Epilepsy Innovation Institute (Ei^2)

MY BRAIN MAP WORKSHOP

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EPILEPSY FOUNDATION | Ei 2

My Brain Map Innovation Institute Workshop Notes

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We graciously thank the workshop attendees for their participation and discussions before, during and after the workshop. Please see appendix for the list of all Workshop Attendees.

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Executive Summary

On September 6th and 7th 2018, the Epilepsy Innovation Institute (Ei^2) hosted an innovation workshop to assess the state of the science on personalized brain networks for epilepsy. The workshop convened multiple stakeholders including people impacted by epilepsy, neuroscientists, basic scientists, clinicians, mathematicians, engineers, and industry representatives. Conversations centered on what is currently possible, what are potential future directions, and what critical infrastructure is needed to move the field forward. The notes from the workshop discussions are outlined below.

Overview

Epilepsy is a common neurological condition characterized by the occurrence of recurrent spontaneous seizures. The World Health Organization estimates that there are over 50 million people living with epilepsy worldwide("World Health Organization: Epilepsy," 2018.). About a third of people living with epilepsy do not have seizure control, and those whose seizures are controlled are at risk of breakthrough seizures (Brodie, Barry, Bamagous, Norrie, & Kwan, 2012). This staggering number has not changed in decades, despite over a dozen new therapies for epilepsy since the 1990s (Löscher & Schmidt, 2011).

In 2017, the Epilepsy Innovation Institute (Ei^2), a research program of the Epilepsy Foundation, released an online survey asking where the scientific community should be focusing their efforts in epilepsy. Over six hundred individuals impacted by epilepsy responded from across the United States and abroad. Understanding the causes of epilepsy was selected as a top priority for researchers. We know people living with epilepsy are not having seizures one hundred percent of the time, so why are the seizures happening when they do? What is it about the pathways in the brain in the moments before a seizure starts? What is it about the brain activity that activates those pathways in that specific area of that brain in that specific moment? And what causes the seizure to then spread or not spread when the initiation occurs? Although researchers have been studying seizures for over a century, we still cannot answer the questions of why seizures start, how seizures spread and why they stop when they do for those impacted by epilepsy.

The International League Against Epilepsy (ILAE) defines a seizure as "a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain."(Fisher et al., 2014) . Evidence suggests that the pathophysiological underpinnings of seizure generation and propagation may involve abnormalities not just within a brain region but abnormalities distributed through multiple brain areas (Englot et al., 2015; Englot, Konrad, & Morgan, 2016; Luo et al., 2012; Morgan, Conrad, Abou-Khalil, Rogers, & Kang, 2015; Morgan, Rogers, Sonmezturk, Gore, & Abou-Khalil, 2011; Zaveri et al., 2009). To complicate matters, several non-epileptic conditions, for example tremor, also involve excessive or synchronous abnormal discharges (Hanson, Fuller, Lebedev, Turner, & Nicolelis, 2012). If we could understand what the epilepsy network is, perhaps this could explain the difference between the abnormal synchrony resulting in tremor, sleep and many other conditions versus seizures. In the past decade, there have been advances in complex system network approaches, such as those used in mathematics and computer science to study effective retrieval of web information or impact of failures in airline networks. Could these approaches also be applied to understanding the neurophysiological mechanisms underlying seizure propagation and termination in epilepsy?

On September 6th and 7th 2018, Ei^2 hosted an innovation workshop to assess how the community is currently applying network analysis to understanding an individual's seizure spread patterns and how to apply network approaches to revolutionize care. Workshop attendees were a diverse multi-disciplinary stakeholder group comprising of those impacted by epilepsy, neuroscientists, basic scientists, clinicians, mathematicians, engineers, and industry representatives. Conversations centered on current initiatives,

potential future directions, and critical infrastructure needed to better understand seizure initiation and propagation in a brain network.

Prior to the meeting, attendees were surveyed and highlighted multiple areas that would be improved and enhanced if we had a better understanding of epileptic networks such as:

- diagnosis,
- prediction of long-term outcome to surgery,
- seizure forecasting,
- treatment of co-occurring conditions such as depression, anxiety and cognitive dysfunction,
- tailoring of treatment to the individual, and
- identifying novel treatment strategies.

Although there was broad consensus that the concept of epileptic networks is important and have the potential to transform current clinical practice, it was less clear about how to apply that concept in practice to push the field forward. The term “epileptic networks” has been used as a catchall phrase to emphasize our need to expand the concept of seizures to incorporate large-scale network behavior and further our understanding of epilepsy and enhance care. A major barrier identified was the lack of a concrete framework for defining and analyzing these large-scale networks.

