SpringerLink Header: Epilepsy (CW Bazil, Section Editor)

Seizure Prediction: Science Fiction or Soon to Become Reality?

Dean R. Freestone[1,2,#], Philippa J. Karoly[1,3], Andre D. H. Peterson[1], Levin Kuhlmann[3], Alan Lai[3], Farhad Goodarzy[3], and Mark J. Cook[1,#]

1. Department of Medicine, St. Vincent's Hospital Melbourne, The University of Melbourne, Fitzroy, Victoria, Australia, 3065.
2. Department of Statistics, Columbia University, New York, New York, USA, 10027.
3. Department of Electrical and Electronic Engineering, The University of Melbourne, Parkville, Victoria, Australia, 3000.

Corresponding authors: Dr Dean Freestone, email: deanrf@unimelb.edu.au, telephone: +61 400 013 949, fax: +61 3 9347 6136; Prof Mark Cook, email: markcook@unimelb.edu.au, telephone: +61 3 9288 3340, fax: +61 3 9347 6136.

Abstract: This review highlights recent developments in the field of epileptic seizure prediction. We argue that seizure prediction is possible; however, most previous attempts have used data with an insufficient amount of information to solve the problem. The review discusses four methods for gaining more information above standard clinical electrophysiological recordings. We first discuss developments in obtaining long-term data that enables better characterisation of signal features and trends. Then we discuss the usage of electrical stimulation to probe neural circuits to obtain robust information regarding excitability. Following this we present a review of developments in high-resolution microelectrode technologies that enable neuroimaging across spatial scales. Finally, we present recent results from data-driven model-based analyses, which enable imaging of seizure generating mechanisms from clinical electrophysiological measurements. It is foreseeable that the field of seizure prediction will shift focus to a more probabilistic forecasting approach leading to improvements in the quality of life for the millions of people who suffer uncontrolled seizures. However, a missing piece of the puzzle is devices to acquire long-term high quality data. When this void is filled, seizure prediction will become a reality.

Keywords: Epileptic seizure prediction; electrophysiology; computational neuroscience; active EEG; ambulatory EEG; microelectrode; review

1. Introduction

"Prediction is very difficult, especially about the future" Niels Bohr (Ellis, 1970).

This article presents a review of relatively new methods in the research field of epileptic seizure prediction. The fundamental goal of seizure prediction is to improve the quality of life for patients with epilepsy. A good seizure prediction method could minimise the risk of injury by providing advanced warning to the patient and carers, and allow the optimisation of anti-epileptic treatment. Given the restrictions and hazards caused by the intermittent and seemingly random occurrence of seizures in most patients, a successful seizure prediction method will enable patients to lead relatively normal lives.

The notion of seizure prediction means different things to different groups, so perhaps the best place to start such a review is with a definition on what we mean by prediction. In particular, we would like to differentiate the notion of prediction to forecasting or anticipation of a future event. Although there is overlap between these concepts, we differentiate prediction to mean a particular outcome will occur at a particular time in the future with 100 percent certainty. Forecasting is a more general scenario, where a range of possible outcomes with associated probabilities of occurrence is anticipated [1]. In this context, the problem of seizure forecasting is probabilistic. The probability may be based on current measurements or historical knowledge (prior beliefs), or both. When the probability of a seizure occurring is sufficiently high the brain is in a pro-seizure, or pro-ictal state. In contrast, with a seizure prediction when the point of no return has been passed, then the brain is in a pre-seizure state.

A central hypothesis in the field of seizure prediction is based on the postulated existence of an altered brain state that is measurably different from a normal state, via electroencephalography (EEG) time series analyses. Originally, the field of seizure prediction was inspired by anecdotal evidence from patients who experienced alterations in behaviour or mood prior to seizures. Although self-reporting is generally considered unreliable [2, 3], there is now conclusive evidence for the existence of changes in brain state from multiple imaging modalities.

Despite the evidence of altered states of consciousness immediately prior to seizures, most EEG-based seizure prediction algorithms have failed to perform better than a random predictor [4]. The earlier studies have been largely based on algorithmic time-series analysis of EEG. A major drawback in the times-series analysis methods is the high level of abstraction of the *features* of the signals from the mechanisms that lead to seizures [5]

Typically, the data used in seizure prediction studies is from a collection of short-term EEG recordings. This is because high-quality long-term data has not been available. The use of short-term data restricts the number of patient-specific seizures that are acquired and imposes limitations in developing algorithms. The low number of seizures per patient is typically overcome by pooling data across patients, although it is well known that the mechanisms that lead to seizures are patient-specific. The consequence of insufficient data has been grandiose claims and questionable science. For example, a popular feature in seizure prediction studies is bivariate synchrony, which quantifies the similarity of EEG from different channels. On a 100 channel EEG (without frequency decomposition, which is generally required) there is 99900 unique signal combinations that can be studied. It is highly probable that at least one of these signals will show changes prior to a seizure greater than a random predictor, which is not particularly meaningful without the proper statistical corrections.

Given the paucity of patient-specific data that has previously been available prior to the Cook et al. (2013) study, it was not possible to tackle the problem of seizure forecasting. The number of recorded seizures has not been sufficient to construct probability distributions. The opacity of a purely signal processing approach oversimplifies the complex neural processing that takes place between the input and output. This further highlights the need to obtain more useable information and develop methods that utilise this information. This will potentially yield physiological insights into how seizures develop, specifically, the ability to clearly delineate a pro-seizure state in the data.

Increasing the resolution of the information can be achieved by recording higher-frequency or longer-term data. More patient-specific seizures can be studied by collecting long-term data, which will enable a more robust analysis of EEG-based features. Advances in collecting long-term data will be discussed in Section 2.

More physiologically meaningful information can also be extracted via an active EEG approach [6, 7]. Active EEG, or probing, involves using electrical stimulation to interrogate the responsiveness of an area of cortical tissue. Small perturbations from normal brain activity can be used to determine neural excitability, which is a known marker for a pre-seizure state [8].

Another obvious way of increasing the information available from electrophysiological signals is to increase the spatial resolution of the data, by using high-resolution microelectrode arrays. High-resolution arrays have the potential to capture seizure-related activity at the single neuron level, where changes have been observed prior to behavioural onset [9]. Progress in this regard is discussed in Section 4.

