFigure6.mp4”.

The effect of changes in inhibitory gain, B, and connection strength, R, on the dynamics of a cortical patch modelled by the 421 compartment system were explored with random initial conditions over different combinations of these two parameters. Fig. 7 (a) maps the presence of fixed point versus oscillatory dynamics and therefore indicates the region appropriate for examining stimulus induced transitions from the lower steady state. It can be seen that fixed point activity is generally found for extremely low or high B. The fixed point region to the left of the oscillatory band is saturated in a higher state, though peripheral compartments still oscillate for smaller R. The band to the right of the oscillatory region resides at the lower steady state and is therefore the starting point for the investigation of responses to stimuli.

The response to stimuli in the region of the lower steady state solution (white region to the right of Fig. 7 (a)) was found to vary depending upon the value of R and B, the effects of which are explored in Fig. 7 (b). Fig. 7 (b) is colour coded by length of activity evoked by stimulation, with darker colours indicating longer transients, and displays approximately three regions of differing activity.

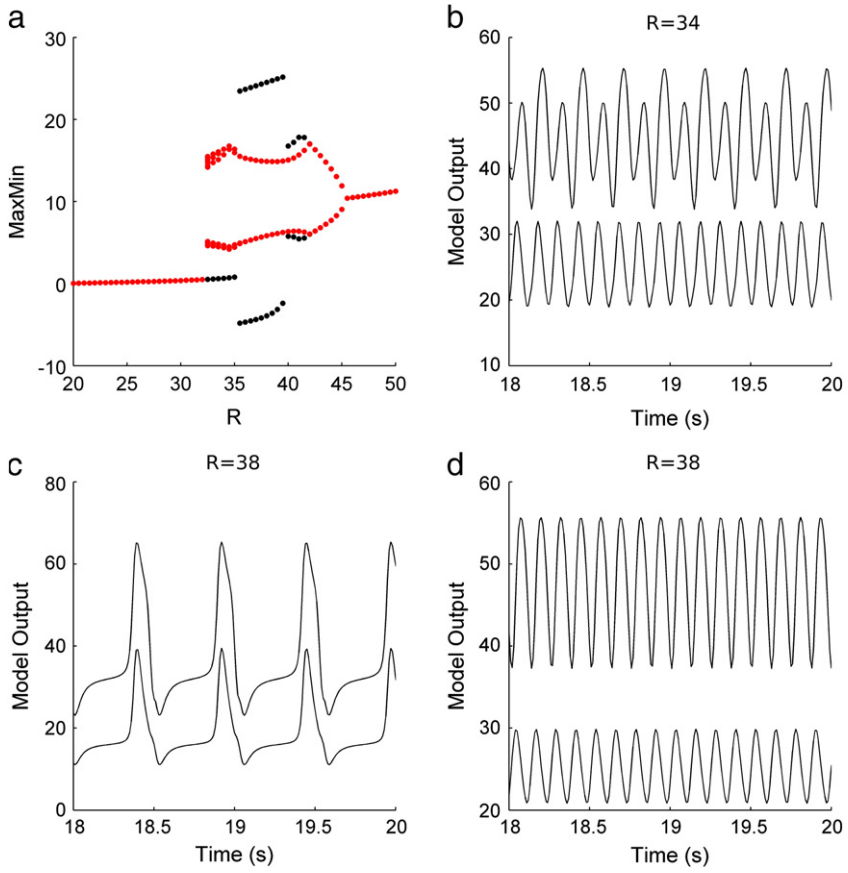

Fig. 4. Dynamics of 7 compartments with hexagonal nearest neighbour coupling. a) Bifurcation diagram for changing *R*. Maxima and minima are plotted for a peripheral compartment. The forward scan is plotted in black and the backward scan is plotted in red. b) Mixed oscillations at $R=34$, c) spiking solution at $R=38$, d) oscillatory solution at $R=38$. In b–d, time series for the central compartment and an outer compartment are plotted with an offset along the vertical axis.

In the very light grey region at the top right (approximately $R\leq 18$ and $B\geq 22$) stimuli evoke no travelling response and therefore the duration of the perturbation to model output is of the order of the length of stimulation. In the darker grey region (approximately $18\leq R\leq 40$ and $B\geq 25$), the stimulus evokes at least one travelling wave. In general, for constant *R*, the responses are more complex for smaller *B*, i.e. near the boundary of the oscillatory domain.

The darker squares within this region, including those coloured black, elicit more than one travelling wave or more complex responses. We note that the number of compartments stimulated, as well as their position in the system, affects activity post-stimulus. For instance, if stimulation of a single compartment does not elicit a response, the stimulation of multiple compartments occasionally can. The response of the system to stimulus at the centre and at the edge of the system is often not equivalent.

3.4. Reverberating activity in a stimulated model of heterogeneous cortex

It is expected that there are spatial heterogeneities in normal cortical tissue, as well as in the case of focal epilepsies. In particular, in cases of intractable epilepsy, often there exist deformations, such as dysplasias, which are capable of conveying abnormal activity (Fauser and Schulze-Bonhage, 2006; Fauser et al., 2009). In addition, a recent modelling study highlighted the importance of considering heterogeneity in a spatially extended neural mass model of epileptic dynamics (Goodfellow et al., 2011). We investigated the effect of spatial heterogeneities in cortical tissue by forming a two-dimensional extended system with a central region containing diminished inhibition. A 421 compartment system (21×21 hexagonally coupled compartments, i.e. with symmetry around the central compartment) was formed with $R=20$. In the central hexagon of 7 compartments, *B* was set to 22 ("disinhibited"), whereas in the surrounding compartments, *B* was set to 28 ("normal"). The layout of this system is illustrated in Fig. 8.

Following our previously described results, it might be expected that the surrounding tissue is more likely to propagate single waves, whereas the compartments of the centre might generate more complex oscillatory activity. From random initial conditions, the system was left to settle into a background fixed point, to which a stimulus was applied. The response to a stimulus of duration 0.1 s and size 300 applied to 8 different locations was investigated, with results shown in Figs. 9, 10 and 11.

Depending upon the location of the stimulus, the system can display different responses, consisting of i) a simple propagating wave (Fig. 9, (a)), ii) 2 waves propagating from the centre (Fig. 9, (b)) or iii) more complex and longer lasting transients (Fig. 9 (c, d, e)). In the latter case, the oscillatory waveform at each compartment is heterogeneous, similar to the results reported previously in evoked oscillations in cortical slices (Bai et al., 2006). Example spatial patterns for stimuli 1 (a) and 8 (e) are shown as snapshots in Fig. 10 (c) and (e), respectively. Movies showing these responses are given in supplementary files "SFigure10c.mp4" and "SFigure10e.mp4", respectively.