Defining and Modeling an Epilepsy Network

A network reduces a complex system like the brain to a map defined by nodes (brain regions) and edges (connections between the nodes). These connections can be defined structurally (i.e. nerve fiber tracts) or functionally (i.e. examining the coupling of different brain regions during activity). Together, the defined nodes and edges enable one to describe the brain in terms of connectome mapping of the brain. Once this connectome has been established, one can apply a conceptual analytical framework to characterize the organization of those epilepsy networks (Kramer & Cash, 2012; Richardson, 2012; Scott et al., 2018; van Diessen, Diederen, Braun, Jansen, & Stam, 2013). Such a network analysis allows for a dynamic model to be overlaid on the map that the connectome provides. For example, due to biological compensatory mechanisms and complex interactions between components, a network analysis could characterize the multiple nonlinear relationships over time and space that may otherwise be difficult to interpret. Moreover, a dynamic network analysis could interpret the propagation patterns in an individual’s connectome-based network that cannot be completely understood by examining individual components (connectome, dynamics) in isolation.

CONSIDERATIONS FOR MODELING AN EPILEPSY NETWORK

Mapping the epilepsy connectome may seem like an insurmountable challenge, as one debates how many nodes and edges to include in the model. For example, there are over one hundred billion neurons in the brain, not to mention glial cells, ion channels, dendrites, and other neural components. The field

of connectomics is still relatively novel and a diversity of methods are employed when constructing a network map. Therefore, when constructing a network map, fundamental decisions need to be made and clearly outlined. Considerations include:

1. How are the nodes/edges selected for the connectome map (i.e. is it spatial and/or functional and what criteria were used to make those determinations?),
2. What is the spatial scale (i.e. is it on the microscale (cellular level) or a macroscale (whole brain network) or mesoscale (somewhere in between?)), and
3. What is the timeframe that the network analysis wants to observe on this overlaid map (i.e. are the dynamics on the level of milliseconds for action potentials or hours, days or longer for modeling seizure occurrence)?

Once those decisions have been made, the next step is to collect data to observe how the network behaves. There are multiple tools that can be used to make observations about the network. Those who study structural connectivity of the epilepsy network often employ magnetic resonance imaging (MRI) with diffusion tensor imaging. Functional connectivity of the epilepsy network is often visualized with electroencephalograms (EEG), electrocorticography (ECoG), magnetoencephalography (MEG), or functional MRI (fMRI). A limitation of these approaches is that their analysis is subjective to human interpretation. For example, when epileptologists were asked to identify the start of a seizure on ECoG recordings, there was variability among the experts on the precise location of the start (Davis et al., 2018). The subjectivity is particularly relevant in network analysis, which may be dependent on human-selected parameters such as connectivity thresholds, brain sampling, and details of the measures used. Generally, a key recommendation for decision making in low-validity environments is the inclusion of algorithmic aids (Kahneman & Klein, 2009). Therefore, when making observations for a network, using a multimodal approach across different scales and computer automation to select the specific features of the network that are of interest, may help reduce the bias of human subjectivity and improve the quality of data observed for constructing the model.

Once the data has been collected, it is possible to create a mathematical model based on the network topology to reproduce the observations from the original data. For example, researchers studying ECoG recordings have identified a stereotyped signature profile at seizure onset, propagation, and termination (for review, see (Kramer & Cash, 2012)). Features that have been described include the “beta buzz,” in seizure initiation which describes the low-amplitude, high-frequency (20Hz) signal in a localized area (de Curtis & Gnatkovsky, 2009), along with a decoupling of 80-200Hz frequency rhythms at distal regions (Bartolomei et al., 2004; Schindler et al., 2010). During the propagation of a seizure, there have been observations of brain voltage dynamics transitioning to low-amplitude, low rhythmic activity that is a bit more varied than the initiation phase. There also seems to be a critical transition period, where voltage rhythms appear to decrease in frequency with time, known as a brain chirp phenomenon (Schiff et al., 2000). During the termination phase of a seizure, another critical transition has been observed, with an increase in temporal and spatial correlations resulting in a near simultaneous cessation of voltage activity across the brain (Kramer et al., 2012). Note that these observations have been based on human interpretation and not algorithmically decided.

Further reduction in bias can be accomplished by using fundamental approaches rooted in algorithms and mathematics. For instance, dynamical systems theory allowed the systematic classification of 16 different EEG seizure signature profiles (Viktor K. Jirsa, Stacey, Quilichini, Ivanov, & Bernard, 2014). This taxonomy was later investigated using experimental and clinical recordings, and a single profile was found consistently across species. When coupled with the underlying connectome of the brain, this computational model of a virtual epilepsy patient simulated how individual seizure propagation profiles could emerge within the network (V.K. Jirsa et al., 2017). Phenomenological approaches of this kind are typically less useful in generating physiologically mechanistic insight but have demonstrated predictive and explanatory power for patient-specific networks. Recognizing that different biological processes and causes might have similar outcomes that result in stereotype seizure dynamics, this phenomenological model approach presents a strategy to identify what those processes might be experimentally.

