EASTERN ASSOCIATION OF ELECTROENCEPHALOGRAPHERS

76th Annual Meeting

Zoom Meeting

February 12–13, 2022

This meeting is supported with funding from:

EAEEG 76th ANNUAL MEETING

Saturday, February 12, 2022

9:00am	Welcome
9:05am	**Mini Symposium #1 – Cycles in the Epileptic Brain**
	Chair: Steve Gibbs
	Maxime Baud, MD, PhD (University of Bern) - *Multidien and circadian rhythms in the epileptic brain*
	Lino Nobili, MD, PhD (University of Genova) - *The influence of sleep on seizures and epilepsy*
10:15am	Break
10:30am	**Kershman Lecture**
	Chair: Paul Hwang
	Guy Rouleau, MD, PhD (McGill University) - *Genetics of essential tremor*
11:30am	**Mini Symposium #2 – Temporal Dynamics & Network State on the Seizure Continuum**
	Chair: Jeremy Barry
	Jeremy Barry, PhD (University of Vermont) – *Spatial learning impairments and entorhinal hippocampal circuit discoordination post experimental febrile status epilepticus*
	Wes Clawson, PhD (Tufts University) - *Disordered information processing dynamics in experimental epilepsy*
	Christos Lisgaras, PhD (Nathan Kline Institute for Psychiatric Research) - *Robust chronic convulsive seizures, high frequency oscillations, and human seizure onset patterns in an intrahippocampal kainic acid model in mice*
12:30pm	Adjournment

EAEEG 76th ANNUAL MEETING

Sunday, February 13, 2022

8:45am Paul Hwang, MD (University of Toronto) - *History of the Eastern Association of Electroencephalographers*

9:20am **Mini Symposium #3 – Using EEG to Study Consciousness**

Chair: Mac Burnham

Catherine Duclos, PhD (University of Montreal) - *Response of the EEG network to anesthesia may help predict recovery from coma and disorders of consciousness*

Simone Sarasso, PhD (University of Milan) - *Local sleep-like cortical reactivity in the awake brain after focal injury*

10:30am **Milner Lecture**

Chair: Mary Pat McAndrews

Robyn Busch, PhD (Cleveland Clinic) - *Automated screening to detect cognitive impairment in epilepsy*

11:30am Break

11:45am **Free Communications**

Chair: Erik Kobylarz

Michelle Kloc (University of Vermont College of Medicine) - *Early life seizures lead to fronto-striatal circuit dysfunction*

Merrick Fallah (University of Toronto) - *Hippocampal hyperexcitability and NMDA sensitivity in a novel model of CDKL5-Deficiency Disorder*

Lukasz Dlugosz (University of Toronto) - *Anti-seizure effects of the cannabinoids in the Maximal Electroshock Seizure model*

Alexandra Santos (University of Toronto) – *Modelling epilepsy in cerebral organoids: Oxygen-glucose deprivation as a convulsant*

Angel Lopez (University of Texas) - *Sleep deficits, repetitive behaviors, and increased slow gamma power in an Ank3 mouse model of epilepsy-mood disorder comorbidity*

Reem Alyoubi (King Abdulaziz University) - *Association of genetic polymorphism of methyl tetrahydrofolate reductase (MTHFR) enzyme with antiepileptic drug response among pediatric patients in Jeddah, Saudi Arabia*

Thaddeus Kobylarz (Bell Laboratories) – *Potential means to circumvent a neural network achievement impasse*

1:30pm **Annual General Meeting**

Chair: Steve Gibbs

1:45pm Adjournment

Thank you to UCB, Eisai and PendoPharm for sponsoring this conference,

and thank you to Sunovion for sponsoring the Kershman Lecture.

Early life seizures lead to fronto-striatal circuit dysfunction

Michelle L. Kloc[1], Madeline G. Shultes[1], R. Davi Pressman[1], Carmel A. Schneur[1], Samuel A. Liebman[1], Matthew C. Broomer[2], Mark E. Bouton[2], Gregory L. Holmes[1]

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Background: Fronto-striatal circuit dysfunction has been implicated in several neuropsychiatric disorders, including autism spectrum disorders (ASD) (1), attention-deficit hyperactivity disorder (ADHD) (2), and obsessive-compulsive disorder (OCD) (3), where repetitive behaviors are a significant phenotype. It has been suggested that striatal dysfunction may not be restricted to the repetitive movements of these disorders, but may also underlie cognitive flexibility, motivation, learning, and attention. Early life epilepsies are associated with higher likelihood of later life temporal lobe epilepsy (TLE) and comorbid disorders such as OCD. Commonalities in hyperexcitability, altered signaling, and hyperconnectivity that have been documented in OCD models have also been demonstrated in the early life seizure (ELS) model by our lab (4, 5).