In order to compare this behaviour to observations from repetitive responses in humans, we must consider the size of the modelled system in relation to brain tissue. A previous whole brain model based on the neural mass framework employed a single compartment as a model for a voxel of diameter 1–3 mm (Sotero et al., 2007). These dimensions are in line with the original formulation of the neural mass model as a model for a cortical column (Jansen and Rit, 1995). Thus we proceed with the assumption that each compartment represents a

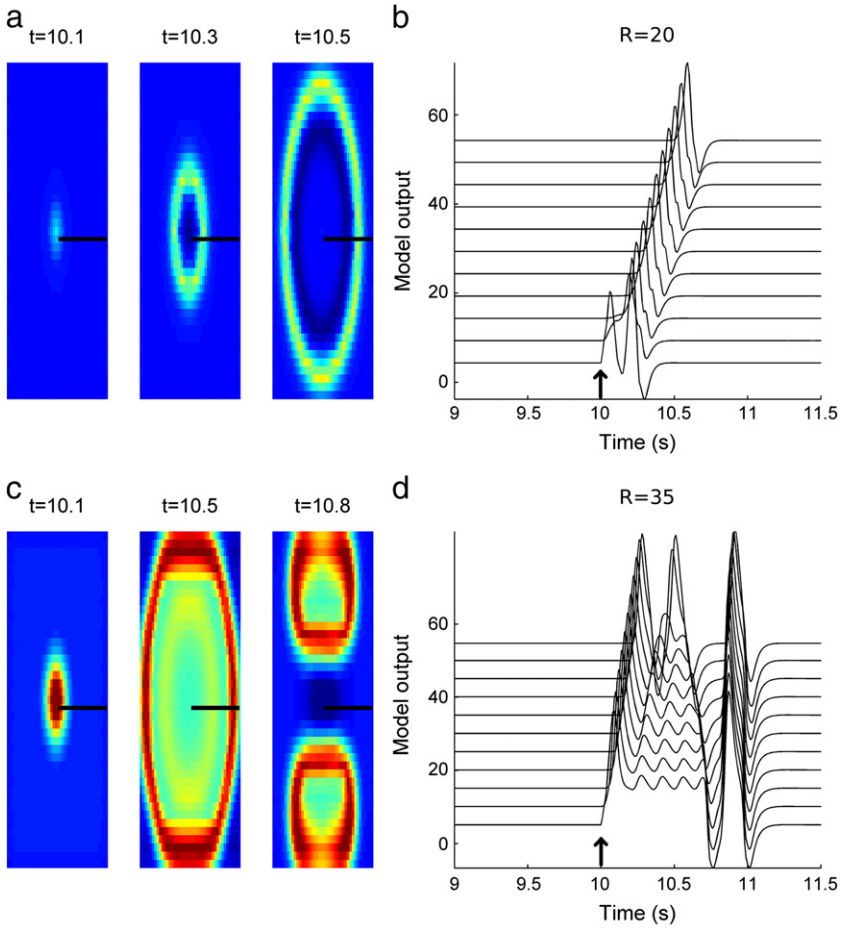

Fig. 5. The effect of perturbation to a central compartment in the two dimensional, homogeneous system. a) Snapshots of wave propagation due to stimulus, $R=20$ and $B=28$, at t = 10.1, 10.2 and 10.5 s The black line indicates a one dimensional projection for the time series plotted in b), which are plotted with an offset on the vertical axis. c) More complex transient due to stimulus, snapshots shown at t = 10.1, 10.5 and 10.8 s. $R=35$ and $B=28$, time series for compartments along the black line in c) are plotted in d) with an offset on the vertical axis. The duration of these responses can be seen in supplementary files "SFigure5a.mp4" and "SFigure5c.mp4", respectively.

1 mm diameter column, which implies a size of 421 mm^2 for the entire 421 compartment model. Each quadrant of this model can therefore be assumed to represent activity recorded by a single electrode of diameter 2.3 mm, separated by 10 mm, as used in (Valentín et al., 2002).

Fig. 10 (d) and (f) each show four mean field time series representing the averaged activity of each of the four corners of the heterogeneous system in Fig. 8 under stimuli 1 and 8, respectively. The mean field of the response of the heterogeneous system to stimulation 8 (see Fig. 8) shows a repeated series of irregular waves, as in the abnormal "repetitive response" described by Valentín et al. (2005) (Fig. 10 (f)). This is in contrast to activity propagated in the homogeneous system, the mean field of which is a single wave lasting approximately half a second, as observed in the "early response" presented in Valentín et al. (2005) (Fig. 10 (b)). For direct comparison, we re-create in Fig. 11 some features of the spatially varying response to perturbation observed in humans.

The time series of a mass adjacent to the stimulated compartment is shown for the homogeneous and heterogeneous cases in Fig. 12. It can be seen that in the case of simple single wave propagation, there is a strong hyperpolarisation immediately following the large amplitude spike, whereas in the case of the more complex transient, there are varying degrees of hyperpolarisation throughout the transient. We note that in the case of the heterogeneous model, the steady state of the compartments with reduced inhibition are at a higher level than those in the heterogeneous system. The depth of the hyperpolarisation in the heterogeneous compartment becomes closest to that of the homogeneous system only during the hyperpolarisation preceding termination of the oscillation.

3.5. Beyond nearest neighbour coupling

The model we presented is governed by nearest neighbour connectivity in order to examine the effect of transmission of neural mass spiking due to local connections. In this section we demonstrate how this assumption can be relaxed in order to investigate more complex connectivity patterns, which will be an important feature of future work. We note that in this section specific examples are provided to guide the reader in the ways that the model can be extended in future, rather than providing a thorough description of system dynamics, which will be left to future work.

Here, we persist with the notion that, at the level of connectivity between neuronal populations, connections to local regions predominate (Boucsein et al., 2011). This has been modelled in large scale neural mass formulations of brain connectivity by an exponential, distance dependent function (Jirsa and Haken, 1996; Sotero et al., 2007). In the model presented here, applying such a function smoothes the coupling to include contributions from beyond the first neighbour. Connectivity in this scheme is given by:

$$R_{ij} = r \cdot \frac{1}{2\sigma} e^{-\frac{|x_i - x_j|}{\sigma}}$$

where R_{ij} is the resulting connectivity between two compartments, r is a scaling factor common to all network edges, σ is a parameter determining the spatial extent of connectivity and x_i, x_j denote the

