Oral Presentation: Paediatric Epilepsy

Abstract #1

The Ketogenic Diet Mediates Its Anti-Seizure Effects through Respiratory-Induced Intracerebral Acidosis in the Triple-Hit Rodent Model of Infantile Spasms

Anamika Choudhary, Karlene Barrett, Chunlong Mu, Behshad Charkhand, Christine Williams-Dyjur, Wendie Marks, Morris Scantlebury

University of Calgary

Rationale
Infantile Spasms (IS) – a catastrophic, epileptic encephalopathy of infancy – are often refractory to current antiepileptic therapies. The ketogenic diet (KD) has emerged as an alternative treatment for the intractable population, though the prospective validity and mechanism of action for IS remains largely unexplored.

Method
We investigated the KD's efficacy as well as its mechanism of action in the triple-hit model of intractable IS. The triple-hit model was used to induce spasms in neonatal rats, who were then artificially reared and put on either the KD (4:1 fats:carbohydrates) or a normal-milk diet (ND; 2:1). 31-phosphorus magnetic resonance spectroscopy, head-out plethysmography and arterial blood gas analyses were examined in conjunction with continuous video-behaviour recordings in spasms and control animals.

Results
The KD resulted in a ketosis observed both in the blood and urine. The KD led to a robust reduction (≤65%) in the frequency of spasms observed, with a two-fold increase in rate of survival. The respiratory profile of the KD-spasm rats was significantly altered as their breathing was slower, deeper and longer – resulting in decreased levels of expired CO2. This resulted in a respiratory acidosis and hypercapnia, as measured in the blood. The systemic acidosis also translated centrally as we observed an intracerebral acidosis. Sodium bicarbonate supplementation reversed the KD's effects by causing relative alkalosis in the blood, coupled with an increase in the spasm frequency.

Conclusions
We conclude that the KD produces its anti-convulsant effects through respiratory-induced intracerebral pH disruptions in the brain. The first of its kind, these findings provide a novel platform for understanding the anti-seizure mechanisms of the KD in IS.

Funding: Alberta Innovates Health Solutions and Alberta Children's Hospital Research Institute

Oral Presentation: Basic Science / Engineering

Abstract #2

Anandamide Signaling Augmentation Rescues Elevated Emotionality, Impaired Fear Memory and Amygdala Physiological Dysfunction Associated with Repeated Seizure Activity

Roberto Colangeli, Maria Morena, Quentin J. Pittman, Matthew N. Hill, G. Campbell Teskey

University of Calgary

Rationale
Temporal lobe epilepsy is often associated with negative emotional disturbances. The endocannabinoid (eCB) system finely regulates both excitatory and inhibitory synaptic transmission and plasticity in the amygdala and related brain regions involved in the regulation of emotional behaviour. While eCB levels transiently elevate to re-establish normal homeostasis after an insult, persistent alteration of the eCB system caused by repeated seizures may contribute to the development of epilepsy-related emotional disorders. Here we investigated the role of the eCB system in the physiological and behavioural alterations induced by repeated seizures in rats.

Method
Kindling procedure consisted of a total of 20, twice daily, electrically evoked seizures. One week after kindling, rats were tested in the elevated plus maze to assess anxiety-like behavior and in a fear conditioning paradigm to test fear memory dynamics. Patch clamp recordings of pyramidal neurons of the basolateral amygdala (BLA) were performed to assess glutamate and GABA transmission as well as endocannabinoid-mediated synaptic plasticity.

Results
Kindling caused dysregulation of GABA and glutamate synaptic transmission and plasticity in the BLA which were paralleled by alterations of emotional behaviour. Assessment of eCB levels in the amygdala revealed a downregulation of anandamide (AEA) content, while 2-arachidonoylglycerol (2-AG) was unaltered. Boosting AEA levels by inhibiting its degradative enzyme, rescued repeated seizure-induced emotional alterations and re-established the pre-seizure homeostatic excitatory-inhibitory balance and synaptic plasticity in the BLA.

Conclusions
Modulation of AEA signaling represents a potential target for the development of a new class of drugs for treatment of seizures and the associated comorbid emotional alterations.

Oral Presentation: Neuroimaging

Abstract #3

Postictal Hypoperfusion and Risk Factors for Sudden Unexpected Death in Epilepsy

Jonathan Liu, Joseph Samuel Peedicail, Ismael Gaxiola-Valdez, Emmy Li, Victoria Mosher, William Wilson, Tefani Perera, Shaily Singh, Gordon Campbell Teskey, Paolo Federico

University of Calgary

Rationale
The strongest risk factor for sudden unexpected death in epilepsy (SUDEP) is frequent tonic-clonic seizures and SUDEP typically occurs within minutes of a tonic-clonic seizure. Studies of animal models have demonstrated postictal hypoperfusion-induced hypoxia in regions of seizure onset and propagation, including brainstem respiratory centres (BRCs), immediately prior to death. In this study, we investigated whether postictal hypoperfusion in BRCs is more common in patients who experience tonic-clonic seizures.

Method
We identified 21 patients with focal epilepsy who underwent postictal perfusion imaging with arterial spin labelling (ASL) MRI. Perfusion changes between baseline and postictal states were visualized by subtracting co-registered cerebral blood flow (CBF) maps. Patients were separated into two groups: those who experienced a bilateral tonic-clonic seizure (BTCS) and those who experienced a focal impaired awareness seizure (FIAS) immediately prior to the ASL MRI scan. Subtraction ASL maps were evaluated for hypoperfusion in BRCs, defined as the dorsal pons, dorsal medulla, and ventral medulla.

Results
Six patients had a BTCS and 15 had a FIAS prior to the ASL MRI scan. All six patients who had a BTCS and 7/15 with a FIAS exhibited postictal hypoperfusion in at least one BRC. The association between seizure type and BRC hypoperfusion was statistically significant ($p = 0.046$, two-tailed Fisher's exact test).

Conclusions
Our study found that postictal hypoperfusion in BRCs occurred more often in patients who experienced a BTCS, who are at a higher risk for SUDEP. BRC hypoperfusion may be a potential neuroimaging biomarker for risk of SUDEP.

Acknowledgements: This work was supported by the Canadian Institutes of Health Research.

Oral Presentation: Neuroimaging

Abstract #4

Localization of the Epileptogenic Zone Using Intracranial EEG-fMRI

William M. Wilson, Daniel J Pittman, Victoria Mosher, Negar Mohammadi, Joseph Peedicail, Craig A. Beers, Paolo Federico

University of Calgary

Rationale
Interictal epileptiform discharges (IEDs) and high frequency oscillations (HFOs) have shown potential for localizing the epileptogenic zone. Simultaneous intracranial EEG-fMRI measures BOLD activation and removal of the area of BOLD activation associated with both IEDs and HFOs may be an important factor contributing to post-operative seizure freedom. We assessed overlap between these areas of BOLD signal and the resection to determine if greater overlap is associated with improved post-surgical outcome.

Method
Twelve subjects with refractory focal epilepsy underwent a 60-minute iEEG-fMRI study. IEDs were marked by electroencephalographers and HFOs (80 – 250 Hz) were identified algorithmically. The timing of these events were used to generate BOLD maps. Patients then underwent surgery and post-operative MRI to define the resection area. Post-surgical outcome was then compared to the extent of removal of the area of maximum spike- and HFO-associated BOLD activation.

Results
Surgery resulted in complete seizure freedom (Engel 1A) in 7/12 patients (follow-up 12-47 months, mean 22.7 months). Seizure freedom was associated with greater overlap of the resection area with the total volume of IED- and HFO-associated BOLD activation (34.6% and 50.3% respectively), whereas less overlap was associated with poor outcomes (0.2% and 8.5% respectively).

Conclusions
This study suggests identification of BOLD activation associated with IEDs and HFOs, may help define the epileptogenic zone, and its removal may result in an improved surgical cure rate.

Acknowledgements: This project is supported by the Canadian Institutes of Health Research.

Neuroimaging

Abstract #5

Brain MRI and Video EEG Patterns in Children with Drug Resistant Epilepsy (DRE) and Structural Etiologies

Andrea Andrade[1], Camila Lancefield[1], Michelle Gratton[2], Ahmad Alanezi[1], Michael Jurkiewicz[1], Maryam Nabavi Nouri[1], Asuri Narayan Prasad[1]

[1]*Western University*
[2]*London Health Sciences Centre*

Rationale
Significant gaps exist identifying clinical, EEG and radiological features that will predict poor outcomes in children with lesional DRE. The aim of our study is to describe the most common brain MRI lesions and video-EEG (vEEG) features found in this population and their relationship with seizure onset (SO).

Method
91 children with DRE were identified. 51 (56 %) had MRI lesions. A paediatric neuroradiologist (M.J) reviewed their brain MRIs describing lesion type, location and extension. We defined discrete lesions as the ones confined within one lobe versus extensive ones, when more than one lobe was involved. We defined early seizure onset as one year or younger versus late onset as older than 1 year. Video EEG and seizure semiology were also reviewed.

Results
29/51 were males (56.8%). Age at seizure onset was from 0-15 years, (median 2). 21/51 (41.1%) had MCD (SO:0 to 12 years, median 3). In terms of localization/extension of the lesion 22/51 (43.1%) had discrete lesions vs. 29 (56.8%) who had extensive lesions. Early seizure onset is more frequent in those with extensive lesions (29.4%) vs. those with discrete lesions (7.8%) ($p=0.014$). From 51 patients, 48 had vEEGs. Interictal EEG was concordant in 21/48 (43.7%), Ictal EEG in 10/48 (20.8%), seizure semiology 21/48 (43.7%).

Conclusions
Malformations of cortical development are the most common brain lesion in children with DRE. Extensive lesions are associated with early seizure onset. Poor concordance between vEEG and MRI in children with DRE makes the surgical evaluation process more challenging compared to adults.

Neuroimaging

Abstract #6

Individual Differences in Resting-State Memory Network Connectivity Predicts Memory Decline After Temporal Lobe Resection

Mary Pat McAndrews[1], Samantha Audrain[2], Alexander Barnett[3]

[1]*Krembil Research Institute*
[2]*University of Toronto*
[3]*UC Davis*

Rationale
Resting-state fMRI can be used to characterize the integrity of neurocognitive networks and to predict post-surgical cognitive morbidity. Determining the best ways to characterize these networks remains a challenge. We devised a technique that compares an individual patient's network to a template based on healthy controls and we assessed its utility in predicting memory outcomes.

Method
We conducted 6-min resting state fMRI scans on 19 healthy controls and 29 individuals with left temporal lobe epilepsy. We calculated correlations between 18 regions of interest (ROIs) selected for their involvement in memory. A correlation matrix template for the healthy control group was generated from these, and each patient's matrix was compared to that template to derive a Matrix Similarity score. Finally, these scores were correlated with a measure of pre-to-post surgical performance on clinical verbal memory tests.

Results
The closer the matrix similarity score to the normative template, the better memory was preserved following surgery. The ROIs that contributed most to this pattern were those outside the surgical resection zone, suggesting that the positive effect of typicality is due to functional reserve of non-epileptogenic components of the network. Furthermore, matrix similarity was not related to preoperative memory scores, and it was a better predictor of post-operative change than those pre-operative scores, suggesting that it contributes unique information regarding memory change.

Conclusions
We found that more 'abnormal' memory networks are less resilient to disruption, which should enhance our ability to counsel patients about cognitive risk.

Funding: Canadian Institutes of Health Research and EpLink – The Epilepsy Research Program of the Ontario Brain Institute

Neuroimaging

Abstract #7

Implementation of Voxel Based Morphometric Analysis to the Manitoba Epilepsy Program Presurgical Evaluation Pipeline: A Proposal

Joshua Dian, Demitre Serletis

University of Manitoba

Rationale
Epilepsy remains one of the most common neurological disorders affecting over 1% of the population. Up to 30% of patients have seizures that are refractory to medical treatment and potentially amenable to surgical management. In evaluation of these patients, identification of 'regions of interest' (ROIs) remains a challenging problem. Voxel based MRI analysis provides an alternative means for highlighting ROIs suitable for surgical resection or invasive microelectrode recordings. Here we apply a voxel based 'morphometric analysis program' (MAP) to the Manitoba paediatric epilepsy surgery database, to investigate its utility in the presurgical epilepsy evaluation pathway.

