eNeuro

Opinion | Disorders of the Nervous System

Seizure Forecasting from idea to reality — Outcomes of the My Seizure Gauge Epilepsy Innovation Institute Workshop

Seizure Forecasting from idea to reality

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DOI: 10.1523/ENEURO.0349-17.2017

Received: 13 October 2017

Revised: 20 November 2017

Accepted: 21 November 2017

Published: 14 December 2017

Author Contributions: C.B., B.E.F., G.W., J.A.F., S.B.D. designed workshop; S.B.D. Wrote the paper.

Funding: http://doi.org/10.13039/100001605Epilepsy Foundation

Conflict of Interest: Authors report no conflict of interest.

Epilepsy Innovation Institute, a research program of the Epilepsy Foundation of America supported this work.

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Cite as: eNeuro 2017; 10.1523/ENEURO.0349-17.2017

1. **Manuscript Title:** Seizure Forecasting from idea to reality – Outcomes of the My Seizure Gauge Epilepsy Innovation Institute Workshop

2. **Abbreviated Title:** Seizure Forecasting from idea to reality

3. **List all Author Names and Affiliations in order as they would appear in the published article**

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4. **Author Contributions:** CB, BEF, GW, JAF, SBD designed workshop; SBD Wrote the paper

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6. **Number of Figures:** 0
7. **Number of Tables:** 1
8. **Number of Multimedia:** 0
9. **Number of words for Abstract:** 229
10. **Number of words for Significance Statement:** 109
11. **Number of words for Introduction:** 317
12. **Number of words for Discussion:** 1,545

13. **Acknowledgements:** We graciously thank the workshop attendees for their participation and discussions before, during and after the My Seizure Gauge Innovation Institute workshop held in Washington DC, on August 28-29th, 2017. Please visit www.epilepsy.com/myseizuregauge for more details on who attended. The Epilepsy Innovation Institute is supported by corporate sponsors (including Eisai and TSymmetry), local organizations (including Epilepsy Foundation Greater Chicago), and individual philanthropic donations.

14. **Conflict of Interest:** Authors report no conflict of interest

15. **Funding sources:** Epilepsy Innovation Institute, a research program of the Epilepsy Foundation of America supported this work.

Abstract:

The Epilepsy Innovation Institute, Ei^2, is a new research program of the Epilepsy Foundation designed to be an innovation incubator for epilepsy. Ei^2 research areas are selected based on community surveys that ask people impacted by epilepsy what they would like researchers to focus on. In their 2016 survey, unpredictability was selected as a top issue regardless of seizure frequency or severity. In response to this need, Ei^2 launched the My Seizure Gauge challenge, with the end goal of creating a personalized seizure advisory system device. Prior to moving forward, Ei^2 convened a diverse group of stakeholders from people impacted by epilepsy and clinicians, to device developers and data scientists to basic science researchers and regulators for a state of the science of assessment on seizure forecasting. From the discussions, it was clear that we are at an exciting crossroads. With the advances in bioengineering, we can utilize digital markers, wearables and biosensors as parameters for a seizure forecasting algorithm. There are also over a thousand individuals who have been implanted with ambulatory intracranial EEG recording devices. Pairing up peripheral measurements to brain states could identify new relationships and insights. Another key component is the heterogeneity of the relationships indicating that pooling findings across groups is suboptimal, and that data collection will need to be done on longer time scales to allow for individualization of potential seizure forecasting algorithms.

Significance Statement:

Unpredictability of seizures is a top issue for those living with epilepsy regardless of seizure frequency and type. There is the fear of not knowing when a seizure will start and not knowing what triggers the seizure onset. In August, the Epilepsy Innovation Institute (Ei^2) convened a diverse group of stakeholders to assess the state of the science on seizure forecasting algorithms. Seizure forecasting shifts away from categorical seizure prediction assessments of whether a seizure will or will

not occur and instead focuses on identifying the brain state wherein there is a high probability of a seizure occurrence. Here, we discuss the outcomes of those discussions and next steps.

Introduction:

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 ("WHO | Epilepsy," 2017). 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 14 new therapies for epilepsy entering the market since the 1990s (Löscher & Schmidt, 2011)

In 2016, the Epilepsy Innovation Institute (Ei^2), a research program of the Epilepsy Foundation, released an online survey asking their community what aspects of epilepsy impact them the most. Over one thousand individuals responded from across the United States and abroad. An overwhelming majority of respondents, regardless of seizure frequency and type, selected unpredictability of seizures as a top issue ("Epilepsy Foundation | Ei^2 Community Survey, 2016). Many wrote about the fear of not knowing *when* a seizure will start and not knowing *what* triggers the seizure onset. In response to this survey, Ei^2 developed the My Seizure Gauge initiative with the end-goal of creating a seizure risk-assessment system that could evaluate the likelihood of a seizure on a daily basis. Before moving forward with the initiative, Ei^2 hosted an innovation workshop to assess the state of the science on seizure forecasting and risk assessment algorithms. Here, we are defining seizure forecasting as the process of identifying body states wherein there is a high probability of a seizure occurrence.