Although the brain is constantly plastic and brain activity is constantly changing, brain activity is not completely random. Therefore, we need to have quality data sets that help us constrain and parametrize the modeling. There are many different types of mathematical approaches that can be applied to modeling the observed dynamic nonlinear network. Mathematical modeling of brain networks is still an emerging field and the epilepsy field would benefit from an influx of new mathematical perspectives on analyzing network properties that could be applied to modeling seizure spread across the brain. For example, one could consider symmetries within the network topology or emerging theories on control principles of complex systems (Liu & Barabási, 2016; MacArthur, Sánchez-García, & Anderson, 2008). Once a computational model has been created, predictions can be formulated and validated on new data sets that have not been collected or trained on the initial model. This approach allows researchers to glean new mechanistic insights and create models which can then be tested prospectively.

Importance of Personalization and Classification of Networks

A huge challenge in the field is understanding which of the many available therapies will have the greatest efficacy and lowest risk for adverse effects in an individual patient. There are many paths to a seizure and multiple causes for epilepsy. The International League Against Epilepsy (ILAE) has stratified the underlying causes for epilepsy into 6 categories: genetics, brain structure abnormalities, metabolism changes, immune system abnormalities, infectious disease, and unknown causes (Berg & Millichap, 2013). What makes the heterogeneity so challenging is that very different mechanisms can give rise to the same clinical manifestation of a seizure. Thus, clinically similar patients may have different underlying mechanisms of epilepsy and therefore respond differently to therapeutic approaches. Network analysis could allow us to potentially classify these individuals separate from underlying mechanisms and potentially better tailor the treatment.

SURGERY AS A CASE-STUDY

Personalized network modeling is currently being considered to predict outcome in patients undergoing epilepsy surgery. When someone is being evaluated for surgery, source localization mapping methodology is used to identify a defined seizure onset zone or epileptogenic zone(Rosenow & Lüders, 2001). If that focal region can be identified, and it is safe to resect, then in theory, the person could be

cured of having seizures. However, the concept of a seizure focus is not as simple as originally believed. For surgeries outside the temporal lobe, even when there is a clear hypothesis for the area of seizure origin, less than half achieve complete seizure freedom (de Tisi et al., 2011; Englot, Breshears, Sun, Chang, & Auguste, 2013; Noe et al., 2013). A third of these candidates have a complex pattern of remission or relapse (de Tisi et al., 2011). It could be that the wrong brain tissue was removed; and the seizure focus was incompletely resected or missed entirely, or that the seizures were multi-focal in nature, or that the complex network reorganized itself. In the current clinical state, doctors do not know when they are right in their selection of brain tissue to be removed for seizure control. They only know after the fact if they were wrong, and generally it is not clear why a failure occurred Could a better understanding of the individual network improve care (Spencer, Gerrard, & Zaveri, 2018)?

There exist many different computational models of personalized networks for assessing epilepsy surgery. For example, using data collected from intracranial monitoring done for presurgical evaluation, and a dynamic network analysis approach, a computational model for neocortical focal seizures was generated that categorized seizures according to different onset mechanism (Wang, Goodfellow, Taylor, & Baier, 2014). The classification, if verified, could be clinically relevant, as it also suggested three different treatment approaches based on the network classification (pharmaceutical, surgical, or neurostimulation). This concept of network analysis having predictive value for surgery has been also studied in other computational models derived from magneto- and electro-encephalographic patient data to reconstruct networks (Coan et al., 2016; Englot et al., 2015; Goodfellow et al., 2016; Sinha et al., 2017). Modeling has also been done using data derived from other modalities such as fMRI, suggesting network changes over the course of disease progression (Morgan, Abou-Khalil, & Rogers, 2015; Morgan, Conrad, et al., 2015). For example, a pilot study coupled structural and functional MRI with longitudinal outcomes to develop a connectivity model for predicting success rates of surgery in temporal lobe epilepsy (Morgan et al., 2017)

Network changes in the different models suggest that there may be dynamic network biomarkers for predicting surgical treatment outcome. A caveat to this work is that it has all been done on retrospective data, and the true test of these different computational models will be in whether they can inform clinicians prospectively for new patients. Validation is needed to test the models in a clinical setting. This will become available, to some degree, through a prospective study, in which patients will be computationally virtualized and optimal resection targets estimated from model and stereotactic EEG in the French clinical trial Epinov (2019-2022) and the European Human Brain Project.

NEUROMODULATION AS A CASE-STUDY

Increasingly, the epilepsy community has turned to brain stimulation as an alternative therapy when surgical resection is not an option. There are several systems for neurostimulation currently available for therapy. The Responsive Neurostimulation (RNS) Device is an FDA-approved device that has been on the market since 2013. The device consists of a microcontroller-based stimulus generator that is implanted in the skull and electrodes that are implanted directly into the predefined seizure foci region of the brain. The implanted device monitors brain signals from the electrode contacts and sends electrical

pulses through the electrode contacts to the brain in response to aberrant electrical signals to disrupt the seizure circuitry close to the seizure onset zone.