Method
Standardized T1, T2 and FLAIR weighted MR images will be collected from the Manitoba paediatric epilepsy surgery database. Morphometric analysis will be carried out using MAP18 (Huppertz et al 2008) in combination with SPM12 (Wellcome Department of Cognitive Neurology, London, UK) running on a locally developed Matlab platform. Thresholds and parameters will be adapted from the literature (Wang et al 2019). A database of healthy control images will serve as a normal control database, within the MAP algorithm.

Results
Recent work suggests that MAP analysis may uncover previously occult ROIs in up to 56% of patients (Wang et al 2019). This algorithm will be internally validated on retrospective imaging data from previously-treated epilepsy patients at our center, to assess the success rate of ROI identification.

Conclusions
Algorithmic post-processing of MR imaging provides an additional method of identifying ROIs in patients with refractory epilepsy. We seek to demonstrate its applicability to the Manitoba paediatric epilepsy program.

Neuroimaging

Abstract #8

Multiscale Profiling of Thalamo-cortical Connectopathy in Generalized and Focal Epilepsies

Yifei Weng[1 2], Sara Lariviere[1], Lorenzo Caciagli[3], Reinder Vos de Wael[1], Neda Bernascono[1], Andrea Bernasconi[1], Zhiqiang Zhang[2], Boris Bernhardt[1]

[1]McGill University
[2]Nanjing University
[3]University of Pennsylvania

Rationale
The thalamo-cortical network has long been recognized as a key pathway in both focal and generalized epileptic syndromes. While numerous neuroimaging studies have indeed demonstrated anomalies in this network in both generalized epilepsy (GE) as well as temporal lobe epilepsy (TLE), both syndromes have rarely been comprehensively assessed to identify common as well as diverging pathological substrates. The current work leveraged an integrative multi-scale neuroimaging and connectomic paradigm to assess shared and dissociable thalamo-cortical signatures of GE and TLE.

Method
We studied 100 patients with GE (mean age = 25.93±8.03 years, 69 males) and 107 with unilateral TLE (mean age = 27.29±7.81 years, 60 males). Based on ILAE criteria, all GE patients had been categorized as those with generalized tonic clonic seizures only. All TLE patients had a unilateral seizure focus and concordant MRI evidence of hippocampal atrophy. Patients were respectively compared to 65 age- and sex-matched healthy controls (mean age = 24.98±4.96 years, 49 males). All individuals underwent multimodal MRI on the same 3T scanner, and a series of surface-based (i.e., cortical thickness, thalamic surface-shape, superficial white matter diffusivity) and connectome (i.e., diffusion MRI tractography, functional connectivity) analyses evaluated structural and functional network changes across different scales.

Results
Compared to controls, while both patient groups presented with microstructural and macroscopic anomalies in thalamo-cortical networks, their overall pathoconnectomic signature diverged. Specifically, although both patient cohorts presented with a similar pattern of superficial white matter diffusivity and thalamo-cortical structural connectivity, they showed markedly distinct morphological and functional findings. Indeed, while TLE showed extensive atrophy of cortical and mediodorsal thalamic divisions, we did not detect any morphological anomalies in GE compared to controls. Between-cohort divergence was furthermore supported in the functional domain, by showing mainly increased thalamo-cortical connectivity in GE to bilateral default-mode and limbic networks, while TLE showed ipsilateral decreases to somotomotor and prefrontal cortices, together with scattered increases to anterior temporal cortices

Conclusions
Although our data confirms the long-standing notion of thalamo-cortical involvement across the spectrum of focal and generalized epilepsies, we were able to nevertheless identify syndrome-specific pathoconnectomic signatures at the level of both brain structure and function.

Neuroimaging

Abstract #9

Asymmetrical Loss of Hippocampal Digitations in MRI-negative Focal Temporal Lobe Epilepsy at 7T: An MRI Marker of the Seizure Focus

Nickolas Christidis, Michael Jurkiewicz, Jonathan Lau, Jorge Burneo, David Steven, Ali Khan

Western University

Rationale
The search for novel non-invasive markers of the seizure focus remains critical to identify suitable surgical candidates in patients with MRI-negative TLE. An interesting morphological feature of the hippocampus that has recently become apparent due to advancements in ultra-high field (7T) MRI is the presence of "bumps" on the inferior surface of the hippocampus (i.e. hippocampal digitations). Striking degrees of digitation asymmetry have been demonstrated in the presence of clear hippocampal pathologies (i.e. hippocampal sclerosis). However, whether digitation asymmetry can be observed in patients with MRI-negative TLE at 7T has yet to be established.

Method
To assess the diagnostic utility of using hippocampal digitation asymmetry as a marker of the seizure focus, ten patients with MRI-negative TLE undergoing presurgical evaluation for refractory epilepsy were imaged using a 7T MRI protocol in addition to standard of care imaging. A blinded expert neuroradiologist assessed the extent of hippocampal digitation across sagittal slices using a semi-quantitative 5-point rating scheme. Evaluations of hippocampal digitation asymmetry were then correlated with the clinically determined seizure focus.

Results
Although hippocampal volumes were normal, 70% of MRI-negative TLE patients displayed asymmetrical hippocampal digitation loss in CA1 ipsilateral to their clinically determined seizure focus. The loss of digitations was restricted to the ipsilateral hippocampus, sparing the contralateral hippocampal architecture.

Conclusions
Ipsilateral loss of hippocampal digitations in patients with refractory MRI-negative epilepsy can be reliably detected at 7T. Asymmetrical digitation loss may serve as an effective marker of focal TLE lateralization that can aid hippocampal sclerosis independent selection of appropriate surgical candidates.

Neuroimaging

Abstract #10

Impact of Temporal and Frontal Lobe Epilepsy on Cerebral Organization of Language Networks in Children

Alejandra Hüsser, Phetsamone Vannasing, Julie Tremblay, Philippe Major, Anne Lortie, Paola Diadori, Lionel Carmant, Anne Gallagher

Université de Montréal - CHU Sainte-Justine

Rationale
Childhood epilepsy is the most common neuropaediatric disease. Left focal epilepsy is known to be associated with atypical language representation, right-hemispheric dominance, bilateral speech profile or recruitment of atypical left hemispheric areas, probably reflecting language network reorganization allowed by early brain plasticity. Specific patterns of cerebral reorganization are unpredictable and the relationship with language and cognitive abilities are still unknown. The current study aims at investigating the specific impact of frontal (FLE) and temporal lobe (TLE) epilepsy on the organization of brain networks related to language functions.

Method
30 children with FLE/TLE and 30 healthy controls aged 6-18 years, French-speaking, and born at term are recruited. Participation includes a neuropsychological assessment, and a simultaneous near-infrared spectroscopy (NIRS) and electroencephalography (EEG) recording during three conditions: 1) resting state (12 mins); 2) expressive language task (categorical verbal fluency, 11 mins); and 3) receptive language task (passive story listening, 12 mins). Preliminary pre-processing includes artifact correction, normalization, high frequency filtering and transformation of optical intensity into relative hemoglobin and deoxyhemoglobin concentrations. Brain reorganization of language networks will be investigated using a multidimensional decomposition method.

Results
Preliminary group comparison between 9 children with FLE (n=4) or TLE (n=5) and 14 healthy controls reveal different cerebral activation patterns. Both groups show cognitive performance within the normative range. However, patients have lower indices in several domains compared to controls.

Conclusions
Despite normal cognitive functioning, cerebral language processing seems altered in children with epilepsy. This project will lead to a better understanding of language dysfunctions in these children.

Neuroimaging

Abstract #11

Towards Personalized Connectome Models of Drug-resistant Childhood Epilepsy

Sara Larivière[1], Kevin Fitzpatrick[2], Danny Kim[2], Dewi Schrader[3,2], Boris Bernhardt[1]

[1]*Montreal Neurological Institute*
[2]*BC Children's Hospital*
[3]*University of British Columbia*

Rationale
Neurosurgery is one of the most effective treatment options to cure drug-resistant paediatric epilepsy, however, surgical resection of tissue harboring the lesion may have detrimental effects on socio-cognitive functioning. Our goal is to acquire high-resolution longitudinal imaging data to assess pre- to post-operative brain reorganization in children undergoing resective surgery, which will be made freely available to the scientific community.

Method
When complete, our open-access multimodal imaging and out-of-scanner behavioral datasets will comprise approximately 40 children suffering from drug-resistant focal epilepsy, measured shortly before and one year after surgery. Using equivalent measures and time intervals, we will also release data from 20 age- and sex-matched healthy children. Brain imaging sessions include: (i) 3D T1w MRI with prospective motion correction (PROMO), (ii) 3D T2- FLAIR PROMO, (iii) 3D qT1 PROMO, (iv) 3D ASL, (v) rs-fMRI (inscapes, movie "The Present"), (vi) task-based fMRI (semantic decision, finger tapping, n-back), and (vii) multi-shell diffusion MRI, as well as (viii) a battery of behavioral and clinical neuropsychological tasks.

Results
As a proof-of-concept, we integrated different scan modalities and accurately lateralized the seizure focus in a child with a right parahippocampal lesion. A seed-based functional connectivity analysis centered on the hypothesized epileptogenic lesion further revealed perturbed connectivity to higher-order cognitive networks and temporo-limbic circuits.

Conclusions
We are eager for a range of scientists and clinicians to leverage these data to test their own hypotheses about paediatric childhood epilepsy and ultimately optimize pre-surgical planning and cognitive prognosis for children undergoing brain surgery.

Neuroimaging

Abstract #12

Imbalance Between Short- and Long-range Connectivity Predicts Surgical Outcome in Drug-resistant Temporal Lobe Epilepsy

Sara Larivière[1], Yifei Weng[2], Reinder Vos de Wael[1], Zhengge Wang[3], Andrea Bernasconi[1], Neda Bernasconi[1], Zhiqiang Zhang[2], Boris Bernhardt[1]

[1]*Montreal Neurological Institute*
[2]*Department of Medical Imaging, Jinling Hospital*
[3]*Department of Radiology, Nanjing Drum Tower Hospital*

Rationale
Temporal lobe epilepsy (TLE) is a recognized surgically-amenable disorder, however, ~30% of operated patients continue to have seizures. Here, we developed a novel resting-state fMRI framework to examine the balance between short- and long-range functional connections in drug-resistant TLE and assessed its utility in predicting post-surgical outcome. As such, our work allowed in vivo testing of previously described experimental and histopathological pathoconnectomic models, in which epileptogenic regions show decreased long-range connectivity yet aberrant local connections.

Method
We studied 30 drug-resistant unilateral TLE patients (15 males, mean±SD=26.9±8.7 years) with histologically-verified hippocampal sclerosis and 57 age- and sex-matched healthy controls using multimodal 3T MRI. We developed a novel resting-state fMRI framework that parameterized functional connectivity distance (i.e., the overall anatomical distance of an area's functional connections), thereby consolidating functional and geometric properties of brain networks.

Results
Marked connectivity distance reductions in dorsomedial prefrontal and temporo-insular regions were observed in TLE, with the latter having stronger effects ipsilateral to the focus in both left and right TLE patients. Notably, patterns of distance reductions in temporo-insular cortices were driven by concurrent increases in short-range and decreases in long-distance connections, indicating topological segregation of functional networks. Supervised pattern learning with conservative 5-fold cross-validation further revealed that unfavorable surgical outcome imparts a distinct signature on connectivity distance profiles, characterized by contralateral and extratemporal distance reductions prior to anterior temporal lobectomy.

Conclusions
Our findings suggest that an imbalance in short- and long-range connectivity may represent a pathoconnectomic substrate in TLE and emphasize the clinical utility of enriching connectomics with physically-grounded information.

