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A general nonlinear neuron model—Thaddeus J.A. Kobylarz [a], Erik J. Kobylarz [b] ([a] Bell Laboratories Retiree, United States , [b] Geisel School of Medicine & Thayer School of Engineering at Dartmouth College, United States)

An accepted conclusion for modeling a physiological neuron is its divisibility into two mathematical processes. These are the digital process and the analog process. In a 1943 paper McCulloch and Pitts presented a neural model performing switching logic (an IT digital process). Their model represents the basis of the model used in the well-known Perceptron, devised by Rosenblatt in 1957. The Perceptron is a neural network of models that included varying weights, which corresponds to a neuron's analog process. This talk will define the digital and the analog processes. These processes will be associated with a physiological neuron's anatomy.

The Perceptron's neuron model continues to be used in current neural networks despite a serious limitation of only realizing linearly separable switching functions. Linearly separable switching functions will also be defined. The currently used "linear" neuron model will be shown to have severely limited switching logic realizations. Linear separability will also be defined.

A general non-linear neuron model will be defined, which is capable of performing all possible switching logic realizations. Examples of both a linear neuron model's and nonlinear neuron models' switching logic realizations will be included.

The proposed nonlinear neuron model, which more accurately takes into account actual neurophysiologic mechanisms, can form the basis of modeling network processes at all levels of the nervous system, including the brain.

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The effects of febrile status epilepticus on hippocampal circuit function—Michelle L. Kloc [a], Megan M. Curran [b], Rhys W. Neidecker [a], Tallie Z. Baram [b,c,d], Gregory L. Holmes [a,1], Jeremy M. Barry [a] ([a] Department of Neurological Sciences, University of Vermont College of Medicine, Burlington, VT, United States , [b] Departments of Anatomy/Neurobiology, University of California-Irvine, Irvine, CA, United States, [c] Pediatrics, University of California-Irvine, Irvine, CA, United States, [d] Neurology, University of California-Irvine, Irvine, CA, United States)

Rationale: Febrile status epilepticus (FSE) in children has been linked to cognitive deficits and epileptogenesis later in life. Recent evidence in the experimental hyperthermia animal model of FSE (eFSE) has shown that spatial memory deficits may be a result of structural and functional changes to specific cells types in the hippocampal circuit. Experimentally, the effects of FSE on cognitive deficits are mitigated by the blockade of neuron-restrictive silencing factor (NRSF) binding to its target chromatin. The goal of the current study is to understand the relationship between cognitive outcomes and the efficacy of hippocampal circuit throughput and whether this relationship is altered by NRSF treatment post FSE.

Methods: Postnatal day 10–11 male Sprague-Dawley rat pups (N = 13) underwent procedures for eFSE hyperthermia induction. Pups were placed, two at a time, inside a 3 L flask, the bottom of which was lined with absorbent paper. Prior to hyperthermia, a glycerin-based hydrating ointment was applied to the paws, ears, and tail of the pups to mitigate potential hyperthermic skin injury. Pups were subjected to a continuous stream of warm air until hyperkinesis and chewing automatisms were identified. Seizure behaviors typically progressed to clonic movements and eventual tonic extension. After approximately 60 min of hyperthermia, eFSE pups were immersed in cool water (−23.0 °C) to aid in the return of core temperature to normothermia and to promote seizure cessation. Pups were then placed on a euthermic pad maintained at 37 °C for 30 min, and then were returned to their home cage and dam.

An intact NRSE or a scrambled (SCR) NRSE sequence oligodeoxynucleotide (ODN) was infused ICV 3 h post eFSE (Sigma-Aldrich). Four experimental groups were used in these experiments. The first was a non-eFSE control animal that received a scrambled sequence of NRSE (CTL-SCR). The second was a non-eFSE control who received the NRSE sequenced ODN (CTL-NRSE). The third were eFSE animals infused with scrambled ODN (eFSE-SCR). Finally, there was a group of eFSE animals infused with NRSE ODNs (eFSE-NRSE). 2.5 nmol of either NRSE or SCR ODN were infused bilaterally into the ventricles at a rate of 0.5 l/min and a volume of 2.5 l/hemispheres. ICV infusions were repeated 24 h after eFSE.

While blind to treatment group, treated and untreated rats were trained on an active avoidance spatial task on a rotating arena in order to measure cognitive outcomes in relation to treatment condition. To measure circuit throughput in the dorsal hippocampus across experimental conditions, we utilized 64-channel silicon probes to measure EEGs and neuronal action potentials across synaptic input regions along the apical and basal dendrites of CA1 pyramidal cells and dentate gyrus granular cells under urethane-anesthesia. Following acute probe recording experiments, animals

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were perfused with fixative and brain tissue was harvested for immunohistochemical procedures.

