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SCIENTIFIC COMMENTARIES
On the modelling of seizure dynamics

This scientific commentary refers to 'On the nature of seizure dynamics', by Jirsa et al. (doi:10.1093/brain/awu133).

In this issue of *Brain*, Jirsa and colleagues offer a masterful account of epilepsy that discloses the universal and invariant properties of seizure dynamics (Jirsa *et al.*, 2014). They derive a formal taxonomy of seizure activity from the basic principles of coupled dynamical systems. In brief, they show that a minimal model—comprising just five states or variables—is sufficient to describe the onset, time-course and offset of seizure activity. This may sound implausible; however, the repertoire of dynamics that coupled systems can generate may be much smaller than people imagine. In effect, Jirsa *et al.* use their understanding of dynamical systems to 'diagnose' the mathematical aetiology of the 'signs and symptoms' expressed in the statistics of seizure activity. Put simply, the existence of dissociable fast discharges and spike-wave events immediately tells them that the dynamics must be generated by two pairs of (hidden) coupled states generating fast and spike-wave oscillations, respectively. The fact that seizure activity waxes and wanes over a slower timescale then calls for a further slow permittivity variable that controls the expression of fast dynamics. Within this model, the onset and offset of seizure activity become well-defined mathematical objects: a saddle node and homoclinic bifurcation, respectively. The tell-tale signatures of these bifurcations were subsequently confirmed using *in vitro* experiments and focal seizures recorded in humans and zebrafish. So why is this important?

Without recourse to Wikipedia, I confess that I could not explain the difference between a saddle node and homoclinic bifurcation. However, this is not important: the authors have done all the mathematical heavy lifting for us and bring three things to the table: first, the notion that seizure onset (and offset) can be cast in terms of bifurcations (qualitative changes in dynamics) that are induced by changing the parameters of a coupled dynamical system—such as synaptic efficacy in neuronal microcircuits. Second, the attending qualitative changes rest upon a separation of temporal scales. For example, slow fluctuations in synaptic efficacy induce qualitative changes in fast dynamics. Finally, there is an inherent circular causality in epileptogenesis; whereby slow fluctuations in synaptic efficacy cause changes in fast neuronal activity—that couple back to the slow variables through processes such as activity-dependent plasticity. This circular causality is a necessary aspect of coupling variables that fluctuate over separable timescales. It is interesting to note that these fundamentals of

dynamical systems are formally articulated in synergetics—an approach to self-organization pioneered by the first author's mentor Herman Haken (Haken, 1983). In short, what is on offer here is a canonical description of seizure activity that has all the necessary ingredients for a formal taxonomy of seizure dynamics. But how does a mathematical taxonomy reach beyond phenomenology?

At this point, we have to consider why the modelling of seizure dynamics is potentially important. In previous years, there have been substantial advances in the use of models of neuronal microcircuits as forward or generative models of observed electrophysiological responses. This is most evident in the advent of dynamic causal modelling, which is now used routinely to address questions about functional brain architectures—and their synaptic underpinnings—in cognitive and systems neuroscience. The key thing here is that dynamic causal models are not just used to reproduce the phenomenology of electrophysiological measurements: they explain empirical data through Bayesian model inversion and subsequent selection. A formal understanding of how seizure dynamics are generated could therefore provide vital constraints on dynamic causal models of seizure activity. In principle, this means that one could identify the biophysical substrates of slow and fast variables in phenomenological models.

A brief history of epilepsy models

The generative mechanisms underlying seizure activity have been modelled extensively; particularly in neocortical and hippocampal systems. A recurring theme in these studies is the interaction between excitatory pyramidal cells and inhibitory interneurons. This speaks to the central role of intrinsic connectivity in maintaining excitation-inhibition balance. The intracellular and extracellular mechanisms underlying slow changes in synaptic efficacy have been the subject of much study. For example, Wendling *et al.* (2005) model seizure onset in terms of slow ensemble dynamics involving pyramidal cells and local interneurons, highlighting the increases in excitability and decreases in slow dendritic and fast synaptic inhibition that peak at seizure onset. The emerging picture from these studies points to slow changes in the excitability of cortical and subcortical microcircuits mediated by interactions between pyramidal cells and inhibitory interneurons. Slow fluctuations—and associated extracellular increases in potassium and decreases in calcium ion concentration—cause, and are