Neuronal circuits and systems mature postnatally, throughout early life, in some cases making them more susceptible to alterations in normal activity. Normal development of the prefrontal and orbitofrontal cortices are critical for correct execution of goal-directed action and normal function of the striatum, a major component of the basal ganglia (6), which is responsible for behavioral control of movement. Disruptive events such as ELS can alter the course of neural circuit development. Altered expression of the power, frequency, or functional connectivity across delta (1-5 Hz), theta (5-12 Hz), beta (12-25 Hz), and gamma (25-90 Hz) bandwidths in the PFC, OFC, and dorsomedial striatum of the fronto-striatal circuit have been associated with cognitive dysfunction and psychiatric disorders that feature repetitive behaviors to varying degrees depending on the animal model. To evaluate changes in physiology and behavior caused by ELS, we measure local field potentials from awake behaving rats.

It remains unclear whether consistent pathological features underlying fronto-striatal circuit dysfunction may occur following ELS rats that express repetitive behaviors observed in other neuropsychiatric disorders. Our lab has previously shown that a rat model of early life seizures (ELS) can exhibit OCD-like behaviors (4). Whether abnormal activity in the fronto-striatal circuit correlates with behavioral outcomes in the ELS model remains unclear. In humans, repetitive behaviors can result from malfunction of a learning process that leads to loss of the ability to repress sensorimotor associations (7-9). There are behavioral similarities between habits and OCD. Instrumental behaviors are thought to take two forms: goal-directed actions, which are emitted if they produce an outcome that the organism currently wants or values, and habits, which are behaviors that automatically occur in a particular situation without regard to the outcome's current value. Actions and habits are typically distinguished with reinforcer devaluation methods, such as taste aversion: a rat is conditioned to a reinforcer via instrumental training, after which the reinforcer is paired with a toxin (such as lithium chloride), and then instrumental responding is tested in extinction. If the response is a goal-directed action, reinforcer devaluation suppresses it; the animal behaves as if it remembers that the action led to the outcome, and that it no longer values the outcome. In contrast, if the behavior is a habit, devaluation has no effect on the response (10-12). Here, we will use an operant reinforcer devaluation task to evaluate habit formation in rats with ELS and their littermate controls (CTL).

Objectives: The goals of this study are to identify whether electrophysiological dysfunction to fronto-striatal circuits following early life seizures may underlie altered habit formation behaviors.

Methods: Rat pups were subjected to 5 flurothyl-induced seizures daily from P1 to P10 for a total of 50 seizures. Following induction of each seizure, pups were removed from the flurothyl exposure after approximately 2 min when tonic extension of both forelimbs and hindlimbs was observed. Littermate CTL pups were removed from the dam and placed in the chamber without flurothyl for a similar time to control for the effects of maternal separation stress. At P50 rats underwent stereotaxic surgery with implantation of 2 tetrodes in the CA1 region of the hippocampus, 2 tetrodes in PFC (lateral part of the orbitofrontal cortex) and 2 tetrodes in the dorsomedial striatum. Rats then underwent food restriction and testing in the operant reinforcer devaluation chamber. During these sessions, one lever is available for the rat to press and 30 pellets are delivered according to a random time 30 s schedule. Once rats learn the task they are removed from the chamber and given an intraperitoneal (i.p.) injection of 20 ml/kg LiCl (0.15 M). Following the LiCl rats will be tested for habit behaviors in the operant chamber. Rats with persistent lever pushing will be classified as having habits or compulsive behavior. Rats were then given food *ad libitum* and EEGs were measured in a low-demand Flower Pot task, where rats predominantly sit in an environment with minimal space to move to provide a behavioral baseline measurement of neural activity.