Funding: FRQS, CIHR, NSFC

Neuroimaging

Abstract #13

Homotopic Coupling in Persons with Epilepsy Using Movie-driven fMRI

Caroline Mantei[1], Jacqueline Yeung[2], Mark O'Reilly[2], Daniella Ladowski[2], Ali Khan[3], Jorge Burneo[4], David Steven[4], Ingrid Johnsrude[2]

[1]*Western University*
[2]*The Brain and Mind Institute, The University of Western Ontario, Western Interdisciplinary Research Building*
[3]*Robarts Research Institute, The University of Western Ontario*
[4]*London Health Sciences Centre University Hospital*

Rationale
For the 30-40% of persons with epilepsy (PWE) with drug-resistant epilepsy, the chance of seizure freedom following surgery is affected by the localization of the epileptogenic zone (EZ). However, functional abnormalities may exist at some distance from the EZ, and this may influence variable outcomes after surgery. Considering epilepsy as a network disorder (Farrell et al., 2019), and evaluating functional coupling among brain areas, may help predict cognitive and functional outcomes. Here, we examine functional connectivity in homotopic regions of the two hemispheres as a first step to studying coupling more generally. Homotopic areas are well connected anatomically and undoubtedly work synchronously to generate cognition.

Method
To determine how such coupling is affected by focal epilepsy, we evaluated 21 PWE and 24 matched neurologically normal controls using fMRI and an ecologically valid, engaging audiovisual film clip that has been used previously (Naci et al., 2014). The Glasser parcellation (Glasser et al., 2016), a surface-based atlas that divides each hemisphere into 180 cortical regions, was applied and a baseline distribution of homotopic connectivity between pairs of regions was established based on a subset of controls.

Results
As expected, correlation between homotopic regions was high. Six patients demonstrated significantly stronger or weaker global homotopic connectivity compared to controls, and patients were found to have significantly more homotopic connectivity abnormalities.

Conclusions
These findings suggest that homotopic connectivity is altered in epilepsy and that epileptic networks may provide a better understanding of abnormalities in epilepsy than does an understanding based strictly on a focal epileptogenic zone.

Basic Science / Engineering

Abstract #14

Proteoglycan (Keratan sulfate) Cortical/U-fibre Barrier to Deep Heterotopia Impedes Participation in Epileptic Networks—It Also Explains Why Axosomatic Synapses Are Inhibitory

Harvey B. Sarnat

University of Calgary Faculty of Medicine and Alberta Children's Hospital

Rationale
Patients with extensive deep white matter heterotopia often do not have severe epilepsy. Axons from heterotopia do not extend through U-fibres to cortex, except transmantle dysplasias. The proteoglycan keratan sulfate (KS) in dorsal and ventral median septa of fetal spinal cord and brainstem repels growing glutamatergic axons, thus prevent aberrant decussations, though facilitates GABAergic commissural axons. KS also might be expressed in the cortex and U-fibre layer; its ontogenesis is unknown.

Method
Immunocytochemical demonstration of KS in neocortex of surgical resections and autopsies was studied in 28 normal brains: 14 fetuses and neonates 9-42wk gestational age (GA); 13 infants, children and adolescents; an additional 4 patients with focal cortical dysplasias (FCD). Cartilage provided KS controls.

Results
Immunocytochemical demonstration of KS in neocortex of surgical resections and autopsies was studied in 28 normal brains: 14 fetuses and neonates 9-42wk gestational age (GA); 13 infants, children and adolescents; an additional 4 patients with focal cortical dysplasias (FCD). Cartilage provided KS controls.

Conclusions
This chemical proteoglycan barrier of the U-fibre layer isolates deep heterotopia and impedes participation in cortical epileptic networks. Adhesion of KS to neuronal somatic membranes may selectively repel glutamatergic but enable GABAergic axons, explaining why axosomatic synapses normally are inhibitory.

Basic Science / Engineering

Abstract #15

The Impact of a Single Brief Seizure on Hippocampal Plasticity and Behaviour

Neil Fournier, Mariana Soutter, Emily Horsey, Teresa-Ann Maletta

Trent University

Rationale
Memory difficulties are especially common among people with epilepsy. However, learning and memory impairments are generally thought to only arise during chronic epilepsy and they tend to be associated with the presence of neuronal cell loss, particularly in the hippocampus. Recent studies have shown that a single generalized seizure, even in the absence of neuronal injury, can result in deficits in both short- and long-term hippocampal-dependent memory. It is currently unclear how one self-limited seizure might affect synaptic processes associated with learning and memory.

Method
In the present study, we set out to examine whether a single brief seizure induced by the chemoconvulsant pentylenetetrazole (PTZ) could disrupt normal trace fear learning in Long-Evans rats--a rat strain that is particularly resistant to the effects of PTZ. Rats were treated with PTZ or saline either 2 hr or 24 hrs before undergoing a standard trace fear learning task. Short-term memory (STM) and long-term memory retention tests were carried out 3 hrs and 24 hrs after training. Western blot analyses were used to examine the impact of a single seizure on intracellular signalling pathways associated with memory formation and synaptic plasticity.

Results
While control and PTZ-treated rats showed similar post-shock acquisition freezing levels during conditioning, rats that were administered PTZ 2 hrs but not 24 hrs before training displayed significantly lower levels of freezing during the STM and LTM retention tests. A single brief seizure produced an immediate and transient activation of mTOR (mammalian target for rapamycin—a pathway implicated in epileptogenesis and plays a role in synaptic plasticity) in the hippocampus. Interestingly, administration of the mTOR inhibitor rapamycin reversed memory deficits induced by a single seizures

Conclusions
The findings suggest a potential involvement of the mTOR pathway in mediating memory deficits that can result from a single seizure episode.

Basic Science / Engineering

Abstract #16

Withdrawn

Basic Science / Engineering

Abstract #17

Albumin-Induced Epileptiform Activities in Mouse Brain Slices in Vitro

Haiyu Liu, Liang Zhang

Krembil Research Institute, University Health Network

Rationale
Albumin extravasation and transforming growth factor β receptor (TGFβ) signaling have been demonstrated to induce seizures in rodent models of stroke and brain trauma. Albumin-induced epileptiform responses have also been observed in brain slices of naïve rats (Ivens et al., 2007; et al., 2012; Lapilover et al., 2012; Salar et al, 2016). These findings inspired us to further examine epileptiform activities in albumin-treated mouse hippocampal slices.

Method
Mouse hippocampal slices (0.4 mm thick) were treated 0.4 mM bovine serum albumin alone, albumin plus pharmacological agent(s) or dextran (control) at 35°C for 1 hour. Extracellular recordings were made in CA3 and CA1 areas at 36°C. Repeated afferent stimulation (10 Hz/1 sec, repeated 10 times at 1-sec interval) was delivered to the CA3 area.

Results
Ictal- and/or interictal-like events were frequently observed from albumin-treated but not control slices. These epileptiform activities occurred spontaneously or self-sustained following repeated afferent stimulation. The ictal events were absent in the slices co-treated with albumin plus VX09-765-410 (10 μm, a caspase-I inhibitor known to suppress interleukin-1 signaling), minocycline (1 μm, an antibiotic known to inhibit microglia activation/cytokine release) or MK8-1 (10 μm, a NMDA channel blocker); whereas ictal field potentials remained detectable in slices co-treated with albumin plus losartan (10 μm, an angiotensin II receptor antagonist previously shown to inhibit TGFβ signaling).

Conclusions
Complex mechanisms involving inflammatory/cytokine signaling and aberrant NMDA receptor activity may underlie albumin-induced ictal-like events in our model.

Acknowledgements: Supported by NSERC and Ontario Brain Institute

Basic Science / Engineering

Abstract #18

In Vivo mGluR5 Availability in Hippocampal Subfields of Mesial Temporal Lobe Epilepsy

Jack Lam[1], Jonathan DuBois[1], Jared Rowley[2], Karina González-Otárula[1], Jean-Paul Soucy[1 3], Gassan Massarweh[3], Jeffery Hall[1], Marie-Christine[4], Pedro Rosa-Neto[1 2 3], Eliane Kobayashi[1]

[1]Department of Neurology & Neurosurgery, Montréal Neurological Institute, McGill University
[2]Translational Neuroimaging Laboratory, McGill University
[3]PET Unit, McConnell Brain Imaging Centre, McGill University
[4]Guiot Department of Pathology, Montréal Neurological Institute, McGill University

Rationale
Immunohistochemistry of hippocampi resected from mesial temporal lobe epilepsy (MTLE) patients show increased metabotropic glutamate receptor type 5 (mGluR5) immunoreactivity compared to necropsy controls. Here, we characterized hippocampal subfield mGluR5 availability in MTLE patients using positron emission tomography (PET) imaging with [11C]ABP688, a radioligand that binds specifically to mGluR5 allosteric site.

Method
We obtained structural MRI and [11C]ABP688 PET from 31 unilateral MTLE patients and 30 controls. Patients were classified as having normal volume ("NV") hippocampi or hippocampal atrophy ("HA") based on hippocampal volumetry. Hippocampal subfields were automatically segmented and manually corrected. Considering the low spatial resolution of PET, three major regions of interest were created: 1) CA1/2/3 (Subfield 1); 2) CA4, dentate gyrus and molecular layer (Subfield 2); and 3) parasubiculum, presubiculum, and subiculum (Subiculum). Partial volume corrected [11C]ABP688 non-displaceable binding potential (BPND) was calculated in the ROIs and compared between patients and controls.

Results
[11C]ABP688 BPND was significantly reduced in both NV and HA patients in ipsilateral Subfield 1 ($p<0.001$) and Subfield 2 ($p<0.001$ and $p = 0.001$, respectively). No significant difference was seen in the Subiculum.

Conclusions
mGluR5 availability was reduced in hippocampal Subfields 1 and 2, which could result from internalization of the receptor or conformational changes induced by excess extracellular glutamate. Similar mGluR5 availability across patients and controls in the Subiculum may reflect increased mGluR5 protein expression and a milder increase in extracellular glutamate tampered by relatively preserved glutamine synthetase expression. Funding: Savoy Foundation (EK, PRN, JD), American Epilepsy Society (EK), Canadian Institutes of Health Research (PRN, EK), Fonds de recherche du Québec (FRQS) (JL, PRN).

Funding: Savoy Foundation (EK, PRN, JD), American Epilepsy Society (EK), Canadian Institutes of Health Research (PRN, EK), Fonds de recherche du Québec (FRQS) (JL, PRN)

Basic Science / Engineering

Abstract #19

The Role of Blood-brain Barrier Pathology in Post-traumatic Epilepsy (PTE)

Olumide Adegunna

Dalhousie University

Rationale
Traumatic brain injury (TBI) is becoming a global epidemic with an up-to-date figure putting its toll at 50 million people affected worldwide. In Canada, TBI accounts for 150,000 annual emergency room visits and about half-a-million people are living with a TBI-related disability. The more debilitating forms of TBI have also been associated with a higher risk of about 10-40% for developing post-traumatic epilepsy (PTE) as well as long-term cognitive impairments, neurodegenerative and neuropsychiatric diseases. There are currently no effective therapeutics for the prevention of PTE and associated co-morbidies. Accumulating evidence indicates that blood-brain barrier dysfunction (BBBD) is common following TBI and has a role in epileptogenesis. The goal of the present study was to test whether imaging BBB dysfunction following TBI can be used to predict the development of PTE.

Method
We used the weight drop model of moderate traumatic brain injury in young rats. Rats (N = 45) were assessed for primary injury using neurological scores at baseline, 24, 48 hours and 1-week after injury. The magnitude of BBBD was assessed using a contrast-enhanced magnetic resonance imaging (CE-MRI) at 48hours and 1-month time points. PTE was assessed using telemetric continuous electrographic recordings between 2 – 5 months after injury and cognitive impairment was assessed using the Morris water maze test at 3 months after injury.

Results
CE-MRI confirmed BBBD 48hrs after injury compared to controls. To this end, 5 rats (22%) developed PTE at 5-months post injury. Epileptic rats showed abnormal pattern of brain activity with increased occurrence of slow frequency events, termed "paroxysmal slow wave events" (PSWEs). Morris water maze confirmed a reduction in learning skills in animals following injury. The extent of BBBD at 48 hours was inversely related to performance at Morris water maze, but not with the development of epilepsy at 5-months.