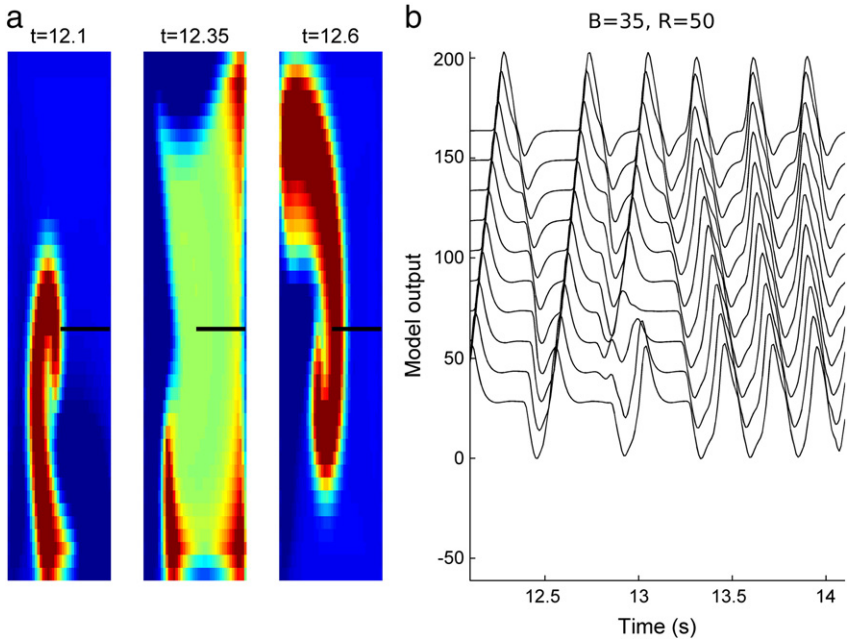

Fig. 6. Example of complex spiral waves in a system with $N=421$, $B=35$, $R=50$. Images in (a) represent t = 12.1, 12.35 and 12.6 s. Time series for the compartments along the black line in (a) are plotted in (b) with an offset along the vertical axis. A movie of these dynamics is provided in supplementary file "SFigure6.mp4".

position of nodes i and j in the square lattice. $|x_i - x_j|$ denotes the Euclidian distance given by:

$$\sqrt{\left(x_i(1)-x_j(1)\right)^2+\left(x_i(2)-x_j(2)\right)^2}$$

With this extended connectivity, the homogeneous system can display complex spatio-temporal patterns and also steady state dynamics depending on its parameters. For example $\sigma=0.5$ and $r=146$ leads to a fixed point in a square system of 31×31 compartments, and the evocation of a single travelling wave due to stimulation (data not shown). Adjusting σ leads to changes in the size of travelling wave fronts (as well as parameters required for steady state). Thus, in exploring the parameters of the model in future studies, one will need to consider the size of the system and its boundary conditions in relation to the variance of connectivity.

This extended coupling scheme also allows the study of additional long-range connectivity (Boucsein et al., 2011), since the propagation of activity is not dependent only on nearest neighbours. We demonstrate how the system might be used in the context of the current

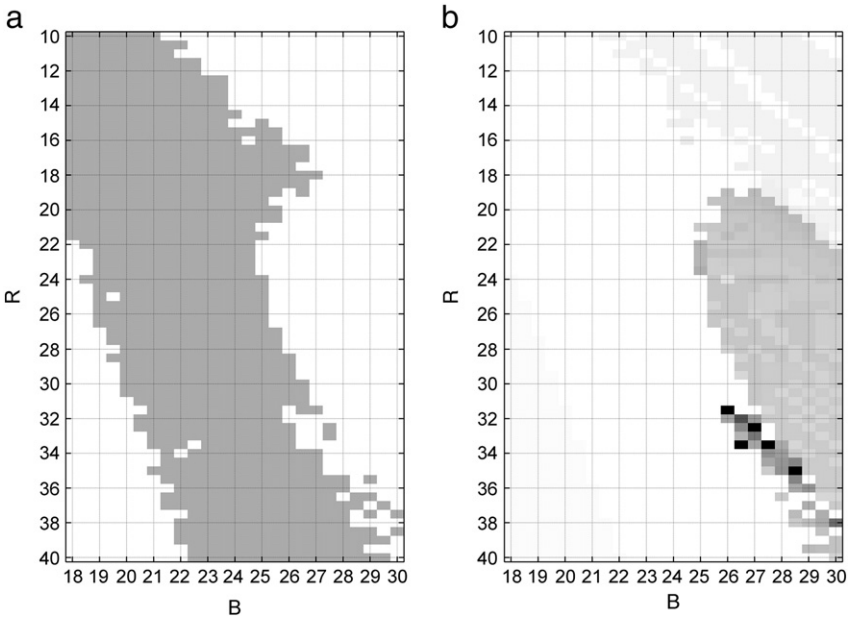

Fig. 7. Investigation of the dynamics and stimulus response of the homogeneous two dimensional system with $N=421$. a) Map of fixed point versus oscillatory dynamics over changes in B and R (other parameters are default values as in Table 1). Systems with fixed points are coloured white. The region of grey represents oscillatory dynamics. Fixed point solutions to the left of this region are at the high steady state, whereas those to the right are at the lower steady state. b) shows the length of response to stimulus, with the system initially in the lower steady state, and stimulus of strength 300 applied for 0.1 s to the central compartment. Darker colours indicate longer responses, with black representative of transients longer than 3 s. Very light grey squares in the top right corner indicate a response only in the stimulated compartment.

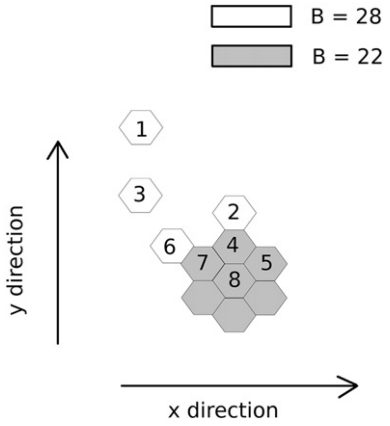

Fig. 8. Schematic of the heterogeneous system with a central hexagonal region of diminished inhibition. Also shown are the locations of 8 compartments which were subjected to a single pulse perturbation.

study by once again introducing a region of diminished inhibition at the centre of the system (here a 4×4 square). With $r=100.7$ the heterogeneous system settles into its steady state, in which stimulus response is space dependent (results not shown).

We now provide an initial demonstration of the capability to explore more complex connectivity patterns. The distance dependent connectivity was supplemented by randomly drawn long-range connections of strength equivalent to that connecting closest neighbours. This was achieved by first constructing the distance dependent adjacency matrix, then scanning over entries and adding connections with a specified probability. An image of the top left corner of the resulting connectivity matrix is given in Fig. 13 (a).

Interestingly, with $p=0.001$, the steady state, under the parameter settings previously employed, is often difficult to recover under random initial conditions. Thus, we can speculate that in this regime, the system is more likely to reside in an oscillatory state due to the distribution of connectivity. If long range connections are restricted to nodes outside this central region, the steady state can be more easily recovered from