Seizure prediction and forecasting methods should be focused towards extracting information related to mechanisms responsible for epileptogenesis and ictogenesis. Information regarding mechanisms can be extracted from EEG signals by assimilating patient-specific data with knowledge of physiological processes. The physiological processes are encoded into a computational model and the mechanisms are reflected as changes in parameters of the model. Estimating changes in key physiological parameters from data could provide direct insight into seizure evolution and identify physiological markers of a pro-seizure state. Advances in this area are discussed in Section 5.

The structure of the rest of the paper will elaborate on some current research directions starting with Section 2 on long-term EEG recordings and the current technology being used to perform these. Next is a Section on active EEG and probing studies, followed by data collection from high-resolution electrode arrays in Section 4. The final new approach in this review paper is a model-based approach to seizure forecasting based on physiological insights into mechanisms of ictogenesis and epileptogenesis.

2. Long-Term Recordings

Previous studies on seizure prediction have been mostly based on the analysis of short-term (days to weeks) intracranial electroencephalography (iEEG) obtained during pre-surgical evaluation. The inherent limitation with using this type of data was that the data sets were small with few seizures and limited interictal iEEG. In practice, seizure prediction using EEG would be long-term (months and more) and based on the individual patient, specifically tuned to the individual patient to optimize performance. Long-term continuous EEG recordings may reveal patient-specific morphology of the EEG during the pre-seizure period. This was actually found to be the case in a first-in-man study by Cook et al. (2013) [2] and another study using dogs with naturally occurring epilepsy by Howbert et al. (2014) [10]. These studies were conducted using an investigational implantable device that recorded iEEG continuously and a real-time seizure forecasting algorithm to indicate seizure likelihood. This is currently the only implantable device that monitors and records EEG continuously.

There are two other devices that continuously monitor the EEG, but they can only store limited segments of electrographic data for post-review. First, the US FDA approved Neuropace Responsive NeuroStimulation (RNS) system, which is a responsive direct brain stimulation treatment for adults with refractory epilepsy [11]. The device was designed to detect epileptiform activity in the EEG after it has occurred and then apply therapeutic stimulation to stop the seizure, so by definition, it employs seizure detection and not prediction. Three computationally efficient seizure detection features are provided that are known as area, line-length, and half wave. The physician can configure the detection parameters to optimize the performance for each individual patient. The definitions of seizure detection and prediction become blurred if the detection algorithm is reliably detecting epileptiform activities that consistently precede clinically manifested seizures in a particular patient, so that the detection algorithm is predicting the occurrence of seizures. It is for this reason that continuous EEG monitoring and recording is important, so that we can determine whether a patient has a consistent pre-seizure EEG pattern.

The second device is a fully implantable closed-loop deep brain stimulation (DBS) system that has recently been developed for investigational use by Medtronic. This system, the Activa PC + S neurostimulator, is based on the Activa PC neurostimulator (approved by US FDA for Parkinson's disease, essential tremor and dystonia), but with additional sensing and detection features [12]. This device has been implanted into dogs to investigate a method for actively tracking excitability of the

brain by Freestone et al. (2013) [13]. This seizure prediction method utilises an active strategy to monitor cortical excitability by measuring responses to low-intensity electrical stimulation. This approach is a paradigm shift from the conventional passive technique of looking for pre-seizure EEG patterns. The results from this approach are promising and the inherent advantage of this technique is that only continuous data analysis, but not continuous recording is needed.

One of the main issues with the current generation of implantable devices is that they are highly invasive, so gaining regulatory approval is difficult with high associated costs. The invasiveness and high costs of these implantable devices impede their adoption into clinical practice. To address this issue, McLaughlin et al. (2012) [14] and our group (unpublished) are working on sub-scalp EEG recording implants for the clinical management of epilepsy patients. These minimally invasive implants are aimed for epilepsy diagnosis, anti-epileptic therapy assessment and optimisation, and seizure warning (advanced seizure warning to the patient to minimise the risk of injury, as well as alerting the carer after the patient has had an event).

The trend for the field of seizure prediction in the near future is moving towards implantable devices that continuously capture and analyse the EEG in a patient-specific approach. In this way sufficient statistics can be computed to obtain a real-time estimation of seizure likelihood in the context of forecasting of future events.

3. Active EEG

Active EEG, or probing, is a method of using electrical stimuli to access more information regarding the excitability of neural networks, compared to passively observing. Probing is similar to evoked potential studies of the sensory systems; however, the quantity that is measured is neural excitability for the purpose of seizure anticipation. Measuring brain excitability using an active EEG and/or TMS approach has been shown to be an effective measure to study the pro- and pre-seizure states (see Badawy et al., (2012) [15] for a review).

The probing method is largely inspired by an engineering technique for reverse-engineering electronic circuits: measuring the impulse response. The impulse response is a measurement of a circuit's response to an infinitesimally brief stimulation. Characteristics of the response, such as amplitude, rise and decay times, are sufficient to completely characterise linear circuits. Importantly, the responses provide insights that are impossible to gain from passive measurements. The clever usage of responses to single pulse stimulation has also been used as an early warning indicator of critical transitions in nonlinear systems, such as ecosystems, finance, climate, and the brain [16, 17]. Early warning indicators exploit a phenomenon known as critical slowing. Critical slowing refers to the time a system takes to recover from a small perturbation. For example, when parameters of a system change, moving the dynamics toward a critical transition point, or bifurcation, the system responses to small stimuli become larger and returning to equilibrium takes longer.

Theoretically, studies have shown that an active paradigm is required to track seizure-related excitability changes in computational models of epilepsy [18, 19]. These theoretical studies showed that passive approaches to predict seizures are less likely to succeed due to a lack of usable information regarding seizure related synchronization. An active method to study seizure can provide more information about the underlying mechanisms of the system.

The mainstream use of electrical stimulation for functional mapping of cortical circuits originates from the pioneering work of Penfield et al., (1937) [20]. Through advances in technology and refinements of electrophysiological techniques, electrical stimulation is now also used to map epileptic networks with methods known as cortico-cortical evoked potentials (CCEPs) and single-pulse electrical stimulation (SPES) [21, 22, 23]. Mapping epileptic networks through electrical stimulation has numerous advantages; the most beneficial of which is alleviating the need to wait for seizures. Furthermore, the responses to stimulation provide a high quality signal that can be used to perform rigorous analyses.

Single pulse electrical stimulation has also been used to track the evolution of the epileptic process in the kindling animal model [24, 24], where the amplitude of neural responses increased with the progression of the pathological changes. More recently, single pulse electrical stimulation has been used to track neural excitability through the evolution of pentylenetetrazole (PTZ) induced seizures

[25]. The responses to electrical stimulation showed characteristics of critical slowing as the time to seizure shortened.