Results: Preliminary data suggests group differences in the ability to learn the active avoidance spatial task while analysis of cell spiking data suggests interhemispheric differences in neuronal activity across all groups. Acute recordings also revealed that there were notable hallmarks during EEG recordings across animals and groups in theta-, beta-, and gamma- range oscillations in deep CA1; dentate gyrus EEGs; and also the response to mechanical perturbation when the probe was lowered.

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EEG features of spontaneous recurrent seizures in a mouse model of extended hippocampal kindling—Haiyu Liu [a,b], Anya Zahra Hameed [b], Jonathan Chow [b], Nila Sivanenthiran [b], Chloe Cheng [b], Yapeng Liu [b], Phinehas Cheung [b], Stellar Lim [b], Yaozhong Jin [b], Yu Qi Lin [b], Min Mao [b], Chiping Wu [b], Peter H. Carlen [b,c,d], James H. Eubanks [b,d,e], Hongmei Song [a,b], Liang Zhang [b,c] ([a] Departments of Neurosurgery, The First Hospital of Jilin University, China, [b] Krembil Research Institute, University Health Network, Canada, [c] Departments of Medicine, University of Toronto, Canada, [d] Physiology, University of Toronto, Canada, [e] Surgery, University of Toronto, Canada)

Introduction: Epilepsy is a disease characterized by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological, and social consequences of this condition. Temporal lobe epilepsy (TLE) is the most common and often drug-resistant type of epilepsies in the adult and aging populations and has greatly diverse in etiologies and electro-clinical manifestations. Kindling through repeated brief stimulation of limbic structures has long been used as a model of TLE. While classic kindling in a few weeks does not induce spontaneous recurrent seizures (SRS), extended kindling is able to induce SRS in several animal species. The SRS induction by extended kindling is generally not associated with gross brain injury, but rather a loss of subgroups of GABAergic interneurons in the hippocampal hilar region. The lack of observed gross brain injury in extended kindled animals is different from post status epilepticus models in which SRS emergence is accompanied with pronounced brain damage. As such the extended kindling model may help explore epileptogenesis in the absence of major brain pathology as is seen in many patients with TLE. To data, there is limited insight about EEG characteristics of SRS in rodent models of extended kindling. We therefore attempted to provide more information in this area using a mouse model of extended hippocampal kindling (Song et al., 2018; Liu et al., 2019; Frontier Pharmacology).

Methods: Male C57 black mice ages 11–13 months were operated to implant intracranial electrodes. Each mouse was implanted with two pairs of bipolar electrodes, one in the hippocampal CA3 for kindling stimulation and local recordings and another in contralateral/ipsilateral hippocampal CA3, dorsomedial thalamus, parietal cortex or entorhinal cortex. Hippocampal kindling (60 Hz for 2 sec) was applied twice daily, and SRS were detected by 24-hour EEG-video monitoring. Age-match mice that received similar electrode implantation and twice daily handling manipulation but not kindling were used as controls. Brain histological examinations were performed in a subset of mice to verify the location of implanted electrodes and to examine potential gross brain lesion.

Results:(1) SRS were observed from 47 mice following 80–140 kindling stimulation; no spontaneous seizure was detected in 12 control mice. (2) SRS remained detectable in individual mice up to 4 months after termination of the kindling stimulation. SRS incidences varied in a range of 2–14 events per day but inter-SRS intervals were $\leq$2 hours for about 65% of SRS events. (3) Most of SRS were featured with EEG ictal discharges and concurrent motor seizures at the Racine scale 3–5. SRS that presented EEG ictal discharges without or with concurrent motor behaviors at the Racine scale 1–2 were also noticeable, particularly in mice with implanted electrode in the dorsomedial thalamus. (4) In $\geq$1500 SRS events examined, nearly all EEG ictal discharges presented low-voltage signals at onset and such ictal onset appeared to concur in the kindled CA3 and unkindled site despite the latter targeted to different brain structures. (5) CA3 and cortical EEG ictal discharges were not substantially affected by intra-peritoneal injection of lorazepam (a benzodiazepine positive GABAa receptor modulator) but concurrent severe motor seizures were greatly suppressed.

Summary: We suggest that epileptogenic network activity encompassing multiple forebrain areas may be responsible for SRS initiation in the mouse model of extended hippocampal kindling. Subcortical structures involving the dorsomedial thalamic circuitry may play an important role in manifestation and/or control of severe motor seizures in this model.