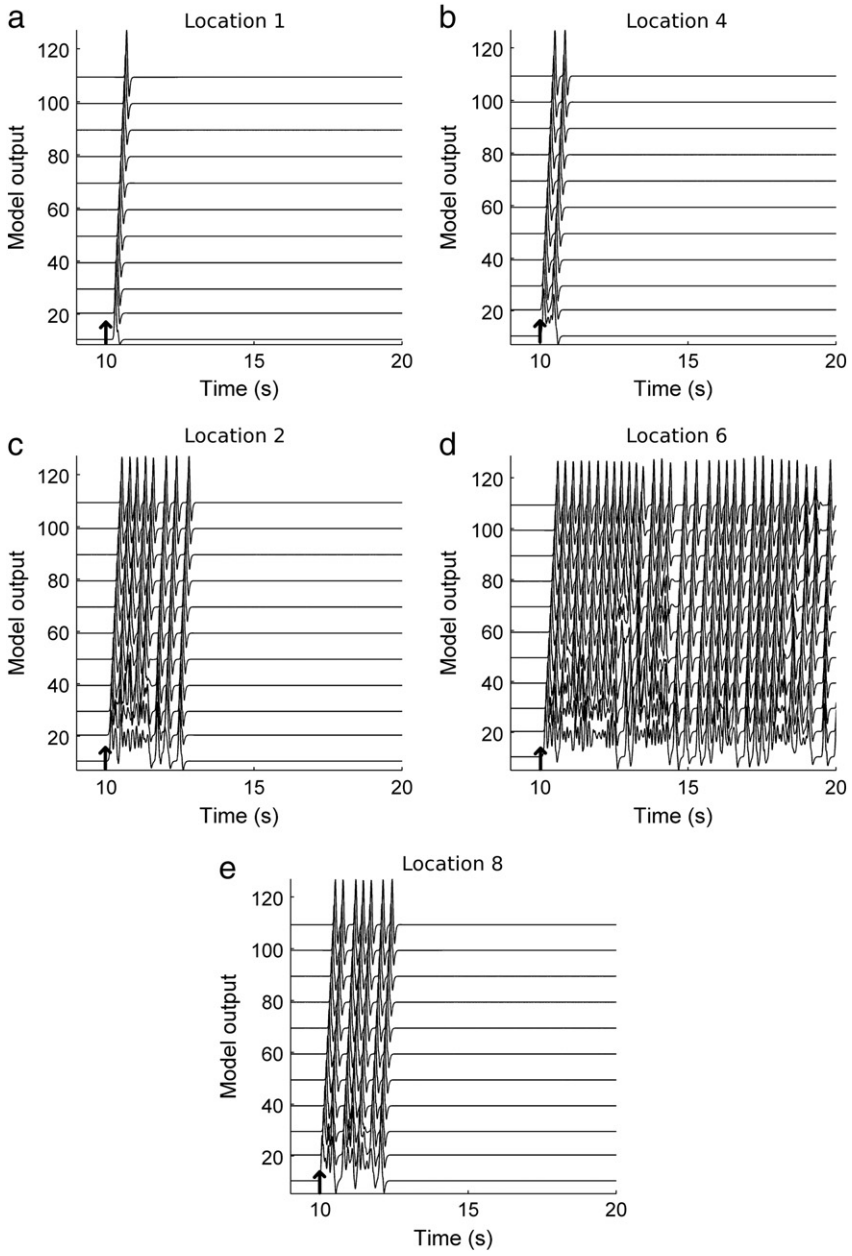

Fig. 9. Time series for response to stimulus at a selection of the different locations marked in Fig. 8. Shown are responses for positions 1 (a), 4 (b), 2 (c), 6 (d) and 8 (e) in Fig. 8. Time series are plotted with an offset on the vertical axis. Stimuli were delivered at 10 s for a duration of 0.1 s and with strength 300.

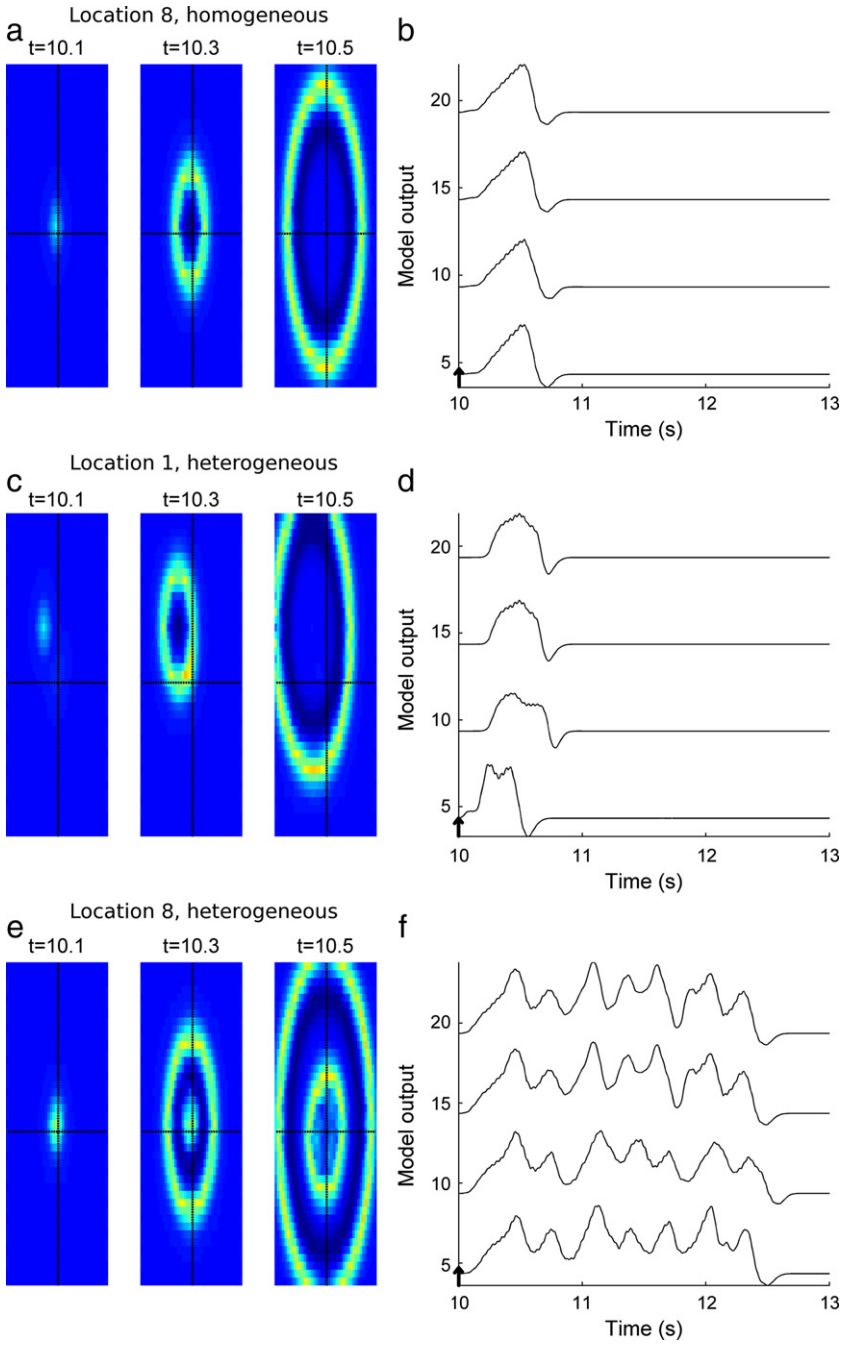

Fig. 10. Comparison of spatio-temporal patterns and model mean field in the case of wave propagation in the homogeneous system (a and b), stimulus 1 in the heterogeneous system (c and d) and stimulus 8 in the heterogeneous system (e and f) (see Fig. 8 for the location of these stimuli). The four channels in b), d) and f) represent averages of activity in the 4 corners of the system, indicated by broken black lines in (a, c, e). These are plotted with an offset on the vertical axis. Movies for the responses shown in c) and e) are given in supplementary files "SFigure10c.mp4" and "SFigure10e.mp4", respectively.

random initial conditions, and stimulating a central compartment elicits a prolonged reverberating response, as shown in Fig. 13 (b).