Conclusions
Post-traumatic epilepsy is fairly common following moderate traumatic brain injury. Paroxysmal slow events may reflect an underlying neuronal hypersynchronous activity, hence become a novel non-invasive biomarker for neural injury and epileptogenesis. BBBD imaging may serve as a predicting biomarker for the development of cognitive impairments.

Basic Science / Engineering

Abstract #20

In Vivo Imaging of Postictal Vasoconstriction in Freely-moving Mice Reveals an Enduring Ca2+ Increase in Vascular Smooth Muscle but Not Astrocyte Endfeet

Antis George

University of Calgary, Cumming School of Medicine

Rationale
Our lab has established that following brief electrographic seizures, areas of the brain involved in the seizure display profound vasoconstriction resulting in severe hypoxia which lasts over an hour. This seizure-induced vasoconstriction has not been visualized in the awake freely-behaving mouse nor the role of astrocytic endfeet and vascular smooth muscle determined. This is important as astrocytes are critical in cerebral hemodynamics and vascular smooth muscle cells (VSMCs) are the effectors which control arteriole diameter.

Method
First, local field potentials (LFP) and oxygen levels were chronically monitored from the barrel cortex of male and female Pdgfrβ (VSMC reporter), Slc1a3 (astrocyte reporter) and C57Bl6/J mice. Mice received one brief seizure a day for three successive days using maximal electroconvulsive shock (MES). Using in-vivo 2-photon Ca2+ imaging, vessel diameter and calcium signals were recorded following a 3rd MES.

Results
Repeated brief seizures lowered oxygen baseline levels and on the third seizure all three strains remained severely hypoxic. Using live imaging we show that MES-induced seizures initiate a local and long-lasting vasoconstriction event that is COX-2 dependent as the pretreatment with the COX-2 inhibitor ibuprofen prevented this phenomenon. Following a seizure, Ca2+ signals increased in VSMC however, at astrocytic end-feet this signal was only associated with the seizure itself.

Conclusions
Our data provide evidence that the enduring Ca2+ signalling in VSMCs mediates postictal vasoconstriction consistent with our previous observations that an L-type calcium channel blocker can prevent postictal severe hypoxia.

Basic Science / Engineering

Abstract #21

The Ketogenic Diet Attenuates Post-ictal Hypoxia

Renaud Gom[1], Dhyey Bhatt[1], Jong Rho[1 2], Richelle Mychasiuk[1 3], Cam Teskey[1]

[1]*Hotchkiss Brain Institute, University of Calgary*
[2]*Alberta Children's Hospital Research Institute*
[3]*Department of Neuroscience, Monash University*

Rationale
The ketogenic diet (KD) has shown efficacy as an anticonvulsant and results in numerous metabolic changes which influence physiological processes. More recently the KD has been shown to downregulate COX-2 expression and subsequent production of vasoactive prostanoids. Recent evidence has determined that postictal hypoxia, a stroke-like event that follows seizures, is COX-2 dependent. Here we tested the hypothesis that the KD can prevent severe postictal hypoxia using a repetitively induced seizure model (electrical kindling).

Method
Young adult Long-Evans rats were used in this study. We measured local tissue oxygenation in the hippocampus before, during and following electrically-induced seizures in awake, freely-moving rats. In the experimental group, the traditional ad libitum diet was replaced with a high fat/protein diet that was maintained 14 days prior to seizure elicitation to ensure systemic ketosis. Seizures were elicited at a suprathreshold current on a fixed schedule. In addition to observing changes in postictal hypoxia, measurements including weight change, seizure duration, seizure thresholds, and blood ketones were taken before and after the kindling protocol.

Results
The KD attenuated postictal hypoxia by raising baseline oxygen levels. As expected, weight gain was reduced in diet exposed rats and a notable increase in blood ketones was measured. Regular chow and KD-treated rats had no significant difference in seizure duration however KD rats had a higher seizure threshold relative to rats receiving regular chow.

Conclusions
These preliminary experiments illustrate that metabolic changes with the KD increased baseline oxygen levels rather than neurovascular responses to seizures and may provide another possible treatment to prevent severe postictal hypoxia.

Basic Science / Engineering

Abstract #22

Dynamic Changes in Hippocampal Oxygen Levels Following Febrile Seizures

Sydney Harris, Antis George, Karlene Barrett, Morris Scantlebury, Campbell Teskey

University of Calgary

Rationale
Febrile seizures are the most common convulsive event, occur in childhood, and are preceded by inflammation and fever (above 38.3oC). Febrile seizures can have long-term negative consequences such as memory deficits and an enhanced predisposition to develop temporal lobe epilepsy. Human adults with brief self-generated seizures and animals with induced brief seizures display a period of low brain oxygen levels after seizures terminate (postictal hypoxia) that can be prevented by administering either COX-2 blockers or L-type calcium channel antagonists. Animals with traumatic-induced seizures or seizures induced with chemical convulsants typically results in hyperoxia. It is currently unknown what the dynamic oxygen profiles are during and following febrile seizures. Here we examined oxygen dynamics in the hippocampus in two juvenile seizure models; hyperthermic seizures and febrile seizures.

Method
Eight-day old rat pups were implanted with an electrode to monitor electrographic activity and an optrode to measure local oxygen in the dorsal hippocampus. In the febrile model pups received one injection of 400 µg/kg lipopolysaccharide (LPS) per day for 5 days. In the hyperthermic model no injections were given. At 12 days of age rat pups were subjected to exogenous heat in a heated dry air chamber, a common method to elicit seizures. Once a behavioural seizure occurred the pup was removed and allowed to recover while hippocampal oxygen levels and local field potentials were monitored.

Results
Infant rats typically display lower baseline oxygen levels in the hippocampus than their adult counterparts. However, in 12/20 pups we also observed a further drop in oxygen followed by a period of higher than baseline oxygen levels. 8/20 young rats did not show hippocampal hypoxia and only displayed higher than baseline oxygen levels following a hyperthermic convulsion.

Conclusions
We have found that oxygen levels in the rat pup hippocampus following a hyperthermic convulsion were variable, with both increased and decreased levels observed. This research provides insight into the oxygen dynamics in the developing brain during common childhood convulsive events.

Funding: NSERC, CIHR, Faculty of Graduate Studies University of Calgary

Basic Science / Engineering

Abstract #23

Influence of Inflammation on Behavioral Function and Seizure Susceptibility After Traumatic Brain Injury

Yuqi Lin[1], Chiping Wu[2], Jackie Liu[2], Aylin Reid[1 2]

[1]*Institute of Medical Science, University of Toronto*
[2]*University Health Network, Toronto*

Rationale
Traumatic brain injury (TBI) can result in cognitive impairment, motor abnormalities and post-traumatic epilepsy. Studies indicate the robust inflammatory response following TBI can be both beneficial and disadvantageous. This study directly compares the effects of increasing or decreasing TBI-related inflammation on behavioral outcome and seizure susceptibility.

Method
Fluid percussion injury was performed in four groups of young adult male Sprague-Dawley rats: 1): sham injury; 2) TBI; 3) TBI with minocycline (MINO); 4) TBI with lipopolysaccharide (LPS). Following injury, we administered a series of behavioral tests including composite neuroscores, rotarod, novel object recognition (NOR) and Barnes Maze at various time points within the first month post-injury. Approximately nine months after injury, a subset of rats from each group were injected with pentylenetetrazol (PTZ) to detect seizure susceptibility.

Results
Similar levels of neuromotor deficits after injury were seen in all injured groups as compared to shams. The probe test in Barnes maze showed TBI + MINO group had better spatial memory than TBI only and TBI + LPS groups ($p<0.05$). NOR testing demonstrated no difference between groups. PTZ testing showed TBI + MINO group had a shorter cumulative seizure duration compared to TBI only and TBI+LPS groups, and was comparable to shams.

Conclusions
Decreasing inflammation in the acute post-injury period can improve spatial memory deficits and decrease seizure susceptibility after TBI. Further increase of post-TBI inflammation did not appear to have a detrimental effect, suggesting a critical threshold may have already been reached.

Basic Science / Engineering

Abstract #24

TGF-beta Inhibition as a Treatment for Blood-brain Barrier Dysfunction and Cortical Network Slowing in a Rodent Model of Repetitive Mild Traumatic Brain Injury

Griffin Mumby[1], Ellen Parker[1], Pooyan Moradi[1], Olumide Adegunna[1], Dan Milikovsky[3], Noa Hacohen[1], Erez Hanael[2], Alon Friedman[1 3]

[1]Department of Medical Neuroscience, Dalhousie University
[2]The Hebrew University, Koret School of Veterinary Medicine Veterinary Teaching Hospital
[3]Departments of Physiology and Cell Biology, Cognitive and Brain Sciences, Zlotowski Center for Neuroscience, Ben-Gurion University of the Negev, Beer Sheva

Rationale
Experiments in rodent models show that traumatic brain injury (TBI) is often associated with blood-brain barrier dysfunction (BBBD) which induces TGF-beta signalling and epileptogenesis. Recordings from electrocorticography in rodents and encephalography in humans have shown abnormal periodic cortical network slowing in epilepsy, termed paroxysmal slow wave events (PSWE). The goal of the present study was to determine if early imaging of BBBD predicts PSWEs and if TGF-beta blockers reduce TBI-induced BBBD and PSWEs.

Method
Using a model of repetitive mild TBI (rmTBI), rats were administered five impacts over five days. Rats were treated with either a specific (IPW, 20 mg/kg) or non-specific, FDA approved (losartan, 60mg/kg) TGF-beta antagonist, or saline following the first impact. BBBD was assessed blindly using contrast-enhanced MRI one week post-impact. PSWEs and seizures were monitored using electrocorticographic recordings conducted six months post-impact for four weeks.

Results
Recordings from rmTBI animals documented an average of 347 and 12 PSWEs/day in rmTBI and sham controls, respectively ($p < 0.001$). PSWEs were more common than seizures. The extent of BBBD one week post-impact was not predictive of the occurrence of PSWEs. IPW, but not losartan, reduces the extent of BBBD following rmTBI.

Conclusions
BBBD is common one week post-impact in a rat model of rmTBI. Abnormal brain activity, including PSWEs and spontaneous seizures indicate long-term neural dysfunction. PSWEs may serve as a new biomarker for delayed neuropathology following brain injury.

Funding: CIHR, NSERC, United States of America Department of Defense, Dalhousie Medical Research Foundation, Nova Scotia Health Research Foundation

Basic Science / Engineering

Abstract #25

Region-Specific Epileptogenicity in a Mouse Model of Neurofibromatosis Type 1

Azadeh Sabetghadam, Chipping Wu, Jackie Liu, Hong Mei Song, Liang Zhang, Aylin Reid

University Health Network, Toronto

Rationale
Neurofibromatosis type 1 (NF1), a genetic neurocutaneous disorder, is associated with higher rates of epilepsy compared with the general population. It is not known whether the genetic mutation itself contributes to the higher epilepsy rate in these patients, as up to 50% of NF1 patients with epilepsy have no intracranial lesions. However, there have been no preclinical studies investigating seizures and epilepsy in NF1. We have performed studies in Nf1+/- mice to investigate alterations in electrical kindling rates and epileptogenesis.

Method
Young male or female adult Nf1+/- or wild-type (WT) mice were implanted with electrodes for extended hippocampal kindling or classic neocortical kindling paradigms (n=10/sex/group). Baseline EEG was recorded for up to 48 hours prior to kindling, followed by determination of afterdischarge thresholds (ADTs). Neocortical kindling was performed for 40 stimulation sessions, and hippocampal kindling was performed until mice exhibited spontaneous seizures, or until a maximum of 120 stimulations.

Results
Approximately 25% of Nf1+/- mice had spontaneous seizures at baseline. There were no differences in hippocampal kindling parameters between groups. However, Nf1+/- mice had lower neocortical ADTs (79.41 +/- 6.55 vs 102.66 +/-8.58) and faster kindling rates, reaching first Racine Stage 5 seizure after 11 +/- 1.03 vs 20 +/- 3.08 stimulations. No sex differences were found.

Conclusions
These results suggest the genetic mutation in NF1 leads to regional variability in seizure predisposition and contributes to seizures in non-lesional NF1 patients with epilepsy. Future molecular studies will help elucidate the mechanisms contributing to regional differences in neuro-excitability.