The following scientific themes emerged from the discussions:

1. Seizures have multi-temporal patterns on ultradian, circadian, and multi-day time scales,
2. Multimodal analysis of seizure events coupling EEG with non-EEG measures may enhance seizure forecasting algorithms,
3. Individualization and personalization of a seizure forecasting algorithm is necessary

Each of these themes is highlighted in more detail below.

Seizures have multi-temporal patterns on ultradian, circadian, and multi-day time scales

An overwhelming body of evidence indicates that seizures have non-random time specific patterns (Bercel, 2006; Griffiths & Fox, 1938; Langdon-Down & Russell Brain, 1929; Loddenkemper, Lockley, Kaleyias, & Kothare, 2011). Recently, these observations have been replicated in long-term ambulatory intracranial recordings from people implanted with the NeuroVista device (Cook et al 2013 and Karoly et al 2017), and in the Neuropace Rapid Neurostimulation (RNS) device (Spencer et al., 2016; Baud et al., in press). 98% of people with an implanted Neuropace RNS device have clear circadian and/or ultradian patterns for electrocordiographic seizures (Spencer et al., 2016). In addition to circadian rhythms, researchers also observed multi-day cycle of interictal epileptiform activity varying between 7 and 35 days across patients, but relatively stable within each patient (Baud et al., in press).

Interestingly, in both the 1938 Griffiths & Fox study, as well as in the recent Neurovista and Neuropace studies, the complexity of detecting time patterns is discussed (Griffiths & Fox, 1938; Griffiths & Fox, 1938, Freestone, Karoly, & Cook, 2017, Baud et al., in press). Across the whole group, there was a lot of variability, but within an individual, seizure time patterns could be very consistent. Understanding these brain rhythms, why they happen and how they can influence seizure occurrences may be key to understanding seizure susceptibility for the individual, and thus to developing a personalized therapeutic strategy.

Multimodal analysis of seizure events coupling EEG with non-EEG measures may enhance seizure forecasting algorithms

The brain is a dynamic organ reacting to internal and external inputs. The temporal rhythm of seizures suggests that there may be several metabolic or biophysical measures that could be detected prior to a seizure event. For example, several biophysical parameters are suggested to change slowly during or preceding a seizure including extracellular levels of potassium, oxygen, pH, and intracellular NADH/FAD+ (Jirsa, Stacey, Quilichini, Ivanov, & Bernard, 2014). Very fast oscillations (VFOs) have also been observed to precede seizure onset, and a review of the literature suggests that their occurrence may be due to gap junctions that are brain pH dependent (Traub, Whittington, & Cunningham, 2010).

With advances in bioengineering, we have the capabilities to measure ionic changes *in vivo* coupled with intracranial EEG recordings. A recent study demonstrated that changes in the extracellular composition of potassium, calcium and magnesium independent of local electrical activity could distinguish which rodents were in a sleep brain state versus an awake brain state (Ding et al., 2016). This study highlights how measuring brain ionic changes *in vivo* could enhance our understanding of seizure vulnerable brain states.

There may also be multiple ways to capture information about an individual noninvasively that were previously impossible. In 2017, Mike Snyder's group provided the proof of principle for how commercially wearable biosensors could identify early signs of Lyme disease and inflammatory responses (Li et al., 2017)**.** With video and 3D imaging analysis, we are also now capable of mapping sub-second units of movement that are indiscernible to the human eye to analyze behavior (Wiltschko et al., 2015). Indeed, sweat sensing technologies have advanced rapidly in the past 5 years. It will soon be possible to have noninvasive continuous monitoring of various metabolites such as cortisol, something that was not possible previously (Bandodkar & Wang, 2014; Rose et al., 2015; Sonner et al., 2015). There are also optical measures of motion and stress that can recognize heart rate and respiration at a

distance (Nam et al., 2016). These tools could be used to analyze potential physiological and behavioral changes occurring hours prior to a seizure event.

Sheryl Haut's group has reported that a subset of people living with epilepsy are very good at predicting their seizures up to 6 hours before the seizure event occurs (Haut, Hall, Borkowski, Tennen, & Lipton, 2013). These individuals kept a diary and reported premonitory features associated with accurate predicted seizure occurrence. The top ten features included blurred vision, light sensitivity, dizziness, feeling emotional, concentration difficulty, hunger/food cravings, noise sensitivity, tiredness/weariness, thirst, and difficulty with thoughts. This all suggests that there may be alterations in body chemistry, associated behaviors and symptoms that could improve seizure forecasting. Some of these body changes could be picked up through existing biosensors, mobile devices, or video monitoring. There are also preliminary findings reported by Dean Freestone, University of Melbourne, that atmospheric change such as humidity and pressure may be a variable in seizure likelihood for people with epilepsy. This intriguing observation suggests that the surround environments may also play a role in the analysis. At the Ei^2 workshop, multiple parameters were identified as potential measurements to consider in addition to EEG recordings when thinking about creating a seizure prediction device (Table 1).