Interestingly, if the probability of long-range connectivity is increased to 0.002, the steady state is also recovered even when the central region is included in the long-range structure. In this case, the response to stimulation has interesting dynamics, with increased synchrony in bursting across the range. This response is shown in Fig. 13 (c).

4. Discussion

In this study we explored spatial extensions to a previously proposed neural mass model of epileptic spiking (Grimbert and Faugeras, 2006; Jansen and Rit, 1995; Spiegler et al., 2010; Wendling et al., 2000, 2001, 2002). It was demonstrated that this model, under the assumption of excitatory nearest neighbour connectivity, is an excitable system which can propagate activity induced in a single stimulated compartment. We found that the system could display complex reverberating responses to a single pulse perturbation and is therefore relevant to the mechanisms underlying macroscopic epileptiform responses in vitro (Pinto et al., 2005) as well as in the human brain (Flanagan et al., 2009; Valentín et al., 2002, 2005).

Specifically, we predict the existence of complex rhythmic responses in excitable media formed by interacting excitatory and inhibitory neural populations, as assumed for the neocortex. This is due to excitability in the vicinity of a saddle-node on limit cycle bifurcation and the (co-)existence of either a fast oscillation or a corresponding saddle-focus. We

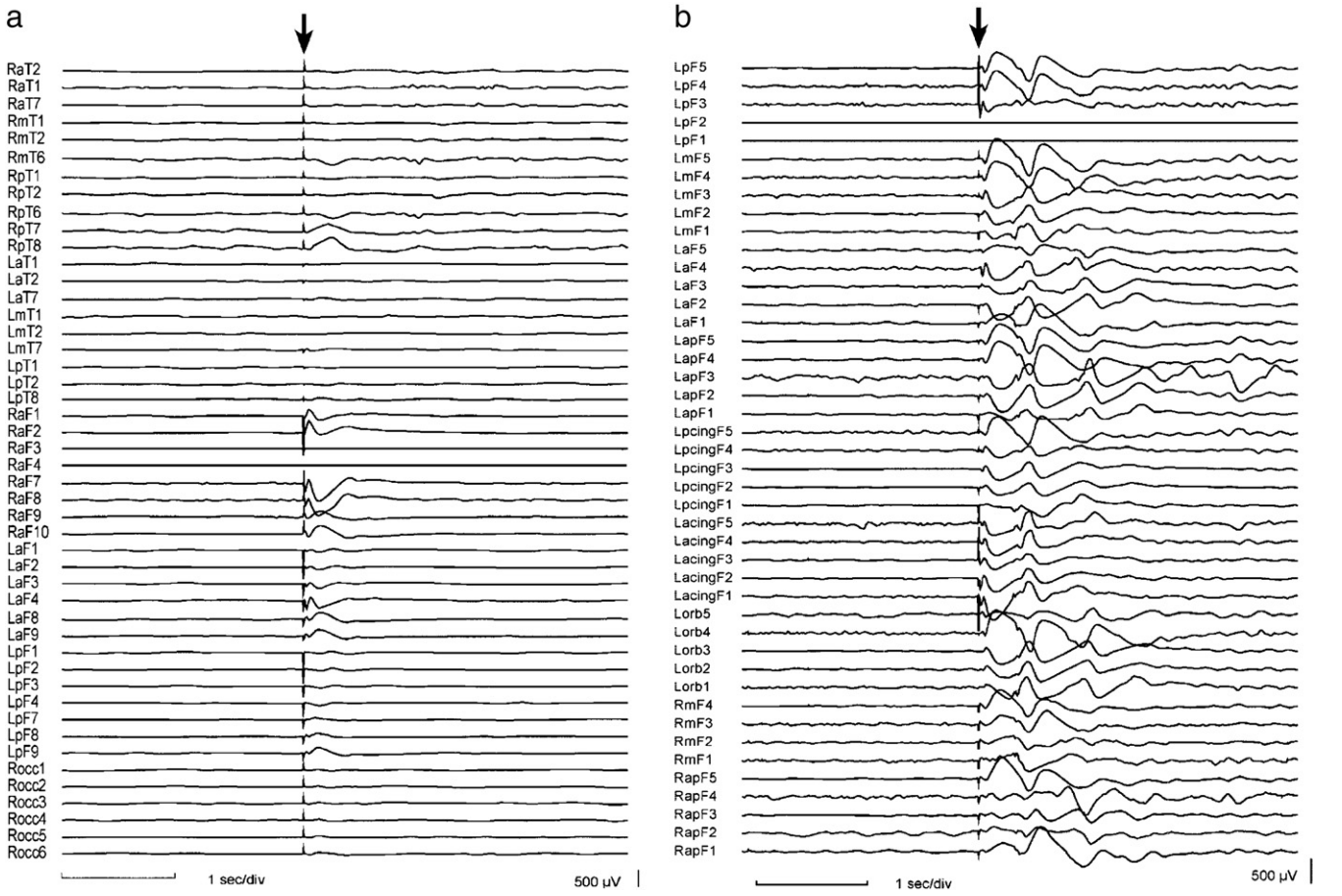

Fig. 11. Examples of (a) "early" and (b) "repetitive" responses observed in human tissue in response to single pulse perturbation. (a) Recreated from Valentín et al. (2005), Fig. 2A and (b) recreated from Valentín et al. (2005) Fig. 4A Valentín, A., Alarcón, G., García-Seoane, J.J., Lacruz, M.E., Nayak, S.D., Honavar, M., Selway, R.P., Binnie, C.D., Polkey, C.E., 2005. Single-pulse electrical stimulation identifies epileptogenic frontal cortex in the human brain. Neurology 65 (3), 426–435. A key feature in relation to the present modelling study is the difference in transient length due to single perturbation, which is space dependent in the epileptic brain. The repetitive response, seen in retrospectively determined epileptogenic tissue is a complex spatio-temporal transient.

demonstrate that this framework allows the investigation of the dynamic consequences of spatial heterogeneity and that this can result in the formation of long lasting rhythmic transients in response to single-pulse perturbations. This allows us to combine insight from smaller scale properties (cortical excitability) with macroscopic clinical observations to propose the specific hypothesis that long EEG transients derive from the spatially transmitted self-activation of regions of diminished inhibition.