Basic Science / Engineering

Abstract #26

Targeted Deletion of Mitochondrial CyclophilinD Mediates Neuroprotection in Epileptic Brain

Bianca R. Villa, Cezar N. Gavrilovici, G. Campbell Teskey, Jong M. Rho

University of Calgary

Rationale
Epilepsy is a neurological disease affecting over 50 million people worldwide. It is characterized by spontaneous recurrent seizures arising from hyperexcitable and hypersynchronous brain activity. Current therapies fail to control seizures in one-third of patients. Mitochondria are critical for energy homeostasis and survival. Mitochondrial cyclophilinD, a determinant of cell death, when inhibited, significantly reduces seizures. We proposed that parvalbumin GABAergic interneurons, which are fast-spiking and very energy-consuming, express high CypD levels and are more susceptible to cellular death. As PV interneurons project onto hundreds to thousands pyramidal cells, any decrease in their firing may contribute to seizure generation.

Method
We used immunohistochemistry and confocal microscopy techniques in a clinically relevant model of epilepsy (Kcna1-null mouse). Dorsal hippocampal interneurons from coronal slices were stained for PV, CR, CB, CypD, and GAD67 using various antibodies. Z-stack images of the CA1 region of the hippocampus were acquired and positive-staining cells quantified.

Results
We found that most neurons with high CypD immunoreactivity express parvalbumin. Kcna1-null mice showed significant PV cell loss, which was prevented by targeted deletion of CypD. Deletion of CypD in wild-type mice was itself neuroprotective. Interestingly, GAD67 interneurons were unchanged, indicating that the majority of interneurons survive in epileptic mice, but only a subpopulation of (most likely PV) interneurons are reduced.

Conclusions
Further studies will detail the role of CypD in modulation of the hippocampal inhibitory network. Collectively, our results will provide evidence for a link between metabolism and seizures genesis, and will establish CypD as a promising therapeutic target for medically intractable epilepsy.

Funding: Alberta Children's Hospital Research Institute and the Alberta Children's Hospital Foundation

Basic Science / Engineering

Abstract #27

Impaired Tuning of Afferent Excitatory Synapses of Hippocampal Fast-spiking Interneurons by Acute Early Life Seizures

Ting Ting (Tina) Wang, Hongyu Sun

Carleton University

Rationale
The neonatal period is characterized as a critical period for plasticity and enhanced susceptibility to early life seizures (ELS). Currently ELS are often refractory to conventional antiepileptic drugs, resulting in an urgent need to identify novel mechanisms and specific treatment strategies. Fast-spiking (FS) interneurons provide strong perisomatic inhibition and are crucial in maintaining the excitation/inhibition balance in the brain. However, the precise effects of ELS on FS interneurons remain elusive. Here, we aim to investigate the acute effects of ELS on the excitatory afferent synapses of hippocampal FS interneurons.

Method
Acute ELS were induced by single dose of 60mg/kg PTZ (i.p.) in P10-12 mice. Whole-cell patch clamp recordings were made in FS interneurons of ELS mice at 1h post-ELS and littermate controls to examine intrinsic membrane properties and AMPAR functions.

Results
We found that intrinsic properties were unchanged in FS interneurons from ELS mice compared to littermate controls. However, AMPAR-mediated spontaneous EPSCs showed a significant decrease in frequency, while the amplitude was unchanged. We further identified that ELS significantly reduced the paired-pulse ratio and short-term plasticity in the FS interneurons from post-seizure mice compared to controls through reduction of the size of the presynaptic ready release vesicle pool. In addition, ELS attenuated asynchronous neurotransmitter release, which significantly impaired the precision and fidelity of action potentials in FS interneurons.

Conclusions
These data strongly suggest that ELS impair afferent excitatory synapses of hippocampal FS interneurons through a presynaptic mechanism and provide a potential synaptic mechanism mediating hippocampal circuit reorganization in early life epilepsy.

Paediatric Epilepsy

Abstract #28

MECP2 Is Reduced in Dravet Syndrome

David Dyment, Sarah Schock, Kevin Ban, Minh Tran

CHEO Research Institute

Rationale
Dravet syndrome (DS) is an early-onset epileptic encephalopathy syndrome caused by variants in the Nav1.1 sodium channel encoded by SCN1A. Individuals with DS experience difficult-to-treat seizures and developmental delay starting around the second year of life after a period of normal development. Long-term outcome is associated with significant psychomotor delays and on-going seizure activity. Variants in MeCP2, a transcription factor essential for proper neuronal function, are responsible for another neurodevelopmental disorder, Rett syndrome. Recently it was shown that MeCP2 mRNA levels are reduced in fibroblasts from a single DS patient.

Method
DS patient fibroblasts and induced neural precursor cells (iNPCs) were used to assess protein and mRNA expression of MeCP2 and its downstream targets. A mouse model of DS carrying a p.H939R variant was also used for mRNA and protein analysis in young and old mice.

Results
The results confirm that MeCP2 levels are reduced in fibroblasts from three DS patients. We also show that the downstream targets of MeCP2 such as brain derived neurotropic factor and Dlx5, are also reduced. Similar findings are observed in iNPCs derived from fibroblasts. The mouse model shows no difference in MeCP2 expression in early life. However, at one year of age, there is significant reduction in MeCP2 levels. These findings correlate with our behavioral studies of these DS mice: showing increased cognitive deficits with increasing age.

Conclusions
Levels of MeCP2 and its downstream targets are reduced DS – this may contribute to the cognitive and motor impairments that accompany seizures in this disorder.

Paediatric Epilepsy

Abstract #29

Cannabis-based Products for the Treatment of Paediatric Epilepsy: A Systematic Review

Jesse Elliott[1], Deirdre DeJean[2], Tammy Clifford[1], Doug Coyle[1], Beth Potter[1], Becky Skidmore, Christine Alexander, Alexander Repetski, Bláthnaid McCoy[3], George A. Wells[1]

[1]*School of Epidemiology and Public Health, University of Ottawa*
[2]*CADTH*
[3]*Division of Neurology, the Hospital for Sick Children Toronto*

Rationale
Interest in cannabis as a treatment for epilepsy has grown over the past decade, driven in part by media reports of children whose epilepsy has responded to cannabis. An up-to-date overview of the available evidence is needed to support clinical decision-making.

Method
We performed a comprehensive systematic review of the literature by searching MEDLINE, Embase, PsycINFO, Cochrane Library, and grey literature (May 9, 2019). We included randomized controlled trials (RCTs) and non-randomized studies involving children with any type of epilepsy who were administered a cannabis-based product (e.g., cannabidiol). The primary outcome was seizure freedom; secondary outcomes included seizure frequency and quality of life. Data were pooled, and risk of bias was assessed. The search will be updated at 6-month intervals to identify new studies.

Results
Thirty-four studies (4 RCTs) were included. Most involved the use of Epidiolex (cannabidiol) administered to children with drug-resistant epilepsy syndromes. Data from RCTs suggest that cannabidiol reduces seizure frequency (median difference –20% [95% confidence interval –27% to –13%]) with no significant effect on seizure freedom (risk difference 5% [–1% to 11%]) or quality of life (mean difference 0.6 [–2.6 to 3.9]). In total, 35 ongoing studies are registered in ClinicalTrials.gov; results will be included in subsequent updates of this review as data become available.

Conclusions
Evidence from high-quality RCTs suggests that cannabidiol may reduce seizures among children with drug-resistant epilepsy. At this time, evidence is primarily limited to cannabidiol, and the findings should not be extended to all cannabis-based products.

Paediatric Epilepsy

Abstract #30

Risk Factors for Epilepsy in Neonates with Hypoxic-Ischemic Encephalopathy and Seizures

William April[1], Simon Frédérick Richard[1], Brigitte Martin[2], Nicolas Déom[1], Béatrice Desnous[1], Zamzam Mahdi[1], Josianne Malo[2], Ala Birca[1]

[1]*Sainte-Justine Hospital Research Center, Université de Montréal*
[2]*Sainte-Justine Hospital*

Rationale
One third of neonates with acute seizures secondary to hypoxic-ischemic encephalopathy (HIE) develop epilepsy, interfering with neurodevelopment. The current ability to predict the risks for epilepsy is very limited and the effectiveness of antiseizure medication to prevent epilepsy hasn't been established. This study aims to determine the clinical risk factors for epilepsy in neonates with seizures in the context of HIE.

Method
We performed a retrospective study of 58 consecutive near-term (>35 weeks) neonates from Sainte-Justine Hospital with HIE experiencing neonatal seizures, followed for a median of 9 months (range, 5-98 months). Perinatal and follow-up data were documented, and Fisher's exact test, T-tests, Mann-Whitney tests and Kaplan-Meier curves were applied to assess associations.

Results
Among 58 neonates, 43 (74%) underwent therapeutic hypothermia 11 (19%) developed epilepsy (median age 18 months; interquartile range, IQR 6-39). Lower median Apgar scores at 10 min ($p=0.024$) and higher average Sarnat scores ($p=0.001$) were associated with epilepsy. All four neonates with status epilepticus developed epilepsy. Recurrence of neonatal seizures over a longer period of time ($p=0.001$), higher median cumulative doses of phenobarbital administered before discharge ($p<0.0005$), increased median number of different anticonvulsants attempted ($p=0.004$), the severity of ischemic brain injury on MRI ($p=0.027$) were associated with epilepsy. Prescription of antiseizure medication at discharge didn't influence outcome.

Conclusions
Severity of cerebral insult and difficulty to control neonatal seizures were both potential predictors of epilepsy in neonates with HIE, highlighting the epileptogenic effects of seizures and the importance to treat them precociously to limit these effects.

Clinical Epilepsy / EEG / Antiepileptics

Abstract #31

Understanding the Patient Perspective of Epilepsy Treatment Through Text Mining of Online Patient Support Groups

Samuel Lapalme-Remis[1], Lixia Yao[2], Kai He[3], Na Hong[2], Yangyang Lan[3], Ming Huang[2], Chen Li[3]

[1]*Centre hospitalier de l'Université de Montréal*
[2]*Mayo Clinic*
[3]*Xi'an Jiaotong University*

Rationale
Epilepsy is among the most common chronic neurological diseases. There is a need for data on patient perspectives of treatment to guide patient-centered care initiatives. Patients with epilepsy share their experiences on social media anonymously, but little is known about the content of these posts. Our aim was to learn what epilepsy patients discuss on online forums and identify treatment-related themes.

Method
355,838 posts were collected from three online support groups for epilepsy patients through a crawling script, and an analytical pipeline was built to identify content through leveraging of multiple text-mining methods. Results were also displayed by network visualization methods.

Results
Patients with epilepsy sought information about medical treatments, shared their treatment experiences and sought help from other posters. Key themes related to treatments included the search for optimal personalized treatment strategies as wells as identifying and coping with side effects.

Conclusions
This study showed the feasibility of learning about concerns of patients with epilepsy, especially treatment issues, through text-mining methods. Providers should be aware of online discussions. Analyses of such discussions could help guide effective patient engagement.

Clinical Epilepsy / EEG / Antiepileptics

Abstract #32

Developing a Local Paediatric Epilepsy Program Website to Improve Information Access for Families and Health Care Providers

Michelle Gratton, Armela Hadzic, Rochelle Sorzano, Maryam Nabavi Nouri, Andrea Andrade

Western University

Rationale
The diagnosis of childhood epilepsy is often accompanied by fear, anxiety and uncertainty. However, families who receive adequate information experience greater satisfaction with their care and decreased anxiety and stress (Gordon & Crisp, 2016). While health literature focuses on the need for epilepsy education for families and healthcare providers, dedicated paediatric epilepsy program websites in Canada do not exist. Inadequate information may result in families and healthcare providers underutilizing hospital epilepsy resources. Families and team members of the Paediatric Epilepsy Program at London Health Sciences Centre identified the need for a program website in order to provide the most accurate and reliable information.