The Deep Brain Stimulation (DBS) device, which was approved by the FDA in 2018, stimulates in a distal region of the seizure circuit, the anterior nucleus of the thalamus. The concept is to target modulatory centers that interface with the network rather than implanting in the seizure focus. In contrast to RNS therapy, a focal region does not need to be defined for the placement of the device. This concept of stimulating distal regions of the network to disrupt seizure propagation is not a novel one. One hypothesis is that these regions are "choke points", or strategic regions in the network that can terminate abnormal activity propagating through the network (Paz & Huguenard, 2015). Previously, the cerebellum, hippocampus, basal ganglia, and other nuclei of the thalamus have been suggested as potential therapeutic targets (Fountas, Kapsalaki, & Hadjigeorgiou, 2010; Velasco et al., 2006; Vuong & Devergnas, 2018; for a review see: Laxpati, Kasoff, & Gross, 2014;) However, the data was mixed on whether there was clinical improvement of seizures when targeting these areas. One of the challenges for neuromodulatory therapies is an understanding what parameters (i.e. amplitude, frequency, and duration) are needed for stimulation to be effective. There is also a need to consider novel spatiotemporal stimulation paradigms, adapting to the extended network nature of the brain. With the currently available FDA approved therapies (DBS and RNS), not every patient has a successful outcome. Furthermore, neuromodulation is not being examined systematically in any clinical or large-scale studies of any kind. Given the community wide agreement that stimulation is promising (high risk, potentially high gain), this could be a good target for an innovative clinical decision-making software. If one could better map the dynamic state of the network, there would be a better understanding of the stimuli needed to tailor the neuromodulation therapy to the individual, and this should improve treatment options.

Next Steps

Our hypothesis is that adopting network analysis and modeling will allow us to stratify individuals. These classifications will enhance our understanding of an individual's epilepsy and therefore tailor treatment to the individual more successfully. The overarching goal of Ei^2 is to lead an effort that would support personalized network modeling to transform care in epilepsy. From the Innovation Workshop, it was clear that we are still in early stages of network modeling. More exploratory analysis is needed rather than a large-scale effort to push the entire community forward towards one specific network modeling approach.

For us to get there, we need the following:

1. Access to more observational curated data to allow exploratory analysis for creating different types of computational network models. It still is not clear which computational model will be the best one, and therefore competition in this area should be encouraged. To promote interest in the field, one needs access to well-curated data, which is not a trivial task. Currently, significant resources have been allocated to start mapping out epilepsy neural circuits such as

through the Human Connectome Project, and the European Human Brain Project. Both initiatives are committed to sharing their large data-sets once complete, but the data will not be available until at least 2020. In the meantime, there are smaller data sets available at individual institutions. If there was support to curate data already collected in the siloed areas and support for preliminary exploratory analysis of those data, along with a culture of sharing those data with outside researchers, this could help accelerate activity in this area locally as well as in the various large-scale projects.

2. Most of the data already collected relies on data from intracranial monitoring for pre-surgical evaluation. These are invasive procedures and focus on a specific epilepsy subpopulation. Utilizing models based on non-invasive technologies such as high-density EEG, MEG, and neuroimaging could facilitate a diversity of new data sets to explore and understand epilepsy networks.
3. For new data collection initiatives, data where possible should be annotated throughout the patient's epilepsy progression from new onset through treatment and beyond due to the dynamic nature of the disorder over time. Such initiatives would allow mathematicians to better constrain and parameterize their modeling of the epilepsy network.
4. Interdisciplinary approaches involving clinicians, neuroscientists, computer scientists, and mathematicians to facilitate different perspectives in these early days of network modeling should be encouraged to move the field forward. This interdisciplinary conversations should also include basic science investigations, such as the use of optogenetic control techniques (Bui et al., 2018; Krook-Magnuson, Armstrong, Oijala, & Soltesz, 2013; Paz et al., 2013), or widefield imaging (Liou et al., 2018; Rossi, Wykes, Kullmann, & Carandini, 2017) to probe seizure networks at the cellular and macroscale levels in the laboratory. This is critical for bridging the knowledge gap between cellular pathologies and processes and large-scale epileptic activity.
5. Investments should be made to not just support exploratory analysis to model the networks but also create visualization tools to make those models easier to interpret. For clinicians to start applying network analysis as clinical decision-making tools (for surgery, neurostimulation, or other activities) there needs to be a tool that is user-friendly, interpretable and recommends an action for the clinician to take. Therefore, tools to visualize the network, model patient-specific brain networks and make predictions should be encouraged as outcomes of the exploratory analysis, which can then be put systematically to the test. It was also observed that there have been many clinical decision-making tools created that recommend non-action (such as no surgery), but when there are limited options and a patient does not have other options, these recommendations are not put into action.