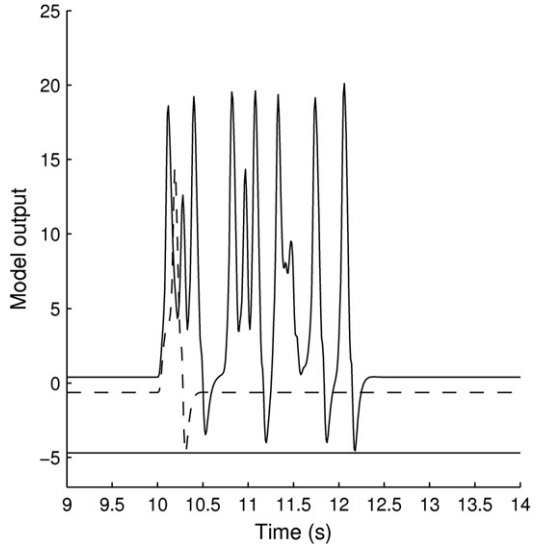

Fig. 12. Time series of a compartment adjacent to the stimulated electrode in the homogeneous system with propagating wave (dashed line, compare Figs. 9 (a) and 10 (a)) and the heterogeneous system with complex transient (solid line, compare Figs. 9 (e) and 10 (c)). The solid horizontal line indicates the minimum value reached by the homogeneous system.

4.1. Complex spatio-temporal responses to stimulation are underpinned by neural mass excitability

An important correlate of epileptiform activity at the *neuronal* level is the paroxysmal depolarising shift (PDS), characterised by an overt depolarisation of neurons (Elger and Speckmann, 1985; McCormick and Contreras, 2001). Certain epileptiform events on the EEG are caused by the synchronous activation of PDSs in local neuronal populations. Thus, at the level of the *neural mass*, we propose that the spiking dynamics observed in the neural mass model can be regarded as representative of locally synchronous paroxysmal depolarising shifts. Accordingly, the neural mass makes a transition from relative quiescence to a brief period of high activity, causing a spike in the output of the mass, with subsequent hyperpolarisation.

This framework assumes a resting state of the neural mass with a low output of principal neurons, which from the dynamical systems perspective is modelled by a fixed point. This state can be perturbed by surrounding tissue undergoing abnormal spiking, or stimulation delivered from an external source. The model of a fixed point at the level of the neural mass is a scheme often employed in models of the transition to epileptic activity (Breakspear et al., 2006; Marten et al., 2009; Wendling et al., 2000) and the apparently random nature of background EEG can be approximated by applying a time dependent

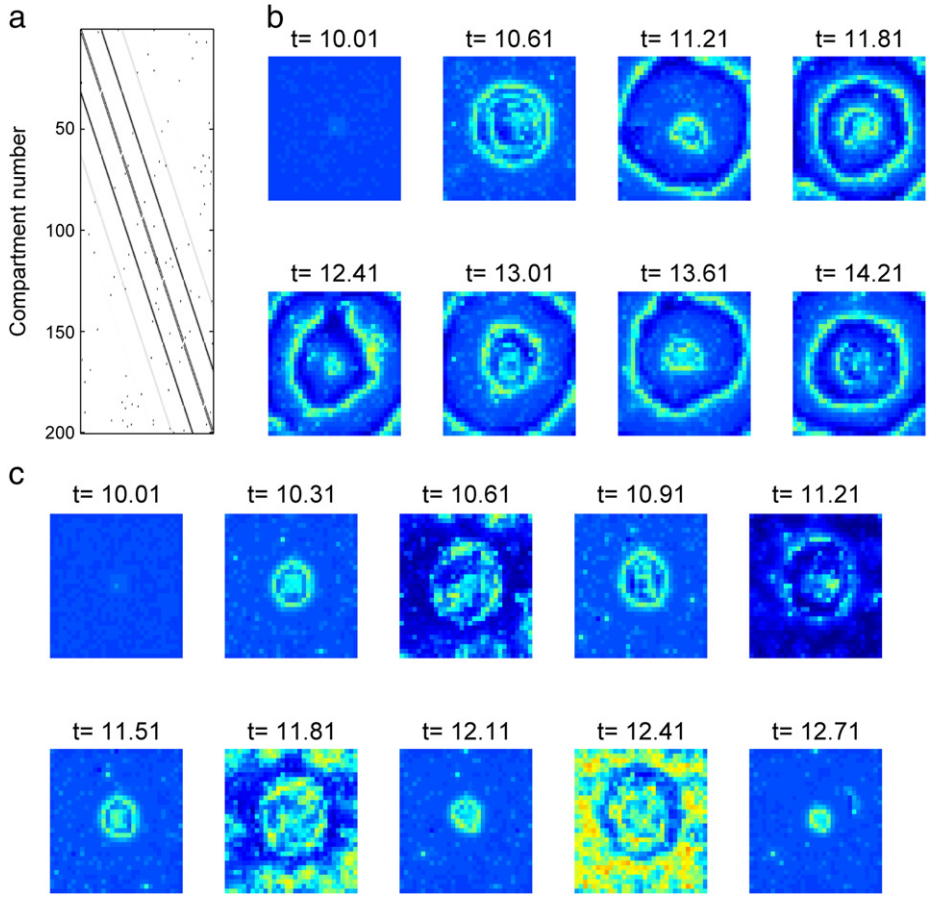

Fig. 13. Dynamics of a system with non-local connections. a) Shows the top left corner of the adjacency matrix (nodes 1 to 200) when $\sigma = 0.5$ and $p = 0.002$. Notice the scattering of long range connectivity in combination with distance dependent connectivity. b) Shows snapshots of the dynamics of the system with $\sigma = 0.5$, $r = 100.7$. In this case long range connectivity is restricted to nodes outside the central region of diminished inhibition. c) Shows snapshots of the same system, but with $p = 0.002$ and long range connectivity allowed also with the central region. See Section ***3.5***: Beyond nearest neighbour connectivity.

noise to the fixed point. Although it might be a reasonable assumption that, at the level of the neural mass in an asynchronous state, activity is averaged out and relatively quiescent, other models of non-quiescent background activity have also been proposed (Goodfellow et al., 2011; Shusterman and Troy, 2008). In order to better understand the nature of the production of epileptic rhythms in neural masses, the equations governing the dynamics of background EEG demand more attention in the future.

The response of epileptic tissue to local perturbations as well as the spontaneous initiation, spreading and termination of seizure activity are represented by transient spatio-temporal rhythms. Complex spatio-temporal transients have been described in excitable media (Jung and Mayer-Kress, 1995; Tel and Lai, 2008; Zimmermann et al., 1997) and we here specifically introduce a dynamic mechanism for the generation of rhythmic transients following a single-pulse stimulus as used in presurgical evaluation of epileptic neocortex. We find that a description at the macroscopic level requires excitatorily coupled spiking mass models. By considering spatially extended systems of population PDS, we offer a framework with which to investigate the transmission of abnormal activity over large regions of cortex, mediated by local, excitatory interactions. The role of these mechanisms in the spreading of epileptiform rhythms is an important unanswered question in epilepsy research (Elger and Speckmann, 1985).

4.2. Spatially extended models of rhythmic activity: benefits of the current model

Previous mathematical models have offered insight into the formation of spatio-temporal patterns and the spreading of activity in nervous tissue. Nervous tissue based excitable media have been demonstrated to be capable of producing propagating waves (Pinto and Ermentrout, 2001) and spiral dynamics (Huang et al., 2004; Laing, 2005), which are in line with experimental results (Bai et al., 2006; Chervin et al., 1988; Huang et al., 2004; Pinto et al., 2005; Schiff et al., 2007; Wu et al., 2008). Mathematical models have also been shown to propagate single and multiple travelling waves (Troy and Shusterman, 2007) or sustained synchronous responses to stimulation (Shusterman and Troy, 2008).