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The effects of CBD and THC in an animal model of depression—Junhan Liu, Brian Scott, McIntyre Burnham (Department of Pharmacology and Toxicology, University of Toronto, Canada)

Objectives: Epilepsy patients frequently suffer from psychiatric comorbidities, such as depression, which seriously affect their quality of life. CBD has been reported to have not only anti-seizure effects, but also to have possible antidepressant effects. Thus, CBD might treat not only seizures but also some of the comorbidities associated with seizures. The present study was designed to test the effects of THC, CBD and a combination of CBD and THC (15:1 ratio) in a mouse of depression (the forced swim test, FST). Previously we had reported that THC decreased immobility in the FST at one dose (2 mg/kg) and that CBD was totally ineffective. The present study was designed to re-test the effects of CBD and CBD/THC when CBD was administered at a shorter interval (30 min) before testing.

Methods: Adult, male CD1 mice were injected i.p. with CBD (0, 15, 30, 60, 120, 240 mg/kg), THC (0, 0.5, 1, 2, 4, 8 mg/kg), CBD + THC (0, 15 + 1, 30 + 2, 60 + 4, 120 + 8 mg/kg) or imipramine (positive control, 0, 30 mg/kg). Subjects were either tested in the FST (6mins) or in open field arena (10mins). CBD and THC were both injected 30mins prior to testing. N = 6–12 for each dose.

Results: As previously reported, imipramine (positive control) decreased immobility times at 30 mg/kg. THC also decreased immobility time in the FST at only one dose, 2 mg/kg (lower and higher doses were ineffective). CBD – injected 30 min pretest – had nearly significant effects on immobility at 60 mg/kg. CBD + THC significantly decreased immobility at 30/2mg/kg and 120/8 mg/kg, with near significant effects at 60 mg/kg. None of the drugs affected open field activity at any dose.

Conclusions: CBD tested at the shorter interval of 30 minutes showed nearly significant effects in the FST. In combination with 2 mg/kg THC, significant CBD effects were seen at 30 and 120 mg/kg of CBD, with nearly significant effects seen at 60 mg/kg. Conceivably, a combination of CBD and THC might be useful in patients with combined seizures and depression.

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Non-epileptic, stereotypical and intermittent symptoms (NESIS) in subdural hematomas – Evidence for the design of a new therapeutic clinical trial—Suzie Adam, Mathieu Lévesque, Charles Deacon, Christian Iorio-Morin (Neurology and Neurosurgery Divisions, Centre Hospitalier Universitaire de Sherbrooke, Canada)

Background: Transient neurological symptoms (TNS) frequently occur in patients with subdural hematomas (SDH) often posing diagnostic dilemna. Most of those patients will receive a diagnosis of provoked seizures despite negative workup and atypical evolution.

Objective: To accumulate evidence about the existence of the distinct NESIS etiology for patients presenting with TNS post SDH, its pathophysiology and optimal management.

Methods: An initial single-center, retrospective, case-control study of patients with TNS post-SDH revealed statistically significant clinical and semiological distinctions between cases (negative EEG) and controls (EEG with ictal or interictal activity). Those differences combined with a thorough review of literature led to the creation of a clinical screening score predictive of a negative EEG. When tested retrospectively, the score showed promise in detecting NESIS for patients with TNS. Its predictive value was replicated in a subsequent single-center, retrospective study.

Results: In the first study, fifty-nine patients with SDH-associated TNS were included (39 cases and 20 controls). Demographic characteristics were comparable in both groups. Dysphasia and prolonged episodes were associated with a negative EEG. Clonic movements, impaired awareness, positive symptomatology, complete response to antiepileptic drugs and mortality were associated with a positive EEG. Using semiological variables, we created a scoring system with a 96.6% sensitivity and 100% specificity in predicting case group patients. In the second study, 22 patients with TNS and chronic SDH were included. Presumptive NESIS occurred in 13 patients (59%), EEG-proven epilepsy in 4 patients. NESIS patients did not respond to standard anti-epileptic drugs contrary to non-NESIS TNS (14% vs 100%).

The differences between both groups support the existence of an alternative etiology than seizures for TNS in our population. We proposed the term NESIS to describe this subgroup and hypothesize that cortical spreading depolarization (CSD) could be its underlying pathophysiology. Relevant studies support the existence of specific treatments (including Topiramate) targeting CSD.

Conclusion: With these results in mind, we aim to carry out a prospective randomized clinical trial to assess the efficacy of Topiramate compared to a conventional AED (LEV), known to have little impact on CSD, in a NESIS sub-group. We believe the recognition of this distinct entity, the understanding of its underlying pathophysiology and the creation of a validated clinical screening score can have important prognostic, paraclinical and therapeutic impact in the care we provide to such patients.