References

Bartolomei, F., Wendling, F., Régis, J., Gavaret, M., Guye, M., & Chauvel, P. (2004). Pre-ictal synchronicity in limbic networks of mesial temporal lobe epilepsy. *Epilepsy Research*, *61*(1–3), 89–104. https://doi.org/10.1016/j.eplepsyres.2004.06.006

Berg, A. T., & Millichap, J. J. (2013). The 2010 Revised Classification of Seizures and Epilepsy. *CONTINUUM: Lifelong Learning in Neurology*, *19*(3 Epilepsy), 571–597. https://doi.org/10.1212/01.CON.0000431377.44312.9e

Brodie, M. J., Barry, S. J. E., Bamagous, G. A., Norrie, J. D., & Kwan, P. (2012). Patterns of treatment response in newly diagnosed epilepsy. *Neurology*, *78*(20), 1548–1554. https://doi.org/10.1212/WNL.0b013e3182563b19

Bui, A. D., Nguyen, T. M., Limouse, C., Kim, H. K., Szabo, G. G., Felong, S., … Soltesz, I. (2018). Dentate gyrus mossy cells control spontaneous convulsive seizures and spatial memory. *Science*, *359*(6377), 787–790. https://doi.org/10.1126/science.aan4074

Coan, A. C., Chaudhary, U. J., Frédéric Grouiller, Campos, B. M., Perani, S., De Ciantis, A., … Lemieux, L. (2016). EEG-fMRI in the presurgical evaluation of temporal lobe epilepsy. *Journal of Neurology, Neurosurgery & Psychiatry*, *87*(6), 642–649. https://doi.org/10.1136/jnnp-2015-310401

Davis, K. A., Devries, S. P., Krieger, A., Mihaylova, T., Minecan, D., Litt, B., … Stacey, W. C. (2018). The effect of increased intracranial EEG sampling rates in clinical practice. *Clinical Neurophysiology*, *129*(2), 360–367. https://doi.org/10.1016/j.clinph.2017.10.039

de Curtis, M., & Gnatkovsky, V. (2009). Reevaluating the mechanisms of focal ictogenesis: The role of low-voltage fast activity. *Epilepsia*, *50*(12), 2514–2525. https://doi.org/10.1111/j.1528-1167.2009.02249.x

de Tisi, J., Bell, G. S., Peacock, J. L., McEvoy, A. W., Harkness, W. F., Sander, J. W., & Duncan, J. S. (2011). The long-term outcome of adult epilepsy surgery, patterns of seizure remission, and relapse: a cohort study. *The Lancet*, *378*(9800), 1388–1395. https://doi.org/10.1016/S0140-6736(11)60890-8

Englot, D. J., Breshears, J. D., Sun, P. P., Chang, E. F., & Auguste, K. I. (2013). Seizure outcomes after resective surgery for extra–temporal lobe epilepsy in pediatric patients. *Journal of Neurosurgery: Pediatrics*, *12*(2), 126–133. https://doi.org/10.3171/2013.5.PEDS1336

Englot, D. J., Hinkley, L. B., Kort, N. S., Imber, B. S., Mizuiri, D., Honma, S. M., … Nagarajan, S. S. (2015). Global and regional functional connectivity maps of neural oscillations in focal epilepsy. *Brain*, *138*(8), 2249–2262. https://doi.org/10.1093/brain/awv130

Englot, D. J., Konrad, P. E., & Morgan, V. L. (2016). Regional and global connectivity disturbances in focal epilepsy, related neurocognitive sequelae, and potential mechanistic underpinnings. *Epilepsia*, *57*(10), 1546–1557. https://doi.org/10.1111/epi.13510

Fisher, R. S., Acevedo, C., Arzimanoglou, A., Bogacz, A., Cross, J. H., Elger, C. E., … Wiebe, S. (2014). ILAE Official Report: A practical clinical definition of epilepsy. *Epilepsia*, *55*(4), 475–482. https://doi.org/10.1111/epi.12550

Fountas, K. N., Kapsalaki, E., & Hadjigeorgiou, G. (2010). Cerebellar stimulation in the management of medically intractable epilepsy: a systematic and critical review. *Neurosurgical Focus*, *29*(2), E8. https://doi.org/10.3171/2010.5.FOCUS10111

Goodfellow, M., Rummel, C., Abela, E., Richardson, M. P., Schindler, K., & Terry, J. R. (2016). Estimation of brain network ictogenicity predicts outcome from epilepsy surgery. *Scientific Reports*, *6*(1), 29215. https://doi.org/10.1038/srep29215

Hanson, T. L., Fuller, A. M., Lebedev, M. A., Turner, D. A., & Nicolelis, M. A. L. (2012). Subcortical Neuronal Ensembles: An Analysis of Motor Task Association, Tremor, Oscillations, and Synchrony in Human Patients. *Journal of Neuroscience*, *32*(25), 8620–8632. https://doi.org/10.1523/JNEUROSCI.0750-12.2012

Jirsa, V. K., Proix, T., Perdikis, D., Woodman, M. M., Wang, H., Gonzalez-Martinez, J., … Bartolomei, F. (2017). The Virtual Epileptic Patient: Individualized whole-brain models of epilepsy spread. *NeuroImage*, *145*(Pt B), 377–388. https://doi.org/10.1016/j.neuroimage.2016.04.049