In addition to these disinhibited systems, cellular automata-like models have been used to investigate the spreading of activity. Kaiser et al. (2007), for example demonstrated that a hierarchical structure is capable of producing a critical state for the sustained transient propagation of activity in a network. Traub et al. (2010) presented a cellular automaton model for the appearance of patches of activity in relation to very fast oscillations observed in epileptic tissue. Examination of the activation of neuronal networks in epilepsy has also been addressed at the microscopic level of modelling, for example in the work of Lytton et al. (2008).

The model we present here, based on interconnected neural masses, provides several important advances compared to these previous models. First of all, it is important to address the mechanisms of clinical epileptic data at the macroscopic level (Goodfellow et al., 2011; Suffczynski et al., 2006; Wendling et al., 2000). By forming spatially extended systems at this level in the form of neural mass models, with physiologically interpretable parameters, the macroscopic propagation of activity, and its dependence on local excitatory and inhibitory processes (Wendling et al., 2000) as well as network interactions (Goodfellow et al., 2011) and heterogeneities can be explored. A key feature relating to the spreading or suppression of

epileptiform activity is the presence of local "surround" and "vertical" inhibition (Elger and Speckmann, 1985) and the modulation of inhibitory processes has been demonstrated to affect the ability of synchronous activities to form and spread (Trevelyan et al., 2006). It is therefore important to consider the role of inhibitory processes, which are preserved in the mass model presented in this study. The model might be extended to include inhibitory nearest neighbour connections, which, when diminished, might then support the spreading of activity, as suggested by (Trevelyan et al., 2006). The physiological interpretability of parameters in the mass model allow us to make more meaningful models of functional deficiencies, such as diminished inhibition, and assess their impact on network dynamics.

Another crucial aspect of the framework presented here is that we consider the transition into epileptiform rhythms as invoked spatio-temporal dynamic transients. This marks a shift in emphasis away from a time dependent modulation in system parameters (bifurcations) to explain epileptiform EEG (Breakspear et al., 2006; Kramer et al., 2005; Kim et al., 2009; Lopour and Szeri, 2010; Marten et al., 2009) and places more weight on the self-organising capabilities of spatio-temporal networks in the brain.

4.3. Network connectivity and dynamics

There is much work regarding network connectivity in neuronal tissue and its relation to epilepsy. Morgan and Soltesz (2008), for example, used a detailed neuronal model of the dentate gyrus to show that the inclusion of hubs in the connectivity network could lead to an enhanced susceptibility of the network to seizure activity. Hierarchical connectivities have been shown to be important for the spreading of activity (Kaiser et al., 2007). Though we focussed here initially on nearest neighbour connectivity and the properties of excitable media, we also demonstrated an extension of the system into more complex network structures through the addition of long range connections. The future investigation of stimulus response dynamics in the model framework presented here must consider different model connectivities. Indeed, our model framework will allow the investigation of the role that network connectivity plays in the formation of complex responses to stimuli at the macroscopic level, and in combination with spatially structured heterogeneities.

The incorporation of different connectivity structures, including hierarchical and long range connectivity, must be supplemented by considerations regarding time delays in transmission between different neuronal populations separated by increased distances in the brain. Several previous formulations of large scale brain dynamics in the neural mass framework have taken into account delays between compartments (Jansen and Rit, 1995; David et al., 2004; Sotero et al., 2007; Wendling et al., 2000). Indeed, the value of an explicitly modelled time delay has been shown to affect the frequency of rhythmic dynamics in a heterogeneous coupled neural mass model (David and Friston, 2003). Future investigations of the dynamics of the system presented here can incorporate transmission delays in the ODE framework by modelling delayed transmission as an additional temporal convolution, as proposed initially by Jansen and Rit (1995).

4.4. Local inhibition and excitation balance determines stimulus response dynamics in connected neural masses

Excitatory coupling induced new types of behaviour in the model composed of compartments set into a region of parameter space conferring fixed point dynamics. In the system composed of two compartments, for example, coupling led to spiking or faster oscillatory activity for certain values of coupling strength, R (see Fig. 1). In larger systems, the region of oscillatory activity for the default value of inhibitory gain, B, was extended, although the fixed point was recovered for increased inhibition. This is in agreement with the notion that a modulation of inhibitory processes is important for the generation of rhythmic activity in epileptic tissue.

Three important features of the experiment of Pinto et al. (2005) can be recreated by our model of stimulus response in brain tissue, namely i) the all or none response depending on the size of perturbation (Figs. 1 (d) and 2 (d)), ii) the dependence of this threshold on the regulation of excitatory and inhibitory activity in the slice (Fig. 3) and iii) the demonstration of simple waves or more complex activity (Figs. 2 (d,e), 5). Thus our model provides evidence for the generation of propagating activity due to proximal excitatory coupling in a model with threshold excitability. In addition, many aspects of our model are also in agreement with analyses of spatio-temporal patterns imaged by voltage sensitive dyes. In particular, the study of (Bai et al., 2006) reported the propagation of activity in a slice preparation with heterogeneous oscillations at different locations in the slice (see Fig. 7 A in Bai et al. (2006)). This is reminiscent of our model activity close to the disinhibited region during reverberating activity (see our Fig. 9 (e), bottom 2 traces). However, certain other observations cannot at present be recreated by our model, such as the potential delay, both temporally and spatially, from the onset of stimulation to the propagation of activity. Such effects have also been observed in humans (Lesser et al., 2008; Valentín et al., 2005). Future improvements to the model in terms of more complex spatial coupling may help to uncover potential mechanisms underlying these phenomena.

4.5. Modelling the implications of functionally heterogeneous regions: A hypothesis for the prolonged transient response to brief stimulation

The effect of introducing a localised region of diminished inhibition was the production of long and complex responses to perturbation (Figs. 9, 10 and 11), which on the mean field were reminiscent of repetitive responses seen in human recordings (Flanagan et al., 2009; Valentín et al., 2002, 2005). Our investigation of travelling wave and complex transient responses to pulse stimulation therefore lead us to the following mechanistic hypothesis for the formation of repetitive responses. Local neural masses capable of generating spiking responses are modelled by the bifurcation structure inherent to the Jansen model framework, i.e. the presence of excitability from a low output state to a high amplitude “spike” orbit (“population PDS”) due to a perturbation of the excitatory input (EPSP). These local masses are connected by nearest neighbour coupling. A spatially contiguous region of “reduced inhibition” within this system can then confer the capability to produce long lasting transient responses to short pulse perturbations due to i) a reverberation within the region of reduced inhibition; and ii) the propagation of non-trivial wave activity from this location, which can then break and cause subsequent activity. Cessation of these transients is autonomous and relies on the system propagating a trivial wave away from the region of reduced inhibition, thus causing no further reverberation.