Results: Neither CTL or ELS groups exhibited significant transitions from goal-directed actions in to habits in the operant chamber task, although ELS group exhibited lower lever-pressing than the CTL group following reinforcer devaluation. EEGs recorded from rats during the operant task and low-demand Flower Pot task showed differences in signaling in the striatum, orbitofrontal cortex, and hippocampus. Theta (5-12 Hz) frequency was higher in all three structures during the operant box task, and normalized theta power was significantly more variable in the ELS group. During low-demand recordings in the Flower Pot, theta frequency was similar across groups in OFC and DMS, but significantly lower in the hippocampus; normalized theta power was higher in the OFC and DMS but similar in the hippocampus. Our preliminary findings suggest that early life seizures alter the signaling properties within the orbitofrontal cortex and striatum.

Significance: These findings suggest that although rats with ELS are not more likely to transition from goal-directed actions to habits than their CTL littermates, they do exhibit task-dependent alterations to signaling properties in striatum and orbitofrontal cortex. This study may highlight novel mechanisms through which early life epilepsies can alter circuit development and function.

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Hippocampal Hyperexcitability and NMDA Sensitivity in a Novel Model of CDKL5-Deficiency Disorder

Merrick S. Fallah[1,2], Elena Sidorova-Darmos[1], Dora Szarics[1,2], Richard Logan[1], Liang Zhang[1,3,5], W. McIntyre Burnham[2], James H. Eubanks[1,2,4,5,6]

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CDKL5-Deficiency Disorder (CDD) is a rare, X-linked, epileptic encephalopathy and neurodevelopmental disorder. CDD is caused by mutations in the Cyclin-Dependent Kinase-Like 5 gene (*CDKL5*), a serine-threonine kinase that is highly expressed in the brain. CDD is characterized by early-onset seizures (typically within the first few months of life), developmental delay, autonomic dysfunction, and sleep disturbances. The majority of *CDKL5* mutations reported to date occur in the region encoding the catalytic (N-terminal) domain. A small number of mutations have been identified in the C-terminal domain; a region important for normal protein trafficking. To investigate the mechanism of pathogenesis in C-terminal *CDKL5* mutations we generated a novel, patient-specific model (Cdkl5^{DCT}) using CRISPR-Cas9 targeted gene editing. This mutation is a two-base pair deletion occurring in exon 19 of *Cdkl5*. These subjects were implanted with two bipolar electrodes in both cortex and hippocampus for EEG recording. Baseline EEG recordings have found the presence of epileptiform activity in a subset of subjects. Subjects were then administered NMDA (30 mg/kg), a dose that was found not to induce any seizure activity in controls. NMDA induced seizures in all Cdkl5^{DCT} subjects with varying severity: brief electrographic seizures, intermittent/recurring seizures with a motor component (Racine scale Stage 3-5), and status epilepticus. At this time, no spontaneous seizures have been recorded, consistent with findings in the *Cdkl5*-KO model. Mutations in the C-terminal region of *Cdkl5* are sufficient to induce hyperexcitable neural networks in this model system and recapitulate several aspects of the clinical condition.

This work was funded by EpLink - The Epilepsy Research Program of the Ontario Brain Institute, operating grants from CDKL5 Canada and the Canadian Institutes of Health Research, as well as a graduate scholarship from the Province of Ontario.

Anti-Seizure Effects of the Cannabinoids in the Maximal Electroshock Seizure Model

Lukasz Dlugosz[1], Brian W. Scott[1], Nicole K. Carroll[2], Leo B. Silenieks[2], Guy A. Higgins[1,2], and W. McIntyre Burnham[1,3]

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Background: Even with more than 20 effective anti-seizure drugs, about 30% of people with epilepsy continue to have seizures. The maximal electroshock (MES) model is used in rodents to screen novel drugs for their possible effectiveness against tonic-clonic seizures. The objective of this study was to assess the efficacy of cannabidiol (CBD), Δ9-tetrahydrocannabinol (THC), and CBD+THC against MES seizures in mice.

Methods: Adult, male CF-1 mice were injected intraperitoneally (i.p.) with 1) CBD (0–640 mg/kg) 2 hours before MES testing, or 2) THC (0–80 mg/kg) 1 hour before MES testing. Next, the ED50 dose of CBD was given with low (non-effective) doses of THC at various CBD:THC ratios (15:1, 20:1, 25:1, 30:1, 40:1, 50:1). Lastly, a dose-response curve was done for the best CBD:THC ratio (15:1). During the MES test, mice received a 45 mA, 0.2 second alternating sine-wave current with a frequency of 60 Hz via corneal electrodes. Tonic-hindlimb extension was scored as "present" or "absent".