Method
A quality improvement framework, Plan-Do-Act-Study, was implemented to design and evaluate a paediatric epilepsy program website. A focus group, consisting of various healthcare providers and family advisors, was formed to determine key components, ease of use, and content development. Using the Knowledge Translation process, website content was created and reviewed by the focus group and then populated to the Children's Hospital Website. The website was advertised to the public via hospital sources and community agencies.

Results
Analytics for the first 6 months of the website showed an increase in use over time. The contents were divided into 4 themes; program information (35%), resources (17%), tests (25%), and treatment options (23%). The most popular content pages were: Our Team (17%) and Paediatric Epilepsy Monitoring Unit (13%).

Conclusions
A local paediatric epilepsy website appears to increase family and healthcare provider access to reputable and reliable information.

Clinical Epilepsy / EEG / Antiepileptics

Abstract #33

Late Onset Focal Epilepsy with Extensive White Matter Abnormalities

Ana Suller Marti, Richard McLachlan, David Diosy, Jorge Burneo

Western University

Rationale
Epilepsy onsetting after age 40 years old is often associated with cerebrovascular disease or tumours and is usually easily controlled with antiseizure medication. We describe a syndrome of late onset refractory epilepsy, associated with prominent white matter abnormalities on MRI of unclear etiology.

Method
From the database of the Epilepsy program at Western University between July 2018 and April 2019 we identified patients with epilepsy starting after the age of 40, refractory seizures and white matter changes on MRI.

Results
Four patients, three women and one man, had extensive white matter abnormalities that could not be explained. Median age of seizure onset was 45.5(range:40-51) and the current age 51.5(range:47-57). The median seizure frequency was 7.5 per month(range:0.5-30.3). All had focal seizures with impaired awareness, and 3 had progression to bilateral tonic clonic seizures. Seizures continued despite up to eight antiseizure drugs trails. Three patients had anxiety-depression, one Crohn's disease and one hypertension. One was a smoker. Physical and cognitive examinations were normal. EEG documented multifocal seizures in two patients and possible left temporal in two. MRI showed mesial temporal sclerosis in one patient. Autoimmune panel in CSF and blood was negative in three. Two patients received immunoglobulin with only temporary improvement in one. None have had epilepsy surgery other than VNS implantation.

Conclusions
We identify a group of patients with refractory late onset epilepsy with widespread white matter lesions of unknown cause. In the absence of vascular risk factors, an autoimmune etiology is suspected, however more cases are required for a better understanding of this condition.

Clinical Epilepsy / EEG / Antiepileptics

Abstract #34

Polymorphism on KCNQ2 Gene Susceptibility in Epileptic Patients of Pakistan

Nadeem Sheikh, Mavra Irfan, Maryam Mukhtar, Saira Kainat Suqaina, Tayyaba Saleem

University of the Punjab

Rationale
KCNQ2 (potassium channel, voltage-gated, KQT-like subfamily, member) gene mutations are responsible for a reduction of the M-current that play a major role in regulation of neuronal excitability, thus leading towards the consequent dysfunctioninig of the neuronal response to synaptic input. Due to this reason; it is advent that several mutations in the gene have been associated with onset of epilepsy. Therefore the current study was designed with an aim to determine the polymorphism on KCNQ2 gene and its association with epilepsy onset in Pakistani population.

Method
A study comprised of epileptic patients as well as age and sex matched control subjects with negative family history of epilepsy was conducted. DNA was isolated and exon 3 and 5 of KCNQ2 gene were amplified by primer specific PCR. Polymorphisms were identified by sangers sequencing method.

Results
Reported SNPs including rs28939684, rs74315391, rs118192203, rs397514581 on exon 3 and rs118192207, rs118192209, rs74315392 and rs794727740 on exon 5 were not found among patients. However a novel addition of adenine was found on exon 5 of the targeted gene.

Conclusions
KCNQ2 gene was not significantly associated with disease onset in adults. However larger populations should be screen for the gene so that the population specific primers can be used as genetic markers for pre diagnosis of the disease.

Clinical Epilepsy / EEG / Antiepileptics

Abstract #35

Polymorphism on GABRG2 Gene Susceptibility in Epileptic Patients of Pakistan

Nadeem Sheikh, Tayyaba Saleem, Maryam Mukhtar, Saira Kainat Suqaina, Mavra Irfan

University of the Punjab

Rationale
Gamma-Aminobutyric Acid Type A Receptor Gamma2 Subunit (GABRG2) polymorphism dysfunctional neuronal ions channel by variable extent as well as mechanisms which ultimately lead to the onset of multiple neurological disorders including epilepsy. Therefore the current study was designed with an aim to determine the polymorphism on GABRG2 gene and its association with epilepsy onset in Pakistani population.

Method
A case control study comprised of epileptic patients as well as age and sex matched control subjects with negative family history of epilepsy. DNA was isolated and exon 5, 7 and 8 of GABRG2 gene were amplified by primer specific PCR. Polymorphism was identified by sangers sequencing method.

Results
Mutation was identified on rs211037 polymorphic site on exon 5 and was found significantly differed in frequency among patients and controls. However no other mutations were found on exon 7 and 8 of the targeted gene.

Conclusions
GABRG2 gene was found significantly associated with disease onset however larger populations should be screen for the gene so that the population specific primers can be used as genetic markers for pre diagnosis of the disease.

Clinical Epilepsy / EEG / Antiepileptics

Abstract #36

Vitamin D Receptor Gene Polymorphism: An Important Risk Factor of Epilepsy Development

Nadeem Sheikh, Saira Kainat Suqaina, Maryam Mukhtar, Tayyaba Saleem, Mavra Irfan

University of the Punjab

Rationale
Epilepsy, a neurological disorder characterized by unprovoked seizures, recurrent, neurobiological, psychological cognitive, and social consequences. Polymorphism on Vitamin D receptors altered brain cells growth regulation and differentiation as well as neuronal protection. Therefore, the aim of current study is to identify polymorphism on VDR gene in epilepsy patients.

Method
For this purpose a case control study was conducted. DNA was isolated and targeted region for rs2228570, rs731236, rs1544410 and rs7975232 were amplified by primer specific PCR. Polymorphism was determined by direct sequencing method.

Results
As a result it was found that in epileptic patients' mutations on all targeted regions were significantly associated at allelic as well as genotypic level. Polymorphism on rs2228570 polymorphic site led to the change of Tryptophan into Arginine. However rs731236 polymorphism do not caused any change in amino acid sequence therefore act as silent mutation.

Conclusions
In conclusion, VDR gene polymorphism was found to be a significant risk factor in onset of epilepsy and altered normal functioning of vitamin D by altering its receptor.

Clinical Epilepsy / EEG / Antiepileptics

Abstract #37

Efficacy and Safety of Adjunctive Perampanel 4 mg/day for the Treatment of Partial-onset Seizures: Pooled Analysis of Four Randomized Phase III Studies

Bernhard Steinhoff[1], Alejandro Salah[2], Anna Patten[3], Manoj Malhotra[2]

[1]*Kork Epilepsy Center*
[2]*Eisai Inc*
[3]*Eisai Ltd*

Rationale
This post hoc analysis reports pooled data from four Phase III, double-blind studies (Study 304, NCT00699972; Study 305, NCT00699582; Study 306, NCT00700310; Study 335, NCT01618695) in patients (aged ≥12 years) with partial-onset seizures (POS), with/without secondarily generalized seizures (SGS), to evaluate efficacy and safety of adjunctive perampanel 4 mg/day received as actual dose, which may have differed from randomized dose.

Method
Efficacy assessments in patients receiving placebo or perampanel 4 mg/day (actual dose) included median percent reductions in seizure frequency per 28 days and seizure-freedom rates for POS and SGS (patients with Baseline SGS). Treatment-emergent adverse events (TEAEs) were assessed in patients receiving perampanel 4 mg/day at TEAE onset.

Results
Overall, 616 and 363 patients with POS received placebo or perampanel 4 mg/day, respectively (SGS: n=235 and n=134, respectively). Compared with placebo, perampanel 4 mg/day conferred significantly greater reductions in seizure frequency per 28 days for POS and SGS (12.6% vs 21.1%, 17.4% vs 49.8%, respectively; both $P<0.001$), and seizure-freedom rates (0.8% vs 3.6% [$P<0.01$], 11.1% vs 18.7% [$P<0.05$], respectively). TEAEs reported with perampanel 4 mg/day occurred in 419/1376 (30.5%) patients with POS and 148/499 (29.7%) with SGS. The most common TEAE was dizziness.

Conclusions
This post hoc analysis based on actual dose of perampanel received, showed that adjunctive perampanel 4 mg/day was efficacious and well tolerated in patients (aged ≥12 years) with uncontrolled POS with/without SGS. Perampanel 4 mg/day may be an appropriate treatment option for patients with uncontrolled POS who cannot tolerate higher perampanel doses.

Clinical Epilepsy / EEG / Antiepileptics

Abstract #38

Inpatient Hospitalization Rates in Patients Diagnosed With Epilepsy and Treated with Perampanel or Lacosamide

Edward Faught[1], Alejandro Salah[2], Xuan Li[2], Jiyoon Choi[2], Manoj Malhotra[2], Russell Knoth[2]

[1]*Emory University*
[2]*Eisai Inc*

Rationale
A previous study of perampanel investigated healthcare resource utilization (HRU) as a proxy for clinical effectiveness using real-world data and demonstrated a reduction in HRU following initiation of perampanel. To address if "active management" could be at work, inpatient hospitalization rates following initiation of perampanel were compared with those of lacosamide.

Method
Symphony Health, a nationally representative medical and pharmacy claims database, was used in this study. Patients were identified if they had filled a prescription of either perampanel or lacosamide during the period 07/01/14 to 06/30/16. The index date was the first fill of the medication. Patients were aged 12 years, with continuous observations for the year prior to and following the index date, had 2 diagnoses of epilepsy or non-febrile convulsions, and 1 additional medication fill following the index date. Using propensity scores, perampanel- and lacosamide-treated patients were matched 1:1 on age, gender, index year, region, Charlson Comorbidity Index (CCI), number of previous antiepileptic drugs, and evidence of previous hospitalizations.

Results
After matching, there were 1717 patients in each cohort. All-cause hospitalization reduced after initiation of perampanel (9.6%) compared with lacosamide (5.8%), $P<0.05$. Epilepsy-related hospitalizations also decreased, 9.9% vs 8.3% for perampanel vs lacosamide, respectively ($P<0.05$).

Conclusions
In patients diagnosed with epilepsy, treatment with perampanel compared with lacosamide was associated with a significantly greater reduction in all-cause and epilepsy-related hospitalizations. Even when considering the effects of active management, these results suggest that choice of adjunctive medication may lead to differences in HRU.

Clinical Epilepsy / EEG / Antiepileptics

Abstract #39

Sustained Seizure-Free Status with Adjunctive Perampanel for Patients with Primary Generalized Tonic-Clonic Seizures during the Open-Label Extension Phase of Study 332

Imad Najm[1], Alejandro Salah[2], Manoj Malhotra[2], Anna Patten[2], Leock Ngo[2]

[1]*Cleveland Clinic*
[2]*Eisai Inc*

Rationale
Limited treatment options are available for patients with primary generalized tonic-clonic (PGTC) seizures, thus, treatment with a narrow range of anti-seizure drugs is often the only option for these patients. Adjunctive perampanel has demonstrated efficacy and tolerability for PGTC seizures in Phase III Study 332 (NCT01393743), which comprised a Double-blind Phase and an Open-label Extension (OLEx) Phase. To determine if treatment response was maintained from the Double-blind to the OLEx Phase in patients from Study 332, PGTC seizure-freedom rates were assessed in this post hoc analysis.

Method
PGTC seizure-freedom rates were assessed for ≤24 months in patients achieving seizure freedom during the Double-blind Phase or ≥12 months in patients who were seizure-free at any time during the Perampanel Treatment Duration (OLEx or OLEx + Double-blind Phases for patients previously randomized to placebo or perampanel, respectively).