Thus we provide a demonstration of the putative mechanism proposed by Valentín et al. (2005), i.e. a “re-entry of neuronal activity” after the initial stimulation. This is supported, in our model, by a local region of reduced inhibition. Thus we predict that the complex space varying, transient responses to perturbation seen in epileptic tissue derive from a spatially localised diminished inhibition. This prediction is open to experimental testing in vitro and comparison to human stimulus responses in the future, and suggests that in understanding the mechanisms of epileptic processes, one should investigate in neural mass models not only the properties of tissue at a single location, but also the effect of spatial variation on pathological dynamics. The use of mechanistic modelling of the stimulus response in heterogeneous, macroscopic systems may in future provide a valuable tool with which to specify the neurophysiological features of the epileptogenic zone in focal epilepsy, which is defined as the brain area that has to be removed to render a patient seizure free (Rosenow and Lüders, 2001). Comparison to clinical stimulus responses in pre-

surgical testing could then aid the localisation of the epileptogenic zone.

4.6. Modelling spatially dependent stimulus response dynamics

That single pulse perturbation might aid in the localisation of ictogenic tissue is of great interest clinically (Flanagan et al., 2009; Valentín et al., 2002, 2005), where resection of epileptic tissue is an important therapeutic option for pharmacologically intractable cases. However, the mechanisms for spatially heterogeneous responses that depend on distance from ictogenic tissue are unknown. Applying perturbations to different regions in our heterogeneous model suggest that a stimulation in and around the region of diminished inhibition can cause an "activation" of this region in terms of subsequent generation of long lasting transients (see Figs. 9, 10 and 11). On the other hand, stimulating further from this region elicited a simple travelling wave, which on passing through the diminished inhibition region did not spark prolonged activity. These contrasting dynamics displayed waveforms on the mean field similar to those of the "repetitive" and "normal" responses seen post-stimuli in humans with epilepsy (Flanagan et al., 2009; Valentín et al., 2002, 2005). Interestingly, stimulating a compartment directly adjacent to the region of diminished inhibition could evoke a longer transient than a stimulation inside this region (compare Fig. 9 (b) and (c)). This offers an initial demonstration of the potential mis-localisation of ictogenic cortex. Future investigation of the mechanisms underlying these phenomena in mathematical models may aid our understanding of the processes relevant to repetitive responses, and therefore inform as to what responses are expected from various locations around an ictogenic region. Assisting the processes of accurately identifying appropriate tissue for surgical resection must be a long term goal for modelling studies such as the one presented here.

The observed time varying response to stimulation (Lesser et al., 2008) suggests the possible involvement of *ictogenic* processes at a variety of different time scales. A more complete understanding of the processes underlying epileptiform activity would therefore consider, in models of epileptic tissue, the contribution of long term, *epileptogenic* processes as well as short time scale and longer time scale *ictogenic* processes. Such considerations might be appreciated in Fig. 7 (c) where the boundary between fixed point and oscillatory dynamics with respect to two of the system parameters can present regions of longer transient activity. In this kind of framework one might suggest that epileptogenicity presents the system with the capability to demonstrate such bifurcation structures, whereas ictogenicity presents a movement in this structure towards regions of oscillatory activity. In our model, as the system moves closer to the oscillatory region over *time*, longer transients due to stimulation can be observed.

However, we also showed in the heterogeneous system the effect of moving closer in *space* to an ictogenic region. In this way we demonstrated the potential importance of considering spatial heterogeneities in models of epileptic tissue, and therefore in the tissue itself. Indeed, it is known that spatial heterogeneities are associated with epileptogenicity. In models of post-trauma epilepsy, for example, it has been suggested that mechanisms leading to an enhancement of local excitatory connectivity (e.g. sprouting) or an impairment of inhibition (reduced effectiveness of inhibitory interneurons) are important epileptogenic processes (Prince et al., 2009). These mechanisms have been shown to contribute to the propagation of rhythmic activity in our model.

4.7. Perspectives on the measured speed of propagation of epileptic activity

The peak to peak time of transmission of spikes from one compartment to its neighbour in our two-dimensional system with $R=35$ was 0.02 s, which means that a distance of 1 mm between compartments gives a velocity of 0.05 ms^{-1}. This is of the same order of magnitude as that reported by, for example, Pinto et al. (2005) and Chervin et al. (1988). However, it is important to note that many different propagation velocities for travelling spiking activity have been reported in the literature. In addition to the aforementioned values, which were derived from slice experiments, Meeren et al. (2002) reported propagation velocities of 1 ms^{-1} in local field potentials recorded from epileptic activity in vivo. Kramer et al. (2005) reported speeds of 0.5 ms^{-1} in ECoG recordings from human epileptic seizures. The differences in these reported velocities raise several important points. The first point is with regards to the scale at which measurements of spatio-temporal patterns are made. In the study of Meeren et al. (2002), activity was recorded bilaterally in the cortex of WAG/Rij rats using 100 μm diameter electrodes separated by 2 mm. In the study of Kramer et al. (2005), ECoG recordings were made from electrodes with 2.3 mm exposed surface and with 10 mm spacing between discs. Thus, neither of these recordings allow to map the transmission of spiking activity between neighbouring cortical columns in the same way as the experiment of Pinto et al. (2005). In addition, we demonstrate in Fig. 10 that transmission velocities in an excitable medium may not be conserved across scale. The underlying travelling wave, when averaged at the macroscopic scale appears synchronous between the four electrodes due to the location of the initiation of the wave at the centre of the system. Further discrepancies relate to whether propagating activity is conserved between *in vivo* and chemically treated *in vitro* recordings, between spontaneous and evoked activity, and also by the different techniques used to measure time delays. Each of these issues will need to be studied in order to resolve the spatio-temporal mechanisms of responses to stimuli in nervous tissue in the future.

4.8. Outlook and conclusions

In addition, future work will be needed to more systematically clarify the dynamics of the system, for example in comprehensive bifurcation and sensitivity analyses. Sensitivity in the current context will be most informative if it relates stimulus response dynamics to changes in the structure of the system, the spatial distribution of heterogeneities and the location of stimulation relative to heterogeneities (i.e. when specifying the concept of the "epileptogenic zone"). It is anticipated that these will be some of the most prominent patient and experiment specific features. However, this raises a number of non-trivial and currently unexplored details, for instance the quantification of spatio-temporal dynamic transients, and methods by which to systematically evolve heterogeneous topologies and assess spatial patterns, parameter distributions and network connectivities. It is therefore expected that future investigations of systems such as the one presented here will require advances in the study of dynamical systems and their computational implementation.

In conclusion, we have demonstrated a spatially extended neural mass model of complex, self-terminating, transient responses to perturbation. The systems creating these responses are excitable media based upon the excitatory transmission of epileptic activity at the level of the neural mass. The model gives potential new insight into the creation of complex reverberating responses due to perturbation in epileptic tissue, the propagation of complex oscillations in in vitro preparations, and introduces new considerations regarding the spatio-temporal manifestations of epileptiform activity in the human brain.

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