Active EEG involving electrical stimulation was first used in the context of seizure anticipation by Kalitzin et al., (2005) [7], where they developed a measure of seizure likelihood by analyzing synchronization of EEG to periodic perturbations. The Kalitzin paper was a hallmark study, since it successfully demonstrated that active EEG approach was applicable for tracking pre-seizure dynamics in humans. The Kalitzin study also motivated the study of Freestone et al., (2011) [6], who used single pulse electrical stimulation for the purpose of seizure prediction. The Freestone et al. study showed the potential for single pulse electrical stimulation to reveal changes in relation to sleep patterns and prior to seizures in patients undergoing incranial EEG monitoring.

The active EEG approach for seizure anticipation can be naturally incorporated into therapeutic devices for seizure abatement via electrical stimulation. The new generation of deep brain stimulation systems are capable of recording, processing, and responding to characteristics of electrical evoked potentials [12]. These devices can respond to abnormal responses with therapeutic stimulation that can modulate cortical excitability [26]. It has also recently been shown that these devices can track changes in neural excitability in canines in relation to circadian rhythms and anti-epileptic drug levels [13, 27]. These studies highlight the potential for the active EEG approach to be used for seizure anticipation, titrating therapies, and controlling seizures.

4. High-Spatial Resolution Measurements

It is remarkable that the tasks of seizure prediction, detection and control can be performed with macroscopic measurements. Ideally for seizure prediction, we would be able to track micro-scale activity within the cellular networks that are directly implicated in the emergence of a seizure [28, 29, 30, 31, 9, 32]. However, we cannot yet implant a sufficiently large number of micro-electrodes to track the coalescence of pre-seizure, micro-scale events across large regions of the brain; so, other strategies are needed. Data assimilation methods that can link macroscopic or mesoscopic recordings to microscopic activity are a promising avenue of investigation. For instance, high-resolution recordings at the mesoscale, which are currently highly tractable, offer the potential to infer neural population firing rates because it has been demonstrated that broadband local field potential power is proportional to local firing rates [33, 34]. However, to validate methods that integrate between spatial scales we need higher spatial resolution electrophysiological recordings [35, 36]. Here we briefly review the current state of the art in high-resolution electrode arrays and consider how high-resolution arrays can be useful for seizure prediction. Table 1 summarises the properties of example high-resolution strategies that are currently available.

In invasive epilepsy monitoring the standard intracranial macroscale electrode arrays and configurations (single subdural strips, grids, or depth arrays and any combination thereof) typically have electrode contacts on the order of 1-10 mm^2 with anywhere between 4 and 256 electrodes, and the typical minimum electrode separation distance is 5-10 mm [37, 38].

More recent research approaches have involved high-resolution non-penetrating or penetrating measurements. In some of these studies very short penetrating (1-3 mm long) or non-penetrating microelectrodes (40 micron diameter) are positioned between the macroscale electrode contacts to give an interlaced combination of micro- and macro-scale measurements with a spacing of 0.5-1 mm between microelectrodes and 5-10 mm between macroelectrodes [39, 40]. Studies with this approach have demonstrated feasibility and safety for standard intracranial monitoring [40], and revealed an improved characterisation of human high frequency oscillations [39], microseizures [31] and the heterogeneous activity linked to focal seizure onset [41]. These studies also involved large numbers of micro- and macro-electrodes (involving up to 320 channel recording systems) and therefore also highlighted the need for ‘big-data’ processing and storage [42, 43].

Another early approach was the application of high-density penetrating microelectrode arrays, such as the NeuroPort™ array with 96 electrodes spanning 16 mm^2 and with spacing of 400 μm [44]. Studies with these arrays also contributed to the discovery of microseizures and interictal microdischarges in humans [28, 30], and the characterisation of high frequency oscillations [29] and their utility for localising the epileptic zone [45].

A third approach has been the development of a flexible high-resolution non-penetrating array composed of ultrathin and flexible silicon nanomembrane transistors embedded in the array [46, 47, 48, 49, 50, 51]. This approach allows for arrays of potentially thousands of amplified and multiplexed electrical sensors that are connected using significantly fewer wires than in standard micro- and macro-electrode arrays. One key version implanted in cats involved 360 sensors (each 300 x 300 μm^2) with 500 μm spacing covering a patch of 10 x 9 mm^2 and allowed for recording of micro-ECoG signals and visualisation of spiral wave patterns in seizures [49]. Although scaling up to clinical sized arrays (80 x 80 mm^2) with 25,600 electrodes is feasible, there still remains a lot of work to be done to develop processing systems that can process and store the data that can be collected with such arrays [50, 52]. Moreover, potential human safety issues regarding active amplification and multiplexing may have to be addressed.

Other recent high resolution approaches include an ultraconformable, biocompatible and scalable neural interface array called the 'NeuroGrid' that contains sensors positioned with a density similar to the density of neurons on the cortical surface [53] and a 4096 microelectrode array chip with 21μm inter-electrode distance and 21 × 21 μm^2 electrode size arranged in a squared area of 2.6 × 2.6 mm^2 [54]. Bottlenecks in the development and long-term clinical utility of high-resolution arrays still exist, such as issues with mechanical properties, scar tissue, active multiplexing, and long-term impedance issues [55]. Nevertheless, future work will seek to overcome these challenges.

Many of the latest insights into epilepsy neurophysiology have relied on the combination of multiple scale (micro- and macro-scale) recordings. In particular, the apparent self-termination of seizures via critical transition [56]; the heterogeneity of single unit activity involved in focal seizures, and synchrony of single unit activity during spike and wave seizures [9, 32]; and evidence of an ictal penumbra involved in inhibitory restraint of seizure spread [57]. It is also worth noting briefly that optogenetics studies [33, 58] combined with high resolution recordings may provide a way to disentangle excitatory and inhibitory population activity and develop improved seizure prediction, detection, and control [59]. Future work focused on linking the micro-, meso- and macro-scales will lead to a deeper understanding of epilepsy, and also potentially point to ways of achieving improvements in seizure prediction or early seizure detection.

5. Data-Driven Model-Based Analysis

The use of model-based predictions to generate testable hypotheses is the foundation of scientific research. However, developing model-based predictions is challenging for seizure prediction Table 2 outlines some innovations in the field. Formulating mathematical models of a system as complex as the human brain is a daunting task. Nevertheless, the task can be achieved by describing the mean field dynamics of neural populations. Mean field models capture emergent dynamics at the mesoscopic scale of cortical regions ($1mm^2$) [60], rather than describing the dynamics of individual neurons. Mean field models of the cortex are the neuroscience counterparts to the mean field approximation used to derive the evolution of macroscopic activity from molecular motion [61].