Results
During the Double-blind Phase, 35/162 (21.6%) patients (10 receiving placebo; 25 receiving perampanel) achieved PGTC seizure freedom. Of these 25 perampanel-treated patients, 14/25 (56.0%) and 6/19 (31.6%) remained PGTC seizure free for 12 and 24 months, respectively. During the Perampanel Treatment Duration, 73/138 (52.9%) and 41/138 (29.7%) patients receiving perampanel achieved PGTC seizure freedom for ≥6 or ≥12 months, respectively. PGTC seizure-freedom rates were similar irrespective of double-blind treatment (placebo vs perampanel). Perampanel was generally well tolerated.

Conclusions
These data are encouraging given the refractory nature of generalized seizure types and suggest adjunctive perampanel may offer a long-term treatment option for patients with PGTC seizures.

Clinical Epilepsy / EEG / Antiepileptics

Abstract #40

Sustained Seizure-Free Status with Adjunctive Perampanel for Patients with Secondarily Generalized Seizures during an Open-Label Extension: Study 307

Trevor Resnick[1], Alejandro Salah[2], Anna Patten[2], Manoj Malhotra[2], Leock Ngo[2]

[1]*Nicklaus Children's Hospital*
[2]*Eisai Inc*

Rationale
In patients with refractory generalized seizure types, the ultimate goal of achieving seizure-free status is often elusive. Adjunctive perampanel has demonstrated efficacy and tolerability for partial-onset seizures, with/without secondarily generalized (SG) seizures, in three Phase III, double-blind studies (Study 304, NCT00699972; Study 305, NCT00699582; Study 306, NCT00700310). Patients completing these studies could enter the open-label extension (OLEx) Study 307 (NCT00735397). To determine if responses were maintained from the double-blind studies to the OLEx, SG seizure-freedom rates were evaluated in patients from Study 307.

Method
In this post hoc analysis, SG seizure-freedom rates were assessed for ≤48 months in: (1) patients achieving SG seizure freedom during the double-blind studies; (2) patients who were SG seizure free at any time during the Perampanel Treatment Duration (OLEx or OLEx and double-blind studies for patients previously randomized to placebo or perampanel, respectively).

Results
Of 80 patients who received perampanel during the double-blind studies and achieved SG seizure freedom, 74/78 (94.9%), 57/78 (73.1%), 42/78 (53.8%), and 22/63 (34.9%) patients remained SG seizure free for 6, 12, 24 and 36 months, respectively. For patients treated with perampanel during the Perampanel Treatment Duration, 197/475 (41.5%), 142/475 (29.9%), 94/470 (20.0%), and 43/366 (11.7%) patients achieved SG seizure freedom for ≥6, ≥12, ≥24, and ≥36 months, respectively. SG seizure-freedom rates were similar irrespective of prior treatment (placebo/perampanel). Perampanel was generally well tolerated during the OLEx.

Conclusions
These data are encouraging given the refractory nature of generalized seizure types and suggest adjunctive perampanel may offer a long-term treatment option for patients with SG seizures.

Clinical Epilepsy / EEG / Antiepileptics

Abstract #41

Perampanel in Real-world Clinical Care of Patients with Epilepsy: Retrospective Phase IV PROVE Study 506

Robert Wechsler[1], James Wheless[2], Marcelo Lancman[3], Sami Aboumatar[4], Alejandro Salah[5], Anna Patten[6], Manoj Malhotra[5]

[1]*Idaho Comprehensive Epilepsy Center*
[2]*University of Tennessee, Le Bonheur Children's Hospital*
[3]*Northeast Regional Epilepsy Group*
[4]*Austin Epilepsy Care Center*
[5]*Eisai Inc*
[6]*Eisai Ltd*

Rationale
We report third interim results of the non-interventional, retrospective, Phase IV PROVE Study (Perampanel Real-world Evidence; NCT03208660; "Study 506") assessing retention rate, safety, and dosing experience of perampanel administered to patients with epilepsy during routine clinical care.

Method
Exposure, safety, and efficacy data were obtained from medical records of patients initiating perampanel after January 1, 2014. Primary endpoint is retention rate (proportion of patients in Safety Analysis Set [SAS] remaining on perampanel). Safety, efficacy, and dosing experience are secondary objectives.

Results
Interim SAS included 1118 patients (mean [standard deviation, SD] age, 29.1 (16.6) years; 54.4% female. At cut-off (October 10, 2018), 591 (52.9%) patients remained on perampanel; 522 (46.7%) had discontinued (most common reasons: adverse event, n=244 [21.8%]; inadequate therapeutic effect, n=143 [12.8%]). Mean (SD) cumulative duration of perampanel exposure was 17.7 (15.5) months; mean (SD) maximum dose 6.7 (3.2) mg. Retention rates at 3, 6, 12, 18, and 24 months were 82.1% (n=910/1108), 72.1% (n=774/1074), 61.2% (n=586/957), 54.6% (n=448/820), and 52.4% (n=343/655), respectively. At Months 22-24, median reduction in seizure frequency/28 days was 98.3% (n=34); 50% responder rate was 76.5% (n=26/34) and seizure-freedom rate 47.1% (n=16/34). Treatment-emergent adverse events (TEAEs) were reported in 490 (43.8%) patients, most commonly dizziness (n=104 [9.3%]), aggression (n=61 [5.5%]), and irritability (n=50 [4.5%]). Serious TEAEs occurred in 27 (2.4%) patients (4 [0.4%] deaths).

Conclusions
This interim analysis further defines the safety profile and demonstrates favorable retention rates and sustained efficacy of perampanel (≤2 years) in patients with epilepsy treated during routine clinical care.

Clinical Epilepsy / EEG / Antiepileptics

Abstract #42

Increased Knowledge and Feeling Ethically Obligated are Predictors of Child Neurologists' SUDEP Discussion Practices

Anne Keller, Robyn Whitney, Elizabeth Donner

The Hospital for Sick Children

Rationale
Practice guidelines indicate that neurologists should discuss the risk of Sudden Unexpected Death in Epilepsy (SUDEP) with all patients with epilepsy; however, current discussion practices are unknown. Here, we report SUDEP discussion practices of child neurologists and evaluate variables associated with discussion practice.

Method
Child Neurology Society members were surveyed in November 2017 and May 2018 regarding their practice of discussing SUDEP with patients with epilepsy or their caregivers. Multivariable proportional odds ordinal logistic regression was used to evaluate factors associated with discussing SUDEP with a greater proportion of epilepsy patients/caregivers.

Results
Among the 369 child neurologist respondents, 36% reported discussing SUDEP with at least half of their epilepsy patients/caregivers including 12.2% who discuss with all or almost all (>90%) of their epilepsy patients/families. Those who discussed SUDEP with an increased proportion of their patients were more likely to agree that they knew enough to talk about SUDEP (OR: 3.49), agree that healthcare providers have an ethical obligation to discuss SUDEP (OR: 5.65), and disagree that there isn't enough time to talk about SUDEP (OR: 2.11). Those who agreed SUDEP could provoke excessive anxiety or worry were less likely to discuss SUDEP with an increased proportion of their patients (OR: 0.41).

Conclusions
Most child neurologists do not follow clinical guidelines regarding SUDEP discussion. Feeling sufficiently knowledgeable and an ethical obligation to discuss SUDEP were associated with increased discussion practice, suggesting an educational intervention may be effective at increasing SUDEP discussion rates.

Funding: The Child Neurology Foundation and EpLink, the Epilepsy Research Program of the Ontario Brain Institute

Clinical Epilepsy / EEG / Antiepileptics

Abstract #43

Paradoxical Nocturnal Status Epilepticus Activated by Rapid Eye Movement Sleep: A Case Study

Marna B. McKenzie, Marcus C. Ng

University of Manitoba

Rationale
Rapid Eye Movement sleep (REM) tends to suppress interictal epileptiform discharges (IEDs) and seizures, however some patients continue to have breakthrough IEDs and seizures during REM. Here, we report a case in which REM consistently activated IEDs and seizures to the point of electrographic status epilepticus.

Method
Retrospective review of continuous electroencephalogram (EEG) recording from the epilepsy monitoring unit (EMU) and detailed chart review in the four-year period surrounding EMU admission (date of admission +/- 2 years) was performed.

Results
A 60 year-old female with longstanding medically refractory temporal lobe epilepsy comprised of both focal onset impaired awareness seizures and bilateral tonic-clonic seizures, was admitted to the EMU where she was identified to have paradoxical REM-activated seizures. The admission included six continuous nights in the EMU where she achieved a total of 286 minutes of REM during which there was continuous (100%) epileptiform activity consistent with electrographic status epilepticus. Additionally, one clinical seizure was captured during REM.

Conclusions
Seizures in REM are typically rare compared to non-REM and wakefulness due to presumed EEG desynchronization acting to interrupt and suppress IEDs and seizures. However, our case highlights the known variability of the effect of REM on seizures between individuals, and ultimately suggests there is an atypical mechanism for seizure generation or inhibition in this patient.

Clinical Epilepsy / EEG / Antiepileptics

Abstract #44

Making Mindfulness Matter (M3): A Randomized Controlled Trial of a Community-Based Family Intervention for Children with Epilepsy

Klajdi Puka, Karen Bax, Andrea Andrade, Margo Devries-Rizzo, Hema Gangam, Simon Levin, Maryam Nabavi Nouri, Asuri N. Prasad, Mary Secco, Guangyong Zou, Kathy N. Speechley

Western University

Rationale
Epilepsy extends far beyond seizures; up to 80% of children with epilepsy (CWE) may have comorbid cognitive or mental health problems, and up to 50% of parents of CWE are at risk for major depression. Past research has also shown that family environment has a greater influence on patients' and parents' health-related quality of life (HRQOL) and mental health than epilepsy-related factors. There is a pressing need for low-cost, innovative interventions to improve HRQOL and mental health. We are currently conducting a randomized controlled trial (RCT) to evaluate whether a family treatment program, Making Mindfulness Matter (M3), positively affects CWE's and parents' HRQOL and mental health (specifically, stress, behavioral, depressive, and anxiety symptoms).

Method
This parallel RCT is recruiting 100 CWE (ages 4-10) and their parents, to be randomized 1:1 to the 8-week intervention or waitlist control and followed over 18 weeks. The intervention, M3, will be delivered concurrently to parents and children in a group setting by non-clinician staff of a local epilepsy support center. The intervention incorporates mindful awareness, social-emotional learning skills, and positive psychology. It is modeled after the validated school-based MindUP program and adapted for provision in the community and to include a parent component.

Results
Study protocol and preliminary feasibility results will be presented.

Conclusions
This RCT will determine whether this low-cost, community-based intervention is feasible and effective for CWE and their parents. The proposed intervention may be an ideal vector to significantly improve HRQOL and mental health for CWE and their parents.

Funding: Canadian Institutes of Health Research

Clinical Epilepsy / EEG / Antiepileptics

Abstract #45

Reported Unmet Mental Healthcare Needs Among People with Epilepsy: Insights from the Canadian Community Health Survey

Tresah Antaya, Jorge Burneo

Western University

Rationale
People with epilepsy report worse mental health and more unmet mental healthcare needs (UMHNs) than the general population despite their higher utilization of healthcare services. Our objective was to identify factors associated with reporting UMHNs in this population.

Method
We conducted a cross-sectional analysis of data from cycles 2.1 and 3.1 of the Canadian Community Health Survey. We included respondents who confirmed or denied their diagnosis of epilepsy, migraines, diabetes, or asthma, and whether they consulted a healthcare professional for mental health in the past 12 months. We used Rao-Scott chi-square tests in bivariate analysis and a binary logistic regression model in multivariable analysis. We applied survey weights in all analyses.

Results
153,592 study respondents were included. People with epilepsy, migraines, and asthma were significantly more likely to report UMHNs ($p<0.05$) in bivariate analysis. However, diagnosis of any of the studied chronic conditions did not significantly increase the likelihood of reporting an UMHN in multivariable analysis. Age, sex, marital status, highest level of education completed, languages spoken, province of residence, mode of survey administration, mental health status, the number of consultations for mental health, not having a regular medical doctor, diagnosis with a mood or anxiety disorder, and having difficulties with activities due to mental health remained significantly associated with reporting UMHNs in multivariable analysis.

Conclusions
Sociodemographic, mental health, and healthcare-related factors, rather than diagnosis with the chronic conditions that were examined, are associated with reporting UMHNs. The distribution of these factors within each population will be described.