Jirsa, V. K., Stacey, W. C., Quilichini, P. P., Ivanov, A. I., & Bernard, C. (2014). On the nature of seizure dynamics. *Brain*, *137*(8), 2210–2230. https://doi.org/10.1093/brain/awu133

Kahneman, D., & Klein, G. (2009). Conditions for intuitive expertise: A failure to disagree. *American Psychologist*, *64*(6), 515–526. https://doi.org/10.1037/a0016755

Kramer, M. A., & Cash, S. S. (2012). Epilepsy as a Disorder of Cortical Network Organization. *The*

Neuroscientist, *18*(4), 360–372. https://doi.org/10.1177/1073858411422754

Kramer, M. A., Truccolo, W., Eden, U. T., Lepage, K. Q., Hochberg, L. R., Eskandar, E. N., … Cash, S. S. (2012). Human seizures self-terminate across spatial scales via a critical transition. *Proceedings of the National Academy of Sciences of the United States of America*, *109*(51), 21116–21121. https://doi.org/10.1073/pnas.1210047110

Krook-Magnuson, E., Armstrong, C., Oijala, M., & Soltesz, I. (2013). On-demand optogenetic control of spontaneous seizures in temporal lobe epilepsy. *Nature Communications*, *4*(1), 1376. https://doi.org/10.1038/ncomms2376

Laxpati, N. G., Kasoff, W. S., & Gross, R. E. (2014). Deep Brain Stimulation for the Treatment of Epilepsy: Circuits, Targets, and Trials. *Neurotherapeutics*, *11*(3), 508–526. https://doi.org/10.1007/s13311-014-0279-9

Liou, J., Ma, H., Wenzel, M., Zhao, M., Baird-Daniel, E., Smith, E. H., … Schevon, C. A. (2018). Role of inhibitory control in modulating focal seizure spread. *Brain*, *141*(7), 2083–2097. https://doi.org/10.1093/brain/awy116

Liu, Y.-Y., & Barabási, A.-L. (2016). Control principles of complex systems. *Reviews of Modern Physics*, *88*(3), 035006. https://doi.org/10.1103/RevModPhys.88.035006

Löscher, W., & Schmidt, D. (2011). Modern antiepileptic drug development has failed to deliver: Ways out of the current dilemma. *Epilepsia*, *52*(4), 657–678. https://doi.org/10.1111/j.1528-1167.2011.03024.x

Luo, C., Qiu, C., Guo, Z., Fang, J., Li, Q., Lei, X., … Yao, D. (2012). Disrupted Functional Brain Connectivity in Partial Epilepsy: A Resting-State fMRI Study. *PLoS ONE*, *7*(1), e28196. https://doi.org/10.1371/journal.pone.0028196

MacArthur, B. D., Sánchez-García, R. J., & Anderson, J. W. (2008). Symmetry in complex networks. *Discrete Applied Mathematics*, *156*(18), 3525–3531. https://doi.org/10.1016/J.DAM.2008.04.008

Morgan, V. L., Abou-Khalil, B., & Rogers, B. P. (2015). Evolution of Functional Connectivity of Brain Networks and Their Dynamic Interaction in Temporal Lobe Epilepsy. *Brain Connectivity*, *5*(1), 35–44. https://doi.org/10.1089/brain.2014.0251

Morgan, V. L., Conrad, B. N., Abou-Khalil, B., Rogers, B. P., & Kang, H. (2015). Increasing structural atrophy and functional isolation of the temporal lobe with duration of disease in temporal lobe epilepsy. *Epilepsy Research*, *110*, 171–178. https://doi.org/10.1016/j.eplepsyres.2014.12.006

Morgan, V. L., Englot, D. J., Rogers, B. P., Landman, B. A., Cakir, A., Abou-Khalil, B. W., & Anderson, A. W. (2017). Magnetic resonance imaging connectivity for the prediction of seizure outcome in temporal lobe epilepsy. *Epilepsia*, *58*(7), 1251–1260. https://doi.org/10.1111/epi.13762

Morgan, V. L., Rogers, B. P., Sonmezturk, H. H., Gore, J. C., & Abou-Khalil, B. (2011). Cross hippocampal influence in mesial temporal lobe epilepsy measured with high temporal resolution functional magnetic resonance imaging. *Epilepsia*, *52*(9), 1741–1749. https://doi.org/10.1111/j.1528-1167.2011.03196.x

Noe, K., Sulc, V., Wong-Kisiel, L., Wirrell, E., Van Gompel, J. J., Wetjen, N., … Worrell, G. A. (2013). Long-term Outcomes After Nonlesional Extratemporal Lobe Epilepsy Surgery. *JAMA Neurology*, *70*(8), 1003. https://doi.org/10.1001/jamaneurol.2013.209