The dynamics of mesoscopic cortical models are governed by parameters that have physical interpretations, for instance propagation delays, connectivity strengths, firing thresholds, and details of membrane physiology (see [62] for review). For certain combinations of parameters these models will generate epileptiform activity [63, 64, 65, 66, 67, 68]. The parameters of mean field models are generally not directly measurable with clinical recordings, but can be inferred from EEG. These parameters should describe abnormal dynamics that are known to occur prior to ictal onset [31, 69]. In this way, it becomes possible to use estimation and tracking of mesoscopic model parameters to identify a pro-ictal state. However, there is a trade-off in mesoscopic models between incorporating enough detail to describe epileptic phenomena, whilst remaining tractable for computation.

Data-driven model-based seizure prediction assimilates measurements with biophysical knowledge (contained in the model) to estimate and track the evolution of hidden variables that govern cortical activity [70]. There are two stages to model-based prediction; estimation of hidden variables, followed by the calculation of seizure likelihood. Seizure likelihood can be evaluated by measuring how close the brain is to a critical transition point. There are distinct patterns of cortical activity that indicate the brain is approaching a critical point [71]; however, detection of these patterns requires accurate estimation of the brain's current state from EEG. It is also important that the approach to critical

transition can be detected with enough time to enable corrective action (e.g. electrical stimulation or drug delivery).

Mesoscopic models have proved to be useful for characterizing pre-ictal and ictal dynamics [72, 73], which is promising for seizure prediction. However, the parameter estimation methods typically impose strict assumptions on the behaviour of populations of neurons that are difficult to validate. Such simplifying assumptions are necessary to create parsimonious models of the large regions of cortex affected by epilepsy [74, 75]. This inability to fuse mesoscopic and microscopic data within a consistent framework is a hurdle for model-based prediction. Further development is needed to integrate experimental data from multiple spatial scales in order to provide physiological insight into epileptic mechanisms. Earlier we used the analogy comparing mean field approximations of neural activity to molecular motion. A major difference between the two aforementioned areas of inquiry is that the later has been experimentally verified [76]. Such an experiment with mean field theory in neuroscience has not yet been conducted.

Recent developments across many fields have exciting applications for model-based prediction. Mathematical techniques to improve accuracy for a broad class of mesoscopic neural models are promising [77]. Statistical methods that enable rapid but accurate estimation of connectivity between thousands of spiking neurons [78, 79] may alleviate some of the assumptions used to model mesoscopic activity. There has also been significant effort to incorporate more accurate anatomical information of cortical circuits into computational models [80, 81]. Furthermore, breakthroughs in imaging techniques that enable simultaneous recording of spiking neurons and EEG [82] will provide an unprecedented opportunity to verify and fine-tune current mathematical models.

6. Conclusion

There is now clear evidence that seizure prediction is possible and feasible [2]. Measuring various bio-markers for seizure prediction has been undertaken since at least the 1920's, when parameters such as blood cholesterol [84], rhythms [85], and time of day [86]. As with more recent studies of circadian cycles [87] many studies have shown distinct temporal patterns, with different patterns between individuals and location of seizure origin. A limitation in achieving a clinically viable warning system has been a result of limited access to sufficiently long EEG recordings from individual subjects. Techniques to acquire sufficiently long and detailed recordings are now becoming available.

A combination of new and innovative methods outlined above, most particularly using long-term high-spatial resolution data, with the clever use of perturbations and model-based analysis, is likely to lead to robust and clinically viable seizure prediction methods. This is great news for epilepsy suffers, especially since new drug discovery has failed to significantly reduce the proportion of patients inadequately controlled by medical therapies. Development of these techniques may fundamentally alter our approach to therapy, permitting tailored treatment 'on demand', rather than the constant dosing strategies currently necessary.

With access to more and higher quality information regarding the physiological mechanisms involved in seizures, the field of seizure prediction can move towards seizure forecasting.

Challenges remain the development of devices of a less invasive nature, and the determination of the optimal number and deployment of electrodes to obtain satisfactory forecasting accuracy. Progress in materials and analysis techniques mean clinically useful seizure forecasting is now within reach.

Acknowledgements: The authors acknowledge the support from the Australian National Health and Medical Research Council Project Grant (APP1065638). Dr Freestone acknowledges the support of the Australian-American Fulbright Commission and would also like to thank Professor Liam Paninski for his support. The authors would also like to thank Associate Professor Bruce Gluckmann for insightful discussions and pointing out that sometimes you have to look backward to go forward.

Compliance with Ethics Guidelines

Conflict of Interest

Dean R. Freestone, Philippa J. Karoly, Andre D. H. Peterson, Levin Kuhlmann, Alan Lai, and Farhad Goodarzy declare that they have no conflict of interest.
Mark J. Cook was lead investigator in the NeuroVista study cited in the publication. However, Dr. Cook had no financial relationship with the sponsors.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

7. References

[1] Y. Matsuo, "Prediction, forecasting, and chance discovery," in *Chance Discovery*, Y. Ohsawa and P. McBurney, Eds., Berlin, Springer, 2003, pp. 30-43.

[2] M. J. Cook, T. J. O'Brien, S. F. Berkovic, M. Murphy, A. Morokoff, G. Fabinyi, W. D'Souza, R. Yerra, J. Archer, L. Litewka and others, "Prediction of seizure likelihood with a long-term, implanted seizure advisory system in patients with drug-resistant epilepsy: a first-in-man study," The Lancet Neurology, vol. 12, no. 6, pp. 563-571, 2013.

* Cook conducted the first clinical trial of a device dedicated to forecasting the likelihood of seizure occurrences in 15 patients. It demonstrated, for the first time, that seizure prediction is possible.

[3] D. Blum, J. Eskola, J. Bortz and R. Fisher, "Patient awareness of seizures," *Neurology*, vol. 47, no. 1, pp. 260-264, 1996.

[4] T. N. Alotaiby, S. A. Alshebeili, T. Alshawi, I. Ahmad and F. E. A. El-Samie, "EEG seizure detection and prediction algorithms: a survey," *EURASIP Journal on Advances in Signal Processing*, vol. 1, p. 183, 2014.

[5] F. Mormann, R. Andrzejak, C. E. Elger and K. Lehnertz, "Seizure prediction: the long and winding road," *Brain*, vol. 130, no. 2, pp. 314-333, 2007.