caused by, the fast fluctuations in synaptic activity that announce seizure onset. Indeed, Nevado-Holgado et al. (2012) have characterized the evolution of seizure activity as a path through the parameter space of a neural mass model, whereas Hocepied et al. (2013) consider a similar formulation for seizure detection. But how can we test these hypotheses—or indeed quantify synaptic variables in a given patient at a given point in time? Here, we turn to dynamic causal modelling.

Dynamic causal modelling of seizure dynamics

Dynamic causal modelling (DCM) is a biophysically informed framework for comparing hypotheses or network models of (neuro-physiological) time series. It is an established procedure in the analysis of functional magnetic resonance time series and is now used increasingly in electrophysiology. DCM rests upon the fact that there is a straightforward mapping between the synaptic connectivity of neuronal circuits and their responses to exogenous or endogenous neuronal input. In some cases, this mapping can be remarkably direct and intuitive (see Fig. 1 for an example).

There is an extensive literature on DCM ranging from face validation studies (David et al., 2006) to construct validation in terms of multimodal measurements and pharmacological manipulations (Moran et al., 2011). Crucially, DCM is now finding a role in understanding pathophysiology in terms of extrinsic (long range) disconnections (Boly et al., 2011) and aberrant intrinsic (local) connectivity that may underlie pathological (beta) oscillations in Parkinson's disease (Marreiros et al., 2012). The hope here is that DCM can be used to quantify slow fluctuations in synaptic efficacy in epilepsy—and perhaps to predict seizure onset. The promise for modelling seizure dynamics is illustrated in Fig. 2.

This figure shows the spectral responses of a canonical microcircuit as a function of intrinsic connectivity; namely, the recurrent self-inhibition of superficial pyramidal cells. This simple manipulation leads to fast epileptiform activity as the system approaches a (transcritical) bifurcation—and is motivated easily by the convergent evidence implicating fast synaptic inhibition in the context of recurrent coupling between pyramidal cells and inhibitory inter-neurons (see above).

The power of DCM lies in its ability to adjudicate among different mechanistic hypotheses using Bayesian model selection. For example, David et al. (2008) analysed seizure activity elicited during electrical stimulation. Bayesian model comparison suggested that seizure onset could be modelled in terms of changes in intrinsic connectivity (as opposed to extrinsic connectivity). Furthermore, DCM identified fluctuations in synaptic efficacy in the ictal zone; suggesting that the mesial temporal lobe epilepsy studied by David et al. (2008) could be explained in terms of a pre-ictal increase in sensitivity to hippocampal afferents from the temporal pole.

Conclusion

This sort of study provides proof-of-principle that the functional anatomy of epilepsy can be characterized in single subjects. If Jirsa et al. are correct; the universal anatomy of seizure dynamics—and associated neural mass models—suggests that we are in a position to create universal models of seizure activity. However, there is one outstanding challenge: a key insight afforded by Jirsa et al. is the circular causality of seizure dynamics. Currently, dynamic causal models only consider the enslaving of fast variables by slow variables but not vice versa. The approach of Jirsa et al. may provide formal constraints on how fast synaptic activity