*Table 1 Potential measurements discussed at the Ei^2 workshop that could enhance a seizure forecasting algorithm. These measurements could be collected in numerous ways: *indicates those that could be captured by patient diary, others could be measured through smartphone, biosensors or through sweat collection*

• Mood* • Cortisol • Orexin • Patient self-prediction* • Electrical Dermal Activity • Heart rate • Temperature / Weather • Respiration	• Stress* • Fatigue* • Irritability* • Sex hormones • pH (brain) • Time of day* • Antiepileptic Drug levels • Blood oxygen • Inflammatory markers • Glucose	• Compliance • Illness* • Food/alcohol intake • Orientation (cognitive) • Gait • Finer movements • Ketones • Speech

• Sleep cycle changes (sleep/wake staging) • Sleep quality	• External environment	• Body Temperature

With the advances in bioengineering and biosensors, we have the capability to acquire noninvasive multimodal data that allow us to identify potential lead candidate signals that inform about seizure probability to circle back and test.

Individualization and personalization of a seizure forecasting algorithm is necessary

There is a complexity and heterogeneity to understanding the susceptibility of seizures. 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). Not only are there multiple causes for a seizure, there are also varying responses to those causes within an individual that could lead to a seizure vulnerable brain state. Therefore, pooling data across individuals becomes suboptimal. The need for individualization also underscores the need for longitudinal data. Seizures are episodic events, and there needs to be enough seizures for the algorithms to be optimized over time.

Previously, we only had short-term intracranial EEG data (typically up to 1 week) for analysis from pre-surgical monitoring units (Mormann, Andrzejak, Elger, & Lehnertz, 2007). The short-term recordings are of too limited a time span with insufficient interictal and ictal data to build patient-specific models for seizure likelihood. There are now over a thousand individuals who have ambulatory intracranial EEG systems through the FDA approved Neuropace RNS system or through the Activa PC system by Medtronic in clinical trials. There are also less invasive seizure monitoring devices in development from ambulatory surface EEG caps to sub-scalp EEG implants. This allows us to have access

to real-time longitudinal data (on the magnitude of years) of EEG recordings. We can use these devices to link measured brain states with peripheral measures to improve our ability to assess seizure likelihood.

One approach could be to utilize machine learning. Deep learning has proven to be highly successful at automated complicated pattern recognition tasks in EEG (Nurse and Mashford et. Al, 2016; I. Kiral-Kornek et al., 2017) and multimodal data, and therefore constitutes a generalisable technique for a seizure prediction system that can be tuned to an individual's unique seizure data signature. Machine learning is not the answer for all problems, but it works well with unstructured data. However, for such an approach to be meaningful, subject matter expertise will be critical to ensure accurate classifications of the data and interpretable results. For example, mathematical modeling of electrophysiological signatures of seizures evolutionarily conserved across species from flies to humans has yielded 16 distinct electrocardiographic seizure profiles (Jirsa et al., 2014). This new taxonomy may spur potential new insights into seizure mechanism that could help interpret the data findings and find correlations in body chemistry associated with these different seizure classifications. Moreover, insights into seizure onset mechanisms from a dynamical systems perspective may help identify useful data features (Meisel & Kuehn, 2012) to integrate into machine learning algorithms.

Once an algorithm is developed, it will also be important to consider the ability to personalize the algorithm. There are different utilities for knowing when someone is at risk for seizures. For example, some individuals may want to know when they are likely to have a subclinical seizure (an electrographical seizure without any outward symptoms) while others may only want to know when they are likely to be experiencing a tonic-clonic seizures (convulsions) or loss of consciousness. Some are troubled more than others by false positive warnings, which can elevate anxiety levels. There should also be considerations about what forecasting ranges are useful and what forecasting probabilities would be meaningful. Lessons learned from the Neurovista trial were that, although it was a

mathematically sound way to characterize performance, a patient might have a different assessment of what a good performance algorithm means. Therefore, for any algorithm, a patient feedback loop is critical to ensure specificity of the algorithm, successful adoption and good performance. One of the workshop participants likened it to a Pandora Music algorithm, where the user would hit like or don't like to the forecasting to ensure that the forecasting algorithm could be optimized and fine-tuned to the individual.

Next Steps

The overarching goal of Ei^2 is to lead an effort that would create an individualized seizure gauge that will allow a person with epilepsy to monitor the ***likelihood*** of a seizure on a daily basis. The word likelihood is emphasized as it shifts the focus from 100% certainty to assessing probability states. Anecdotally, there are some patients who report that after decades of living with epilepsy they can know when they are likely to have a seizure event. Our goal is to speed that process up for the community. From the Innovation Workshop, it became clear that we need to focus on identifying and better understanding the changes in the body that may precede the onset of a seizure, at a time course that may be hours or days before the clinical (observable) seizure. Therefore, linking an ambulatory long-term seizure monitoring approach (from already implanted in-depth intracranial EEGs, sub-scalp EEGs, to wearable surface EEG caps, or video monitoring) to a host of non-EEG based methods from emerging biosensors, wearable device technology, and digital markers on a longitudinal time scale would help us identify new relationships between brain state and non-invasive or minimally invasive read-outs. Insights from this study can then be used to design less-invasive approaches to a future seizure gauge device for forecasting seizures.

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