[6] D. R. Freestone, L. Kuhlmann, D. B. Grayden, A. N. Burkitt, A. Lai, T. S. Nelson, S. Vogrin, M. Murphy, W. d'Souza, R. Badawy and others, "Electrical probing of cortical excitability in patients with epilepsy," *Epilepsy & Behaviour*, vol. 22, pp. 110-118, 2011.

[7] S. Kalitzin, D. Velis, P. Suffczynski, J. Parra and F. L. da Silva, "Electrical brain-stimulation paradigm for estimating the seizure onset site and the time to ictal transition in temporal lobe epilepsy," *Clinical neurophysiology*, vol. 116, no. 3, pp. 718-728, 2005.

[8] R. Badawy, R. Macdonell, G. Jackson and S. Berkovic, "The peri-ictal state: cortical excitability changes within 24 h of a seizure," *Brain*, vol. 132, no. 4, pp. 1013-1021, 2009.

[9] W. Truccolo, J. A. Donoghue, L. R. Hochberg, E. N. Eskandar, J. R. Madsen, W. S. Anderson, E. N. Brown, E. Halgren and S. S. Cash, "Single-neuron dynamics in human focal epilepsy," *Nature neuroscience*, vol. 14, no. 5, pp. 635-641, 2011.

[10] J. J. Howbert, E. E. Patterson, S. M. Stead, B. Brinkmann, V. Vasoli, D. Crepeau, C. H. Vite, B. Sturges, V. Ruedebusch, J. Mavoori and others, "Forecasting seizures in dogs with naturally occurring epilepsy," *PLoS ONE*, vol. 9, no. 1, p. e81920, 2014.

[11] C. N. Heck, D. King-Stephens, A. D. Massey, D. R. Nair, B. C. Jobst, G. L. Barkley, V. Salanova, A. J. Cole, M. C. Smith, R. P. Gwinn and others, "Two-year seizure reduction in adults with medically intractable partial onset epilepsy treated with responsive neurostimulation: Final results of the RNS System Pivotal trial," *Epilepsia,* vol. 55, no. 3, pp. 432-441, 2014.

[12] P. H. Stypulkowski, S. R. Stanslaski, T. J. Denison and J. E. Giftakis, "Chronic evaluation of a clinical system for deep brain stimulation and recording of neural network activity," *Stereotactic and functional neurosurgery,* vol. 91, no. 4, pp. 220-232, 2012.

[13] D. R. Freestone, S. N. Long, S. Frey, P. H. Stypulkowski, J. E. Giftakis and M. J. Cook, "A method for actively tracking excitability of brain networks using a fully implantable monitoring system," 2013.

[14] B. L. McLaughlin, L. J. Mariano, S. R. Prakash, A. L. Kindle, A. Czarnecki, M. H. Modarres, A. Rotenberg, T. Loddenkemper, A. Shoeb and S. C. Schachter, "An electroencephalographic recording platform for real-time seizure detection.," in *Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, 2012.

[15] R. Badawy, D. Freestone, A. Lai and M. Cook, "Epilepsy: ever-changing states of cortical excitability," *Neuroscience,* vol. 222, pp. 89-99, 2012.

* This review organizes evidence highlighting that hyper-excitability associated with seizures is governed by predictable slow processes. It promotes a critical rethink from using passive EEG to active measurement techniques involving electrical stimulation and TMS to solve the problem of seizure prediction.

[16] L. Dai, D. Vorselen, K. S. Korolev and J. Gore, "Generic indicators for loss of resilience before a tipping point leading to population collapse," *Science*, vol. 336, no. 6085, pp. 1175-1177, 2012.

[17] M. Scheffer, J. Bascompte, W. A. Brock, V. Brovkin, S. R. Carpenter, V. Dakos, H. Held, E. H. Van Nes, M. Rietkerk and G. Sugihara, "Early-warning signals for critical transitions," *Nature,* vol. 461, no. 7260, pp. 53-59, 2009.

[18] P. Suffczynski, S. Kalitzin, F. Lopez da Silva, J. Parra, D. Velis and F. Wendling, "Active paradigms of seizure anticipation: Computer model evidence for necessity of stimulation," *Physical Review E,* vol. 78, p. 051917, 2008.

[19] E. O'Sullivan-Greene, I. M. Y. Mareels, D. R. Freestone, L. Kuhlmann and A. N. Burkitt, "A paradigm for epileptic seizure prediction using a coupled oscillator model of the brain," in *Proceedings of the 31st IEEE Engineering in Medicine & Biology Conference*, Minneapolis, 2009.

[20] W. Penfield and E. Boldrey, "Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation," *Brain: A journal of Neurology,* vol. Ix, p. 389, 1937.

[21] R. Enatsu, Z. Piao, T. O'Connor, K. Horning, J. Mosher, R. Burgess, W. Bingaman and D. Nair, "Cortical excitability varies upon ictal onset patterns in neocortical epilepsy: a cortico-cortical evoked potential study," *Clinical Neurophysiology,* vol. 123, no. 2, pp. 252-260, 2012.

[22] M. Iwasaki, R. Enatsu, R. Matsumoto, E. Novak, B. Thankappen, Z. Piao, K. Horning, W. Bingaman and D. Nair, "Accentuated cortico-cortical evoked potentials in neocortical epilepsy in areas of ictal onset," *Epileptic disorders,* vol. 12, no. 4, pp. 292-302, 2010.

[23] G. Alarcon and A. Valentin, "Cortical stimulation with single electrical pulses in human epilepsy," *Clinical Neurophysiology,* vol. 123, no. 2, pp. 223-224, 2012.

[24] R. J. Racine, J. G. Gartner and W. M. Burnham, "Epileptiform activity and neural plasticity in limbic structures," *Brain research,* vol. 47, no. 1, pp. 262-268, 1972.

[25] D. C. Medeiros, L. B. Oliveira, F. A. G. Mourão, C. P. Bastos, N. G. Cairasco, G. S. Pereira, E. M. A. M. Mendes and M. F. D. Moraes, "Temporal rearrangement of pre-ictal PTZ induced spike discharges by low frequency electrical stimulation to the amygdaloid complex," *Brain stimulation,* vol. 7, no. 2, pp. 170-178, 2014.

[26] P. H. Stypulkowski, S. R. Stanslaski, R. M. Jensen, T. J. Denison and J. E. & Giftakis, "Brain Stimulation for Epilepsy–Local and Remote Modulation of Network Excitability," *Brain Stimulation,* vol. 7, no. 3, pp. 350-358, 2014.