$$g(\omega) = \frac{1}{(\omega - \beta)^2 + \alpha^2}$$
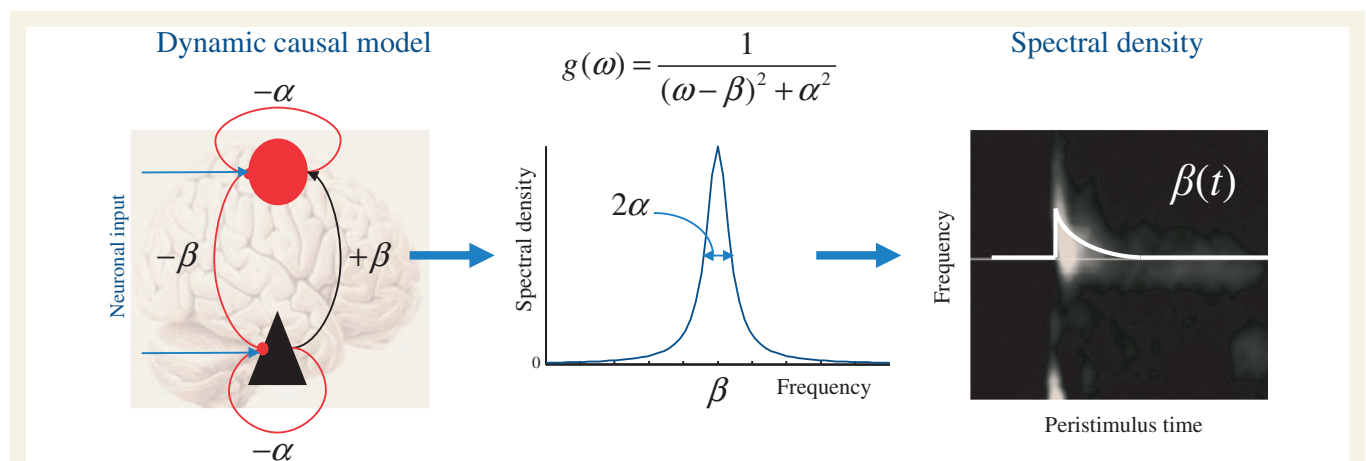
Figure 1 This schematic illustrates the mapping between the (synaptic efficacy) parameters of a dynamic causal model and their spectral signatures. *Left*: A simple dynamic causal model of recurrently and reciprocally coupled excitatory (black) and inhibitory (red) neuronal populations. *Middle*: The corresponding spectral responses under linear coupling. The equation (based on standard dynamical systems theory) shows that the (Lorentzian) spectral density function of frequency (ω) is centred on the connection strength of reciprocal connections (β), while the dispersion (full width at half maximum) of the spectral peak is determined by recurrent connection strengths (α). Connection strengths are naturally converted into frequencies because (in dynamical models) connections are measured in hertz—and therefore play the role of rate constants. *Right*: Time-dependent changes in the spectral peak therefore reflect changes in the strength of intrinsic (reciprocal) connectivity.
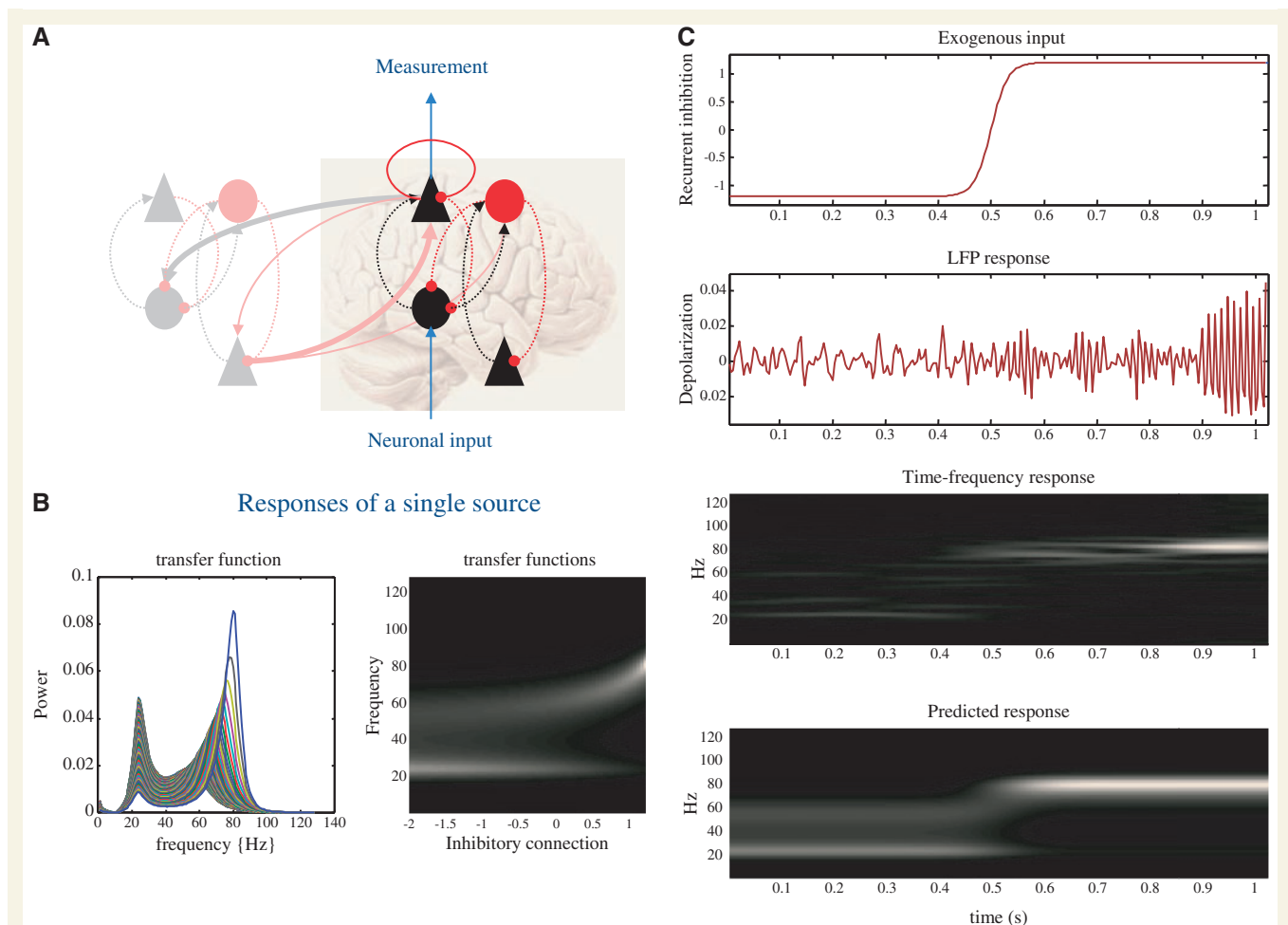
Figure 2 (**A**) A simple two source architecture with the (four) populations of a single source highlighted. The intrinsic connectivity (dotted lines) and extrinsic connectivity (solid lines) conform to a canonical microcircuit and the known laminar specificity of extrinsic connections. Excitatory connections are in red and inhibitory connections are in black. Endogenous fluctuations drive the input cells and measurements are based on the depolarization of superficial pyramidal cells. (**B**) These summarize the response characteristics of a single source in terms of the impulse response in frequency space, shown graphically (*left*) and in image format (*right*). These are (modulation) transfer functions of (the log scaling of) recurrent inhibitory connectivity (solid red line in the microcircuit). (**C**) These panels illustrate changes in neuronal activity when increasing recurrent inhibition. The *top* panel shows the strength of recurrent inhibition as a function of time, while the second panel shows a simulated response obtained by integrating the neural mass model on the left with random fluctuating inputs. The empirical time frequency is shown below in terms of the spectral power over 1 to 128 Hz. The *lower* panel shows the predicted response based upon the transfer functions in **B**. LFP = local field potential.