Paz, J. T., Davidson, T. J., Frechette, E. S., Delord, B., Parada, I., Peng, K., … Huguenard, J. R. (2013). Closed-loop optogenetic control of thalamus as a tool for interrupting seizures after cortical injury. *Nature Neuroscience*, *16*(1), 64–70. https://doi.org/10.1038/nn.3269

Paz, J. T., & Huguenard, J. R. (2015). Microcircuits and their interactions in epilepsy: is the focus out of focus? *Nature Neuroscience*, *18*(3), 351–359. https://doi.org/10.1038/nn.3950

Richardson, M. P. (2012). Large scale brain models of epilepsy: dynamics meets connectomics. *Journal of Neurology, Neurosurgery & Psychiatry*, *83*(12), 1238–1248. https://doi.org/10.1136/jnnp-2011-301944

Rosenow, F., & Lüders, H. (2001). Presurgical evaluation of epilepsy. *Brain : A Journal of Neurology*, *124*(Pt 9), 1683–1700. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11522572

Rossi, L. F., Wykes, R. C., Kullmann, D. M., & Carandini, M. (2017). Focal cortical seizures start as standing waves and propagate respecting homotopic connectivity. *Nature Communications*, *8*(1), 217. https://doi.org/10.1038/s41467-017-00159-6

Schiff, S. J., Colella, D., Jacyna, G. M., Hughes, E., Creekmore, J. W., Marshall, A., … Weinstein, S. R. (2000). Brain chirps: spectrographic signatures of epileptic seizures. *Clinical Neurophysiology : Official Journal of the International Federation of Clinical Neurophysiology*, *111*(6), 953–958. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10825700

Schindler, K., Amor, F., Gast, H., Müller, M., Stibal, A., Mariani, L., & Rummel, C. (2010). Peri-ictal correlation dynamics of high-frequency (80–200Hz) intracranial EEG. *Epilepsy Research*, *89*(1), 72–81. https://doi.org/10.1016/j.eplepsyres.2009.11.006

Scott, R. C., Menendez de la Prida, L., Mahoney, J. M., Kobow, K., Sankar, R., & de Curtis, M. (2018). WONOEP APPRAISAL: The many facets of epilepsy networks. *Epilepsia*, *59*(8), 1475–1483. https://doi.org/10.1111/epi.14503

Sinha, N., Dauwels, J., Kaiser, M., Cash, S. S., Brandon Westover, M., Wang, Y., & Taylor, P. N. (2017). Predicting neurosurgical outcomes in focal epilepsy patients using computational modelling. *Brain*, *140*(2), 319–332. https://doi.org/10.1093/brain/aww299

Spencer, D. D., Gerrard, J. L., & Zaveri, H. P. (2018). The roles of surgery and technology in understanding focal epilepsy and its comorbidities. *The Lancet Neurology*, *17*(4), 373–382. https://doi.org/10.1016/S1474-4422(18)30031-0

van Diessen, E., Diederen, S. J. H., Braun, K. P. J., Jansen, F. E., & Stam, C. J. (2013). Functional and structural brain networks in epilepsy: What have we learned? *Epilepsia*, *54*(11), 1855–1865. https://doi.org/10.1111/epi.12350

Velasco, A. L., Velasco, F., Jimenez, F., Velasco, M., Castro, G., Carrillo-Ruiz, J. D., … Boleaga, B. (2006). Neuromodulation of the Centromedian Thalamic Nuclei in the Treatment of Generalized Seizures and the Improvement of the Quality of Life in Patients with Lennox–Gastaut Syndrome. *Epilepsia*, *47*(7), 1203–1212. https://doi.org/10.1111/j.1528-1167.2006.00593.x

Vuong, J., & Devergnas, A. (2018). The role of the basal ganglia in the control of seizure. *Journal of Neural Transmission (Vienna, Austria : 1996)*, *125*(3), 531–545. https://doi.org/10.1007/s00702-017-1768-x

Wang, Y., Goodfellow, M., Taylor, P. N., & Baier, G. (2014). Dynamic Mechanisms of Neocortical Focal Seizure Onset. *PLoS Computational Biology*, *10*(8), e1003787. https://doi.org/10.1371/journal.pcbi.1003787

World Health Organization: Epilepsy. (n.d.). Retrieved September 24, 2018, from http://doi.wiley.com/10.1111/epi.13294

Zaveri, H. P., Pincus, S. M., Goncharova, I. I., Duckrow, R. B., Spencer, D. D., & Spencer, S. S. (2009). Localization-related epilepsy exhibits significant connectivity away from the seizure-onset area. *NeuroReport*, *20*(9), 891–895. https://doi.org/10.1097/WNR.0b013e32832c78e0