[27] S. Long, S. Frey, D. R. Freestone, M. LeChevoir, P. Stypulkowski, J. Giftakis and M. Cook, "Placement of deep brain electrodes in the dog using the brainsight frameless stereotactic system: A pilot feasibility study," *Journal of Veterinary Internal Medicine,* vol. 28, no. 1, pp. 189-197, 2014.

[28] C. A. Schevon, S. K. Ng, J. Cappell, R. R. Goodman, G. McKhann Jr, A. Waziri, A. Branner, A. Sosunov, C. E. Schroeder and R. G. Emerson, "Microphysiology of epileptiform activity in human neocortex," *Journal of clinical neurophysiology,* vol. 25, no. 6, p. 321, 2008.

[29] C. A. Schevon, A. Trevelyan, C. Schroeder, R. Goodman, G. McKhann and R. Emerson, "Spatial characterization of interictal high frequency oscillations in epileptic neocortex," *Brain,* p. awp222, 2009.

[30] C. Schevon, R. Goodman, G. McKhann Jr and R. Emerson, "Propagation of epileptiform activity on a submillimeter scale," *Journal of clinical neurophysiology,* vol. 27, no. 6, p. 406, 2010.

[31] M. Stead, M. Bower, B. Brinkmann, K. Lee, R. Marsh, F. Meyer, B. Litt, J. Van Gompel and G. Worrell, "Microseizures and the spatiotemporal scales of human partial epilepsy," *Brain,* 2010.

[32] W. Truccolo, O. J. Ahmed, M. T. Harrison, E. N. Eskandar, G. R. Cosgrove, J. R. Madsen, A. S. Blum, N. S. Potter, L. R. Hochberg and S. S. Cash, "Neuronal ensemble synchrony during human focal seizures," *The Journal of Neuroscience,* vol. 34, no. 30, pp. 9927-9944, 2014.

[33] G. Buzsaki, C. A. Anastassiou and C. Koch, "The origin of extracellular fields and currents—EEG, ECoG, LFP and spikes," *Nature reviews neuroscience,* vol. 13, no. 6, pp. 407-420, 2012.

[34] J. R. Manning, J. Jacobs, I. Fried and M. J. Kahana, "Broadband shifts in local field potential power spectra are correlated with single-neuron spiking in humans," *The Journal of neuroscience,* vol. 29, no. 43, pp. 13613-13620, 2009.

[35] W. Stacey, "Recording from over 1,000 cells: a new toy in place for epilepsy research?," *Epilepsy Currents,* vol. 14, no. 2, pp. 95-96, 2014.

[36] G. G. Szabo, C. J. Schneider and I. Soltesz, "Resolution revolution: epilepsy dynamics at the microscale," *Current opinion in neurobiology,* vol. 31, pp. 239-243, 2015.

[37] G. A. Worrell, L. Parish, S. D. Cranstoun, R. Jonas, G. Baltuch and B. Litt, "High-frequency oscillations and seizure generation in neocortical epilepsy," *Brain,* vol. 127, no. 7, pp. 1496-1506, 2004.

[38] J. J. Van Gompel, G. A. Worrell, M. L. Bell, T. A. Patrick, G. D. Cascino, C. Raffel, W. R. Marsh and F. B. Meyer, "Intracranial electroencephalography with subdural grid electrodes: techniques, complications, and outcomes," *Neurosurgery,* vol. 63, no. 3, pp. 498-506, 2008.

[39] G. A. Worrell, A. B. Gardner, S. M. Stead, S. Hu, S. Goerss, G. J. Cascino, F. B. Meyer, R. Marsh and B. Litt, "High-frequency oscillations in human temporal lobe: simultaneous microwire and clinical macroelectrode recordings," *Brain,* vol. 131, no. 4, pp. 928-937, 2008.

[40] J. J. Van Gompel, S. M. Stead, C. Giannini, F. B. Meyer, W. R. Marsh, T. Fountain, E. So, A. Cohen-Gadol, K. H. Lee and G. A. Worrell, "Phase I trial: safety and feasibility of intracranial electroencephalography using hybrid subdural electrodes containing macro-and microelectrode arrays," *Neurosurgical focus,* vol. 25, no. 3, p. E23, 2008.

[41] M. R. Bower, M. Stead, F. B. Meyer, W. R. Marsh and G. A. Worrell, "Spatiotemporal neuronal correlates of seizure generation in focal epilepsy," *Epilepsia,* vol. 53, no. 5, pp. 807-816, 2012.

[42] B. H. Brinkmann, M. R. Bower, K. A. Stengel, G. A. Worrell and M. Stead, "Large-scale electrophysiology: acquisition, compression, encryption, and storage of big data," *Journal of neuroscience methods,* vol. 180, no. 1, pp. 185-192, 2009.

[43] M. Shoaran, C. Pollo, Y. Leblebici and A. Schmid, "Design techniques and analysis of high-resolution neural recording systems targeting epilepsy focus localization," in *Engineering in Medicine and Biology Society (EMBC), 2012 Annual International Conference of the IEEE*, IEEE, 2012, pp. 5150--5153.

[44] A. Waziri, C. A. Schevon, J. Cappell, R. G. Emerson, G. McKhann 2nd and R. R. Goodman, "Initial surgical experience with a dense cortical microarray in epileptic patients undergoing craniotomy for subdural electrode implantation," *Neurosurgery,* vol. 64, no. 3, p. 540, 2009.

[45] S. Weiss, R. Connors, G. Banks, G. McKhann, B. Zhao, C. Filippi, R. Emerson, A. Trevelyan and C. Schevon, "Resection of Ictal Phase Locked HFOs Is Correlated with Outcome Following Epilepsy Surgery," *Neurology,* vol. 82, no. 10S, pp. S50-003, 2014.

[46] D.-H. Kim, J. Viventi, J. J. Amsden, J. Xiao, L. Vigeland, Y.-S. Kim, J. A. Blanco, B. Panilaitis, E. S. Frechette and D. Contreras, "Dissolvable films of silk fibroin for ultrathin conformal bio-integrated electronics," *Nature materials,* vol. 9, no. 6, pp. 511-517, 2010.

[47] J. Viventi, J. Blanco and B. Litt, "Mining terabytes of submillimeter-resolution ECoG datasets for neurophysiologic biomarkers," in *Engineering in Medicine and Biology Society (EMBC), 2010 Annual International Conference of the IEEE*, Buenos Aires, 2010.