couples back to slow changes in synaptic efficacy; in other words, the induction of activity-dependent plasticity by fast dynamics. One hopes that modelling this key link will attract further attention over the years to come.

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Calcium currents regulate dopamine autoreceptors

This scientific commentary refers to 'Ca$_v$1.3 channels control D2 autoreceptor responses via NCS1 in substantia nigra dopamine neurons' by Dragicevic et al. (doi:10.1093/brain/awu131).

Appropriate activity of substantia nigra dopamine neurons is required for proper motor function, habit formation and motivation, and degeneration of these neurons in Parkinson's disease leads to disrupted control of voluntary movement. In this issue of *Brain*, Dragicevic *et al*. unite two previously separate lines of research on the regulation of substantia nigra dopamine neuron activity—one based on L-type calcium channels and the other on D2 autoreceptors—and suggest that these mechanisms converge in a previously unsuspected way in Parkinson's disease (Dragicevic *et al*., 2014).

One of the two lines of research stems from decades of work to define how the activity of midbrain dopamine neurons is controlled. These neurons alternate between a relatively slow, baseline, pacemaking activity (∼4 Hz) that presumably supplies the striatum with tonic low levels of extracellular dopamine, and bursts of activity of variable duration and only slightly higher frequency (∼15 Hz) (Grace *et al*., 2007). The resulting 'bandwidth' is not large: in contrast, activities of cortical output neurons can range from silent states to firing at frequencies of 20 Hz or more. While questions such as how salient sensory stimuli cause bursting are active areas of research, the pacemaking activity—which is autonomous, occurring even in cultured substantia nigra neurons—is fairly well elucidated, albeit subject to continuing elaboration in papers such as the one being discussed here.

In contrast to most other tonically active CNS neurons, which depend on monovalent cation channels to generate spontaneous action potentials, depolarization of mature pacemaking substantia nigra dopamine neurons may involve the opening of L-type calcium Ca$_v$1.3 channels, together with hyperpolarization-activated, cyclic nucleotide-gated (HCN) sodium channels (Puopolo *et al*., 2013). The large calcium conductance through Ca$_v$1.3 channels has been suggested to underlie the specific vulnerability of substantia nigra (as well as locus coeruleus and dorsal motor nucleus of the vagus) neurons to cell death in Parkinson's disease (Surmeier and Schumacker, 2013). These neurons, moreover, exhibit wide action potentials (>2 ms), giving rise to further calcium entry via voltage-activated channels in the interspike interval (Puopolo *et al*., 2013). Substantia nigra dopamine neurons also

lack significant calcium buffering by proteins such as parvalbumin and calbindin—the latter of which is more highly expressed in ventral tegmental area dopamine neurons, which are relatively spared in Parkinson's disease.

Studies by James Surmeier and collaborators demonstrate that the high intracellular calcium load in substantia nigra dopamine neurons causes mitochondrial and oxidative stress, and others have provided evidence that high calcium can exacerbate neurodegeneration through the accumulation of neurotoxic levels of cytosolic catecholamines (Mosharov *et al*., 2009). Inhibition of L-type calcium channels with dihydropyridines protects substantia nigra pars compacta neurons against neurotoxins associated with Parkinson's disease in a variety of animal studies (Surmeier and Schumacker, 2013). These data suggest that inhibition of Ca$_v$1.3 channel activity may be neuroprotective for the remaining substantia nigra pars compacta neurons in patients with Parkinson's disease, and isradipine, a dihydropyridine L-type calcium channel blocker shown to be effective in mouse models of the disorder, is currently in a clinical trial as a Parkinson's disease therapy (Parkinson Study Group, 2013).

The second line of research extends from the study of dopamine receptor-mediated auto-inhibition of neuronal activity. In substantia nigra neurons, this is mediated by D2-type receptors, which activate G protein coupled potassium channels (GIRKs) that hyperpolarize neurons and block cell firing (Lacey *et al*., 1987). The response of substantia nigra neurons to dopamine is highly regulated, with chronic loss of dopamine leading to receptor sensitization (Schultz and Ungerstedt, 1978), a phenomenon strongly implicated in Parkinson's disease and its animal models. Work by John Williams and collaborators has shown that somatodendritic dopamine release drives rapid D2 receptor-mediated hyperpolarization of neighbouring dopaminergic neurons (Beckstead *et al*., 2004). It may be, therefore, that dopamine autoreceptor activation inhibits the voltage and activity-dependent calcium-mediated stress associated with Parkinson's disease, and it is further possible that this is another advantage of clinical treatment with L-DOPA and dopamine agonists, although this has not been directly addressed.

In their new study, Dragicevic *et al*. connect these two lines of research by demonstrating that L-type calcium channels can promote D2 receptor function in juvenile substantia nigra pars compacta dopamine neurons (in contrast to the above D2