Results: CBD and THC both suppressed MES seizures (CBD ED50: 200 mg/kg; THC ED50: 48 mg/kg). CBD with low, sub-therapeutic doses of THC at various ratios, was more effective than CBD alone – the 15:1 ratio was the most effective. The 15:1 ratio suppressed MES seizures at an ED50 of 150.83+10.05 mg/kg (CBD+THC).

Conclusion: Both CBD and THC alone protect mice against MES seizures. Ratios of CBD with THC, however, are more effective than CBD alone, and may be relevant for future epilepsy therapy.

Modelling Epilepsy in Cerebral Organoids: Oxygen-Glucose Deprivation as a Convulsant

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Rationale: Epilepsy is a complex neurological condition characterized by recurrent seizures. Human cerebral organoids can be used to model epilepsy and permit personalized drug testing. Oxygen-glucose deprivation (OGD) is a known cause of neonatal seizures in humans; therefore, it was hypothesized that this will induce epileptiform activity in cerebral organoids.

Methods: Cerebral organoids derived from human embryonic stem cells were provided by L. Attisano at 4 and 7 months. Electrophysiological recordings with two local field potentials were conducted: 5 minutes baseline, 15 minutes OGD, and 15-30 minutes washout. Signals were processed in MATLAB to extract power spectral density. Raw traces were analyzed in Clampfit 9.0 to identify spontaneous bursting. T-tests were used to compare means.

Results: There were significantly more spontaneous burst events per minute during the post-OGD washout period when compared to baseline (0.27 events/minute and 0.09 events/minute respectively, p=0.01). The power spectral density area under the curve was significantly greater than baseline in both the OGD (p<0.02) and washout (p<0.05) conditions, for all signal frequencies. This increase in power spectrum was prevented at 7 months with pre-treatment of Bumetanide, a drug used experimentally to treat neonatal seizures.

Conclusions: These findings support the presence of epileptiform changes in the cerebral organoid tissue, which to our knowledge is the first induction of seizures in healthy 3D cerebral organoids. Furthermore, the changes respond to an anti-seizure compound used in similar lab models. Investigation of the mechanisms and other drug responses is warranted to develop cerebral organoids as a high-throughput, drug testing platform.

Sleep Deficits, Repetitive Behaviors, and Increased Slow Gamma Power in an *Ank3* Mouse Model of Epilepsy-Mood Disorder Comorbidity

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The *ANK3* gene is a leading bipolar disorder candidate gene in humans. Previous studies showed that a bipolar disorder (BD)-associated variant of *ANK3* (*ANK3-1b*) leads to increased firing threshold and diminished action potential dynamic range of parvalbumin (PV) interneurons and absence epilepsy in mice, thus providing a potential mechanistic link between epilepsy and BD. To better understand the impact of PV interneurons on network activity and behavior in these mice, we examined spectral correlates of behaviors seen in *Ank3-1b* knockout (KO) mice during overnight home-cage activity using paired video-EEG recordings. PV interneuron dysfunction and aberrant gamma rhythms have been implicated in BD. Also, the fast-spiking properties of PV interneurons make them important for generating and modulating high frequency gamma oscillations. Thus, we anticipated changes in the power of EEG signals in the gamma frequency range (> 25 Hz) during behaviors related to BD symptoms seen in human patients such as changes in sleep and activity levels. *Ank3-1b* KO mice exhibited an overall increase in slow gamma (~25-45 Hz) power compared to controls, and slow gamma power correlated with seizure phenotype severity across behaviors. Notably, during sleep, increased slow gamma power co-occurred with decreases in time spent in the rapid eye movement (REM) phase. We also identified a repetitive behaviors phenotype in *Ank3-1b* KO mice that co-occurred with increased slow gamma power. These results further support the association of *Ank3-1b* with BD and suggest modulation of gamma oscillations as a potential therapeutic target.