[48] J. Viventi, D.-H. Kim, J. D. Moss, Y.-S. Kim, J. A. Blanco, N. Annetta, A. Hicks, J. Xiao, Y. Huang and D. J. Callans, "A conformal, bio-interfaced class of silicon electronics for mapping cardiac electrophysiology," *Science translational medicine,* vol. 2, no. 24, p. 24ra22, 2010.

[49] J. Viventi, D.-H. Kim, L. Vigeland, E. S. Frechette, J. A. Blanco, Y.-S. Kim, A. E. Avrin, V. R. Tiruvadi, S.-W. Hwang and A. C. Vanleer, " Flexible, foldable, actively multiplexed, high-density electrode array for mapping brain activity in vivo," *Nature neuroscience,* vol. 14, no. 12, pp. 1599-1605, 2011.

[50] T. Kim, N. S. Artan, J. Viventi and H. J. Chao, "Spatiotemporal compression for efficient storage and transmission of high-resolution electrocorticography data," in *Engineering in Medicine and Biology Society (EMBC), 2012 Annual International Conference of the IEEE*, IEEE, 2012, pp. 1012-1015.

[51] M. A. Escabi, H. L. Read, J. Viventi, D.-H. Kim, N. C. Higgins, D. A. Storace, A. S. Liu, A. M. Gifford, J. F. Burke and M. Campisi, "A high-density, high-channel count, multiplexed μECoG array for auditory-cortex recordings," *Journal of neurophysiology,* vol. 112, no. 6, pp. 1566-1583, 2014.

[52] J. Wang, M. Trumpis, M. Insanally, R. Froemke and J. Viventi, "A low-cost, multiplexed electrophysiology system for chronic μECoG recordings in rodents," in *Engineering in Medicine and Biology Society (EMBC), 2014 36th Annual International Conference of the IEEE*, IEEE, 2014, pp. 5256-5259.

[53] D. Khodagholy, J. N. Gelinas, T. Thesen, W. Doyle, O. Devinsky, G. G. Malliaras and G. Buzsaki, "NeuroGrid: recording action potentials from the surface of the brain," *Nature neuroscience*, 2014.

[54] E. Ferrea, A. Maccione, L. Medrihan, T. Nieus, D. Ghezzi, P. Baldelli, F. Benfenati and L. Berdondini, "Large-scale, high-resolution electrophysiological imaging of field potentials in brain slices with microelectronic multielectrode arrays," *Frontiers in neural circuits*, vol. 6, 2012.

[55] K. A. Sillay, P. Rutecki, K. Cicora, G. Worrell, J. Drazkowski, J. J. Shih, A. D. Sharan, M. J. Morrell, J. Williams and B. Wingeier, "Long-term measurement of impedance in chronically implanted depth and subdural electrodes during responsive neurostimulation in humans," *Brain stimulation*, vol. 6, no. 5, pp. 718-726, 2013.

[56] M. A. Kramer, W. Truccolo, U. T. Eden, K. Q. Lepage, L. Hochberg, E. N. Eskandar, J. R. Madsen, J. W. Lee, A. Maheshwari and E. Halgren, "Human seizures self-terminate across spatial scales via a critical transition," *Proceedings of the National Academy of Sciences*, vol. 109, no. 51, pp. 21116-21121, 2012.

[57] C. A. Schevon, S. A. Weiss, G. McKhann Jr, R. R. Goodman, R. Yuste, R. G. Emerson and A. J. Trevelyan, "Evidence of an inhibitory restraint of seizure activity in humans," *Nature communications*, vol. 3, p. 1060, 2012.

[58] F. B. P. Wagner, W. Truccolo, J. Wang and A. Nurmikko, "Spatiotemporal dynamics of optogenetically-induced and spontaneous seizure transitions in primary generalized epilepsy," *Journal of neurophysiology*, pp. jn--01040, 2014.

[59] E. Krook-Magnuson, C. Armstrong, M. Oijala and I. Soltesz, " On-demand optogenetic control of spontaneous seizures in temporal lobe epilepsy," *Nature communications*, vol. 4, p. 1376, 2013.

[60] D. Sornette and I. Osorio, "Prediction," in *Epilepsy: The Intersection of Neurosciences, Biology, Mathematics, Engineering, and Physics*, CRC Press, 2011, pp. 203-241.

[61] W. Freeman, "Topological Properties," in *Mass action in the nervous system*, London, Academic Press, 1975.

[62] G. Deco, V. Jirsa, P. Robinson, M. Breakspear and K. Friston, "The dynamic brain: from spiking neurons to neural masses and cortical fields," *PLoS computational biology*, vol. 4, no. 8, 2008.

[63] Y. Wang, M. Goodfellow, P. N. Taylor and G. Baier, "Dynamic mechanisms of neocortical focal seizure onset," *PLoS computational biology*, vol. 10, no. 8, 2014.

[64] J. Kim, J. Roberts and P. Robinson, "Dynamics of epileptic seizures: Evolution, spreading, and suppression," *Journal of theoretical biology*, vol. 257, no. 4, pp. 527-532, 2009.

[65] F. Wendling, A. Hernandez, J.-J. Bellanger, P. Chauvel and F. Bartolomei, "Interictal to ictal transition in human temporal lobe epilepsy: insights from a computational model of intracerebral EEG," *Journal of Clinical Neurophysiology*, vol. 22, p. 345, 2005.

[66] F. Wendling, F. Bartolomei, J. Bellanger and P. Chauvel, "Epileptic fast activity can be explained by a model of impaired GABAergic dendritic inhibition," *European Journal of Neuroscience*, vol. 15, pp. 1499-1508, 2002.

[67] G. a. G. M. Baier, P. N. Taylor, Y. Wang and D. J. Garry, "The importance of modeling epileptic seizure dynamics as spatio-temporal patterns," *Frontiers in physiology*, vol. 3, 2012.

[68] D. R. Freestone, D. Nesic, A. Jafarian, M. J. Cook and D. B. Grayden, "A neural mass model of spontaneous burst suppression and epileptic seizures," in *Engineering in Medicine & Biology*

Conference, 2013.

[69] I. Timofeev and M. Steriade, "Neocortical seizures: initiation, development and cessation," *Neuroscience,* vol. 123, no. 2, pp. 299-336, 2004.

[70] D. R. Freestone, P. Aram, M. Dewar, K. Scerri, D. B. Grayden and V. Kadirkamanathan, "A data-driven framework for neural field modeling," *NeuroImage,* vol. 56, no. 3, pp. 1043-1058, 2011.