Appendix: Workshop Attendees

Daniel Abrams, MD CEO & Co-Founder Cerebral Therapeutics	**Sonya Dumanis, PhD** Senior Director of Innovation Epilepsy Foundation	**Yang-Yu Liu, PhD** Assistant Professor, Harvard Medical School Associate Scientist, Brigham and Women's Hospital
Costas Anastassiou, PhD Assistant Investigator, Translational Neuroscience Lead Allen Institute for Brain Science	**Robert (Bob) Fisher, MD, PhD** Maslah Saul Professor of Neurology Stanford University Medical Center	**Randy McIntosh, PhD** Vice President, Research Director of Rotman Research Institute University of Toronto, Baycrest Centre
Kari Ashmont, PhD Health Program Specialist National Institute of Neurological Disorders and Stroke National Institutes of Health	**Patrick Forcelli, PhD** Assistant Professor Pharmacology, Georgetown University	**Victoria (Vicky) Morgan, PhD** Associate Professor of Radiology & Radiological Sciences and Biomedical Engineering Vanderbilt University Medical Center
Christophe Bernard, PhD Head of the Physiology and Physiopatholgy of Neuronal Networks Group (PhysioNet) Institute de Neurosciences des Systemes (INSERM), Aix-Marseille University	**Jacqueline (Jackie) French, MD** Professor, Neurology, New York University; co-director of epilepsy research and epilepsy clinical trials New York University Comprehensive Epilepsy Center	**Jeff Muller, PhD** Technical Coordinator at the Human Brain Project
Boris Bernhardt, PhD Assistant Professor in the Department of Neurology and Neurosurgery McGill University	**Brandy Fureman, PhD** Vice President of Research and New Therapies Epilepsy Foundation	**Jeanne Paz, PhD** Assistant Investigator Gladstone Institute of Neurological Disease
Hal Blumenfeld, MD, PhD Mark Loughridge and Michele Williams Professor of Neurology and Professor of Neuroscience and of Neurosurgery Yale School of Medicine	**Philip (Phil) Gattone, M.Ed** CEO & President Epilepsy Foundation	**Mark Richardson, BM, BCh, FRCP, PhD** Vice Dean Neuroscience Kings College London
Milan Brazdil, PhD Research Group Leader CEITEC (Central European Institute of Technology)	**Tanja Hellier, PhD** VP Clinical Applications, Epilog Affiliate Assistant Professor, Department of Neurosurgery Medical University in South Carolina	**Sridevi (Sri) Sarma, PhD** Assistant Professor Neurology Johns Hopkins University
Gail Cassidy Caregiver	**John Huguenard, PhD** Professor of Neurology, Professor of Neurosurgery Stanford University	**Catherine (Cathy) Schevon, MD, PhD** Associate Professor of Neurology Columbia University
Kailey Cassidy Patient Representative	**Nigel Isaacs, PharmD, JD, BCPS** Senior Medical Science Liaison Neurology & Metabolics, Eisai, Inc	**Steven Schiff, MD, PhD** Director, Penn State Center for Neural Engineering, Brush Chair Professor of Engineering Professor of Neurosurgery, Professor of Engineering Science and Mechanics Penn State Huck Institutes of Life Sciences
Penny Dacks, PhD Director of Research American Epilepsy Society	**Barbara Jobst, MD, PhD** Director Dartmouth-Hitchcock Epilepsy Center	**Theodore (Ted) Schwartz, MD** Professor of Neurosurgery, Otolaryngology & Neuroscience, Director of Surgical Neuro-Oncology, Epilepsy & Pituitary Surgery Weill Cornell Medical College, New York Presbyterian Hospital
Kathryn (Kate) Davis, MD Assistant Professor of Neurology Medical Director of the Epilepsy Monitoring Unit and Penn Epilepsy Surgical Program University of Pennsylvania	**Mark Kramer, PhD** Associate Professor Boston University	**Ashwini (Ash) Sharan, MD** Professor, Department of Neurosurgery Thomas Jefferson University
Kristin Davis Caregiver Representative	**Esther Krook- Magnuson, PhD** Assistant Professor, Department of Neuroscience University of Minnesota	**Doug Sheffield, VMD, PhD** Chief Scientific Officer Cadence Neuroscience

Robert (Bob) Smith, MBA Chair of Board of Directors, Epilepsy Foundation	**John Stern, MD** Professor Department of Neurology, Director of the Epilepsy Clinical Program, and Director of the Epilepsy Residency Training Program David Geffen School of Medicine at UCLA	**Fabrice Wendling, PhD** INSERM Senior Research Scientist University of Rennes, France
Ivan Soltesz, PhD James R Doty Professor of Neurosurgery and Neurosciences Stanford University	**Peter Taylor, PhD** Faculty Newcastle University	**Kareem Zaghloul, MD, PhD** Investigator, Functional and Restorative Neurosurgery Unit NINDS, NIH
William (Bill) Stacey, MD, PhD Associate Professor of Neurology Michigan University School of Medicine	**Joost Wagenaar, PhD** Co-Founder, VP Scientific Applications Blackfynn	**Hitten Zavari, PhD** Assistant Professor Yale School of Medicine