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Association of genetic polymorphism of methyl tetrahydrofolate reductase (MTHFR) enzyme with antiepileptic drug response among pediatric patients in Jeddah, Saudi Arabia

Reem Alyoubi, Rania Magadmi, Osama Muthafer, Abdullah Althomali & Hadiah Almahdi

Background: Epilepsy is a chronic neurological disease of the brain with inherent and non-inherent factors. More than 20 antiepileptic drugs (AEDs) are available in the marked but still one- third of patients had drug-resistance epilepsy.

Objective: The objective is to evaluate the association of clinical features and methyl tetrahydrofolate (MTHFR) rs1801133 polymorphism with responsiveness to AED among pediatric epileptic patients.

Methods: This study is a multicentric, retrospective, case-control study on 101 children diagnosed with epilepsy in Jeddah and 59 healthy individuals. Genotyping of MTHFR rs1801133 polymorphism was done using real time polymerase chain reaction- TaqMan Genotyping assay.

Results: Among epileptic patients, 56 showed good response to AEDs, 45 patients with poor response. A significant good response to AEDs was reported among younger age, those who didn't report parental consanguinity, didn't have family history of epilepsy, diagnosed with partial seizure and with no reported adverse effects. Levetiracetam regimen was statistically significant regarding responsiveness to AEDs. Patients on monotherapy regimen showed better response to levetiracetam than patients on polytherapy (p<0.001). This study revealed no significant genetic association of the single nucleotide polymorphisms (SNPs) rs1801133 within MTHFR gene with responsiveness to AEDs in the majority of children. There was no significant association between response to AEDs and CBC and vitamin B12. There is a significant association between reporting drug-induced toxicity and the increase in allele A frequencies (p=0.04). The MTHFR rs1801133 genotype was significantly associated with the incidence of electrolyte disturbance among AED good and poor responders (p = 0.011).

Conclusion: This study is the first pharmacogenetic study of MTHFR gene in Saudi Arabia epileptic showed no significant association of the SNP, rs1801133 within MTHFR gene with susceptibility and drug responsiveness. AED response in pediatric epileptic patients could be predicted by knowing patients demographic and epileptic history. Large sample size for testing gene polymorphism are needed for future work.

Potential means to Circumvent a Neural Network Achievement Impasse

Thaddeus J. A. Kobylarz[1] & Erik J. Kobylarz[2]

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Current neural network methodology has encountered an impasse to further operational progress. This has been recently exemplified by the AI failure of predicting real estate values for Zillow, a well-known real estate investment corporation. Once touted[1] as a revolutionary means to predict when to buy/sell real estate, by gleaning decisions from enormous past performance data which are beyond humans' perception, Zillow's flawed AI nearly brought the corporation to bankruptcy[2] . Since then, papers have been published describing that available computer processing power poses a limit to what neural networks are capable of achieving[3] . Furthermore, the literature suggests that the computational power needed to exceed this limit will require a quantum leap in computer technology. To a great extent current AI must limit activities for which erroneous results are innocuous; e.g., changing TV channels, playing requested music, etc. Innocuous consequences is not the situation for business decisions[4].

We believe that this limitation is due to two traditional properties inherent of current neural networks. These are; a neuron model only capable of linearly separable switching functions and fixed network structures of neurons. (Both of these properties will be defined in the presentation.)

The ratio of total switching functions to linearly separable switching functions, with respect to the number of variables, is astronomical. For 7 variables, there exist 8.4 X 10^9 linearly separable switching functions. Whereas, there exist a total of 3.4 X 10^{38} switching functions for 7 variables. This indicates that a neuron model, capable of performing all switching functions is 4.0 X 10^{28} more versatile than a linearly separable neuron model. The versatility distinction of the two neuron models grows more rapidly than exponentially, as the number of variables increase. This presentation will define a general neuron model capable of performing all switching functions, for any number of variables.

Because of plasticity, human brains do not possess a fixed structure. The property of plasticity causes structural changes throughout one's lifetime, principally during and soon after birth. Association of stimuli, often termed inter-association, is recognized as a mechanism which changes interconnections of neurons. We also define intra-association, which alters the behavior of a neuron model; again by association of stimuli. That is, plasticity provides our ability to learn. These aspects of plasticity do not exist for training current neural networks.

We believe that the dramatic, versatile improvement of our general neuron model, plus the introduction of plasticity in training, will allow for the building of novel neural networks that evade the current impasse experienced by traditional models; while deploying current computer processing power.

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