[71] E. Negahbani, D. A. Steyn-Ross, M. L. Steyn-Ross, M. T. Wilson and J. W. Sleigh, "Noise-Induced Precursors of State Transitions in the Stochastic Wilson–Cowan Model," *The Journal of Mathematical Neuroscience,* vol. 5, no. 1, pp. 1-27, 2015.

[72] A. Aarabi and B. He, "Seizure prediction in hippocampal and neocortical epilepsy using a model-based approach," *Clinical Neurophysiology,* vol. 125, no. 5, pp. 930-940, 2014.

[73] D. Freestone, L. Kuhlmann, M. Chong, D. Nesic, D. Grayden, P. Aram, R. Postoyan and M. Cook, "Patient-specific neural mass modelling: stochastic and deterministic methods," in *Recent Advances in Predicting and Preventing Epileptic Seizures*, 2013, pp. 63-82.

[74] J. R. Terry, O. Benjamin and M. P. Richardson, "Seizure generation: the role of nodes and networks," *Epilepsia,* vol. 53, no. 9, pp. 166-169, 2012.

[75] M. A. Kramer and S. S. Cash, "Epilepsy as a disorder of cortical network organization," *The Neuroscientist,* vol. 18, no. 4, pp. 360-372, 2012.

[76] A. Einstein, Investigations on the theory of the brownian movement, New York, NY: Dover Publications, 1956.

[77] D. Freestone, P. Karoly, D. Nesic, P. Aram, M. J. Cook and D. Grayden, "Estimation of effective connectivity via data-driven neural modeling," Frontiers in neuroscience, vol. 8, 2014.

* The Authors developed a framework for creating patient specific mathematical models from clinical data. This technique will enable imaging of the physiological mechanisms that govern seizure dynamics. Tracking such physiological variables is the ideal scenario for seizure anticipation.

[78] Y. V. Zaytsev, A. Morrison and M. Deger, "Reconstruction of recurrent synaptic connectivity of thousands of neurons from simulated spiking activity," arXiv preprint arXiv:1502.04993 , 2015.

[79] L. Buesing, T. A. Machado, J. P. Cunningham and L. Paninski, "Clustered factor analysis of multineuronal spike data," Montreal, 2014.

[80] T. C. Potjans and M. Diesmann, "The cell-type specific cortical microcircuit: relating structure and activity in a full-scale spiking network model," *Cerebral Cortex,* vol. 24, no. 3, pp. 785-806, 2014.

[81] A. M. Thomson and C. Lamy, "Functional maps of neocortical local circuitry," *Frontiers in Neuroscience,* vol. 1, no. 1, pp. 19-42, 2007.

[82] R. Prevedel, Y.-G. Yoon, M. Hoffmann, N. Pak, G. Wetzstein, S. Kato, T. Schrodel, R. Raskar, M. Zimmer and E. Boyden, "Simultaneous whole-animal 3D imaging of neuronal activity using light-field microscopy," *Nature methods,* 2014.

[83] O. David and K. Friston, "A neural mass model for MEG/EEG:: coupling and neuronal dynamics," *NeuroImage,* vol. 20, pp. 1743-1755, 2003.

[84] M. Gosden, J. T. Fox and W. R. Brain, "The Cholesterol Of The Blood Plasma In Epilepsy," *The*

Lancet, vol. 214, no. 5523, pp. 12-16, 1929.

[85] G. M. Griffiths and J. T. Fox, "Rhythm in epilepsy," *The Lancet*, vol. 232, no. 5999, pp. 409-416, 1938.

[86] M. Langdon-Down and W. Russell Brain, "Time of day in relation to convulsions in epilepsy," *The Lancet*, vol. 213, no. 5516, pp. 1029-1032, 1929.

[87] T. Loddenkemper, S. W. Lockley, J. Kaleyias and S. V. Kothare, "Chronobiology of epilepsy: diagnostic and therapeutic implications of chrono-epileptology," *Journal of Clinical Neurophysiology*, vol. 28, no. 2, pp. 146-153, 2011.

Table 1. Example high-resolution electrophysiological recording strategies						
Strategy/Device	Electrode size	Minimum electrode separation	Number of electrodes	Array Size	Advantages	Disadvantages
Hybrid Micro/Macro Grids (Worrell et al., 2008; Van Gompel et al., 2008a)	Micro: 40 μm diameter Macro: 1-10 mm^2	Micro: 0.5-1 mm Macro: 5-10 mm	Up to 320	Up to 80 x 80 mm^2	Macro-grids used routinely in clinical practice; Simultaneous micro- and macro- data	Micro-electrodes still for research only use; Micro-electrodes can break; Can get clotting between array and cortex; Both lead to unstable impedances; Lots of wires; Spatially sparse sampling; Invasive
Non-penetrating flexible arrays(Viventi et al., 2011)	300 x 300 μm^2	500 μm	360	10 x 9 mm^2	High density μECoG recordings; Flexible for hard to reach places; Low wire count; Less invasive	Active multiplexing needs to be assessed for clinical safety; Needs acquisition and processing technology to improve for scalability
Penetrating arrays (Waziri et al., 2009)	3-5 μm diameter microelectrode tips	400 μm	96	4 x 4 mm^2	High density single unit recordings	Bed of nails effect; Also a potential wiring issue; Typically restricted to small patch; Invasive

Table 2: Innovations in Data-Driven Model-Based Analyse of EEG.			
Contribution	Future Application	Author	Date
Demonstrated use of a simple population model to capture a range of EEG/MEG phenomena	Simplified models may be spatially enlarged to capture multi-channel EEG recordings	David and Friston [83]	2003
Provides anatomically detailed summary of connections between neural sub-types	May be used to improve realism of mathematical models	Thomson and Lamy [81]	2007
Derivation and proof of principle for a method to relate large-scale spatially distributed neural field models to electrophysiological data	Modeling of high-resolution microelectrode data from Utah array recordings or optical imaging.	Freestone et al. [70]	2012
Demonstrated relevance of population model parameters to pre-ictal state	Possibility of scaling up this technique to larger brain regions	Freestone et al. [73] Aarabi and He [72]	2013 2014
Estimation of mesoscopic connectivity structures from microscale spiking data	May inform mesoscopic model design and allow experimental validation of population models.	Buesing et al. [79] Zaytsev et al. [78]	2014 2015
Provides a measurement of individual neural activity with the potential of simultaneously recording from a macroscopic electrode	The ability to validate mesoscopic model estimates with experimental data	Prevedel et al. [82]	2015