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Continuous spike-waves of slow-wave sleep: A case study with 20-year follow-up—Soumia Djirar, Arina Bingeliene, Dragna Jovanovitch, Inna Voloh, Janet Shaw, Paul Hwang (North York EEG Lab, University of Toronto Epilepsy Research Program, Paediatric Neurology Division, Departments of Paediatrics & Medicine, University of Toronto, Ontario, Canada)

Objective: To understand the pathogenesis of continuous spike-waves of slow-wave sleep in autistic spectrum disorders, and how to precisely manage such a challenging complex chronic case.

Abstract: This is the case of PM, a 5 year old right-handed girl from Gujrat India who first presented with dizziness and vomiting while sleeping. Onset of such events started one and a half year ago. She also cried in between and lost consciousness for about 10 minutes' duration. She suffered a partial seizure and her parents started AED therapy-one year and a half later. She first presented when she was five years and 3 months of age in India. PM is currently a 20-year-old right-handed woman who was followed for 16 years by the same neurologist (PAH), had seizure onset at 1.5 years: afebrile seizures secondarily generalized with automatisms, duration about 5 minutes, recurrent every 2–5 weeks. Initial treatment consisted of Phenytoin 12 mg/kg, then Carbamazepine 30 mg/kg+ (starting dose), Valproate at 18 mg/kg/day with improvement. SGA 2.7 kg at birth, after 7–8 hours labour, her "right leg was bent" at birth in India. Family history was negative for fits or epilepsy. Her early development was "normal": walked at 12 months, spoke words in Gujarati at 18 months, started English as a second language (ESL) at four years old in Junior kindergarten when she first came to Canada with her family. Since then she had completed high school at age 20 years and planned post-secondary studies at college to be determined by her parents. Her EEGs showed almost continuous high amplitude spike-waves 60% or more in SWS, but only mildly abnormal when awake. Her last clinical seizure occurred a few years ago, still in high school, off all AEDs. The general neurological examination was unremarkable but was rather delayed.

Discussion: The relationship between sleep and epilepsy is a challenging issue. In this case the correlation between sleep and possible ASD is unequivocally important. Poor quality in sleep for the pediatric age group often leads to future cognitive and psychosocial issues. These issues must be addressed precisely and handled with parent and psychosocial intervention. An increased level of education and awareness of her condition may help improve the long-term prognosis and improve the quality of life of the patient.

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Sleep-related hypermotor seizures of insulo-opercular origin: A review of 27 cases—Pauline M. Lobbezoo [a,b], Lino Nobili [c], Giorgio Lo Russo [d], Steve A. Gibbs [a] ([a] Center for Advanced Research in Sleep Medicine, Department of Neurosciences, Université de Montréal, Montréal, Canada, [b] University of Utrecht, Netherlands, [c] IRCCS G. Gaslini Institute, University of Genova, Italy, [d] C. Munari Center for Epilepsy Surgery, Niguarda Hospital, Milan, Italy)

Introduction: Insular epilepsy is known to be a "great mimicker" of various types of focal epilepsy, including sleep-related hypermotor epilepsy (SHE) in about 15% of cases. Because SHE tends to have a frontal origin, misdiagnosis can result in a poor surgical outcome when epilepsy surgery is considered. In this study, we reviewed the existing literature to identify electro-clinical features suggestive of an insulo-opercular (IO) origin in SHE.

Methodology: We found 11 case series of SHE or insular epilepsy with sufficiently detailed patient data. We identified 27 patients with IO SHE from 6 studies. When available, the semiology patterns (SP), early nonmotor manifestations, alteration of consciousness (AOC), EEG and MRI features and histopathology were collected.

Results: SP analysis of the 27 identified patients showed a wide variety of indiscriminate SP, including hyperkinetic and/or dystonic features. Early nonmotor manifestations were observed in 80%, most commonly somatosensory auras (44%). Laryngeal constriction, pain, oral and widespread paresthesia were observed in IO SHE but not in frontal SHE. AOC was uncommon (20%). EEG was rarely suggestive of an IO origin (17%) and MRI was diagnostic in 48%. Focal cortical dysplasia was the most common diagnosis (78%). Following surgery, 83% were seizure-free (follow-up: 12–60 months).

Conclusions: Few electro-clinical features, except early non-motor manifestations, are suggestive of an IO onset in SHE. Therefore, in MRI-negative patients, a heightened vigilance for subtle subjective or behavioral signs is warranted to avoid misdiagnosis and poor surgical outcome.

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