Clinical Epilepsy / EEG / Antiepileptics

Abstract #46

Classification of Epileptic Brain States Based on Bispectrum-extracted Features

Laura Gagliano[1], Elie Bou Assi[2], Dang K. Nguyen[2], Mohamad Sawan[1]

[1]*Polytechnique Montreal*
[2]*University of Montreal Hospital Center*

Rationale
Seizure forecasting is a growing field of research which aims at offering an alternate treatment strategy to patients suffering from refractory epilepsy. While recent studies have presented promising seizure prediction capabilities, a proper understanding of seizure mechanism would allow the implementation of interpretable algorithms. This study evaluates the appropriateness of using bispectrum analysis, an advanced signal processing technique, to accurately characterize different epileptic brain states in humans.

Method
Three quantitative bispectrum features were extracted from long-term intracranial EEG recordings acquired using the NeuroVista Ambulatory monitoring device in 5 patients (858 seizures) and obtained online through the University of Melbourne. Five, 10, and 30-sec extraction windows were used to measure bispectrum features during the preictal, ictal, and postictal intervals and ANOVA tests assessed the existence of statistical differences in the features between the three brain states. Each feature was individually used as input to a linear support vector machine classifier in a subject-specific manner to determine the optimal extraction window size and consequently characterize preictal and ictal recordings using bispectrum features.

Results
Statistical tests showed that for all 5 patients, all sorted out bispectrum features can significantly characterize the three brain states ($p<0.01$) regardless of the extraction window size. Furthermore, while preictal vs ictal classification accuracies increase unanimously for all features, extraction speed decreases as window size increases across all 5 patients.

Conclusions
This work demonstrates that a) bispectrum-extracted features can characterize different epileptic brain states in humans; and b) longer extraction windows yield superior classification accuracies but compromises the computation speed.

Acknowledgements: Authors acknowledge financial support from the Natural Sciences and Engineering Research Council of Canada (NSERC), and the Institute for Data Valorization (IVADO)

Clinical Epilepsy / EEG / Antiepileptics

Abstract #47

Eslicarbazepine in Focal Epilepsy and Acute Intermittent Porphyria: A Case Report

Tamara Herrera Fortin, Raluca Pana, Dang K. Nguyen

Centre Hospitalier de l'Université de Montréal (CHUM)

Rationale
Porphyrias are rare genetic disorders which affect enzymes involved in the biosynthesis of heme. For epileptic patients with this condition, achieving seizure freedom can be difficult, as many anticonvulsants can increase heme synthesis and trigger porphyria attacks. We report an epileptic patient with acute intermittent porphyria (AIP) successfully treated with eslicarbazepine.

Method
This patient, now 35 years old, started having seizures at age 10 years which were drug-resistant (monthly clusters and occasional convulsive status). Investigations led to a diagnosis of left frontotemporal nonlesional epilepsy. Eventually, her epileptic condition became better controlled (0-2/year between age 29 and 33 years) using a combination of carbamazepine, clobazam, and levetiracetam.

Results
At age 33 years, she was hospitalized for acute psychosis, seizures, pericardial effusion, and pulmonary embolism which led to the diagnosis of AIP (urine coproporphyrin: 2098 nmol/day; HMBS mutation) and lupus (high ANA/Anti-Ro Ab titers). Panhematin was given and carbamazepine replaced by lacosamide as the former can stimulate heme synthesis and induce lupus. Although she recovered well from this acute condition, her epilepsy fell out of control with monthly seizures. Lacosamide was replaced by pregabalin with no benefit. It was then decided to replace pregabalin by eslicarbazepine (1000mg/d) considering its low level of hepatic induction. At 9 months follow-up, she had only experienced 2 brief focal unaware seizures.

Conclusions
Eslicarbazepine may be tried in patients with AIP and focal epilepsy not successfully controlled by more classical agents such as gabapentin, pregabalin, and levetiracetam.

Clinical Epilepsy / EEG / Antiepileptics

Abstract #48

Unforeseen Consequences: Understanding Cardio- And Cerebrovascular Disease in the Elderly with Epilepsy

Nafisa Husein[1], Colin Bruce Josephson[2], Mark Keezer[1]

[1]*Université de Montréal*
[2]*University of Calgary*

Rationale
Cerebrovascular disease is a frequent cause of epilepsy in adults but there is strong evidence that the risk of stroke is higher even in people whose epilepsy aetiology is unrelated. Cardiovascular disease is the most prevalent cause of death in people with epilepsy. The reasons for this increased risk of cardio- and cerebrovascular disease in people with epilepsy remain uncertain. We hypothesize that epilepsy-associated sociodemographic/lifestyle factors, as well as possible pro-metabolic syndrome effects of certain AEDs, explain an important component of these associations.

Method
The proposed study aims to determine whether vascular risk factors interact with epilepsy status and AED use to influence the vascular health of the elderly with epilepsy. We will conduct these analyses in the Comprehensive subsample (n = 30,000+) of the Canadian Longitudinal Study on Aging (CLSA), more than 500 of whom, aged at least 45 years, have epilepsy. We will study the associations between these factors and cardio- and cerebrovascular outcomes such as ischaemic heart disease and carotid intima thickness.

Results
We have recently obtained the necessary CLSA data and the analyses will soon begin. We expect to identify strong interactions which will serve as evidence that the epilepsy status of a person and the use of AEDs alter the effect of vascular risk factors on associated outcomes.

Conclusions
Our novel analyses of CLSA data will provide new insights and will serve as the basis for the development of programs to prevent the onset of cardio- and cerebrovascular comorbidities in people with epilepsy.

Funding: Canadian Frailty Network

Clinical Epilepsy / EEG / Antiepileptics

Abstract #49

Title: Investigating Rater Reliability in the Assessment of SEEG Implantation Accuracy

Paul Istasy

University of Western Ontario

Rationale
Stereoelectroencephalography (SEEG) is increasingly becoming the chosen method for intracranial EEG monitoring of patients with focal refractory epilepsy. Measuring SEEG implantation accuracy is an important step in quality control for the procedure and it is important that there be a reproduceable method of measuring this accuracy. The purpose of this study to was analyze the implantation accuracy and the intra- and inter-rater reliability in a cohort of patients undergoing robotically assisted SEEG implantation.

Method
Two raters performed entry and target point fiducial translocations for 115 SEEG implanted electrodes on two separate occasions (total of 460 points placed) using data from post-operative CT scans of 10 patients (3M, 7F; median age=37.5, range=21-57). Target point fiducials were translocated to the center of the tip of the electrode while entry point fiducials were translocated to the middle of the electrode on the CT scan, and centered in the middle of the dura on the MRI scan.

Results
Results show an excellent reliability (ICC=0.981) of the intra-rater localization error of 0.385mm (SD=0.033). The inter-rater localization error of 0.659 mm (SD=0.092) showed a very-good-to-excellent reliability (ICC=0.894). Preliminary data on implantation accuracy shows a mean entry and target point localization errors of 1.29 mm (SD=0.73) and 2.15 mm (SD=1.36) respectively.

Conclusions
The protocol used for fiducial translocation in the analysis of robot-assisted SEEG accuracy yields excellent intra-rater and very-good-to-excellent inter-rater reliabilities. SEEG accuracy results show that the implantation procedure at the LHSC is comparable with the current literature on the procedure.

Clinical Epilepsy / EEG / Antiepileptics

Abstract #50

Spatial Extent and Sleep-Wake State Concordance of Interictal Epileptiform Discharges in Rapid Eye Movement Sleep

Parandoush Abbasian, AmirHossein Ghassemi, Conrad Rycyk, Marcus Ng

University of Manitoba

Rationale
There are reports that interictal epileptiform discharge (IED) fields in rapid eye movement (REM) sleep are smaller than in either non-REM sleep or wakefulness. The goals of our study are to confirm this reduction in IED field size, and to determine the relative concordance of IED fields in REM, NREM, and wakefulness.

Method
We examined IEDs from Epilepsy Monitoring Unit (EMU) patients. To determine absolute field size, we visually counted the number of 10-20 electrodes included in IEDs for REM, NREM, and wakefulness. We then treated the ensemble electrode locations in REM, NREM, and wakefulness IEDs as mathematical sets (e.g. A,B). We defined discordance as sets with no mathematical intersection ($A \cap B = \emptyset$), partial concordance as non-empty mathematical intersection ($A \cap B$), and proper concordance as mathematical subset ($A \subset B$) or superset ($A \supset B$).

Results
We analyzed 276 IEDs from 13 epilepsy patients. Mean IED electrode field in REM was 3.04±0.72, awake 3.57±0.90, and NREM 4.27±1.16. Comparing concordance, $REM \subset NREM$~54%(7/13), $REM \cap NREM$~31%(4/13), $NREM \supset REM$~7.5%(1/13), $\{REM \cap NREM = \emptyset\}$~7.5%(1/13), $REM \subset awake$~23%(3/13), $REM \cap awake$~46%(6/13), $awake \supset REM$~31%(4/13), and $\{REM \cap awake = \emptyset\}$~0%(0/13).

Conclusions
We found that the REM IED field is smaller than NREM or wakefulness. We did not find discordance between REM and wakefulness, and only one patient had discordance between REM and NREM. However, concordance was split between partial and proper between REM and these states. Our findings suggest that REM shrinks the IED field, not usually into a completely discordant new location, but within an existing IED field, or extends this field into novel adjacent electrodes. These findings highlight the localizing potential of REM in evaluating the epileptogenic zone.

Clinical Epilepsy / EEG / Antiepileptics

Abstract #51

Technological Advances in the Treatment of Photosensitive Epilepsy: The Influence of Coloured Lenses on Inhibition of Photoparoxysmal Response

Rachelle Sass

University of Manitoba

Rationale
Epilepsy affects approximately 20,000 Manitobans and 50 million individuals worldwide regardless of demographic. Among these worldwide sufferers, 5% are afflicted with photosensitive epilepsy, the presence of an abnormal brain signal response – a "photoparoxysmal response" (PPR) – to photic stimulation during an EEG.

The influence of visual stimuli to propagate seizures has long been recognized, yet little has been done to apply this knowledge toward finding methods with which to prevent photic-triggered seizures. Furthermore, despite a century of pharmaceutical development, one third of patients fail to respond to medication altogether – a non-pharmacological approach is therefore desperately required to mitigate the fear, stigma, and physical harm that often accompany this pervasive disorder.

Method
In the present research, we tested whether specific tints of lenses in Uvex® glasses can reduce the incidence of PPR during an EEG using photic stimulation in a patient with photosensitive epilepsy. The 13 pairs of glasses we tested utilize Uvex Spectrum Control Technology® that incorporates unique dyes formulated to manipulate light by absorbing specific wavelengths.

Results
According to the EEG results, five tints showed a significant reduction in PPR, including three tints that mitigated PPR completely.

Conclusions
Coloured lenses hold tremendous potential to mitigate seizures in photosensitive epilepsy patients. Since TV, video games, computer screens, and fluorescent lighting are so prevalent in today's society, new technological developments in optical care that incorporate these tinted filters can provide much-needed relief to patients and reduce the need for potentially harmful medications. Exciting new research avenues we are pursuing involve tests of tinted contact lenses.

Clinical Epilepsy / EEG / Antiepileptics

Abstract #52

Exploring the Effects of Functional Connectivity to Depict Key Differences Between Stages of Sleep to Determine Why REM Protects Against Seizures

Darion Toutant, Marcus C. Ng

University of Manitoba

Rationale
The purpose of analyzing the different stages of sleep by means of functional connectivity metrics is due to the overwhelming unlikelihood of seizures occurring during REM sleep. In a study by Ng and Pavlova (2013), less than 1% of 1,458 patients with epilepsy experienced seizures during REM sleep.

Method
Oscillatory coupling essentially eliminates higher-order neurons and refers all communication between networks through separate frequency bands (Bastos & Schoffelen, 2016). Common functional connectivity metrics include coherence, phase slope index and granger causality. These metrics are formulated for the theory of oscillatory synchronization between different EEG channels.

Results
Due to the physiology of REM sleep we know it is most prominent in the pontomesencephalic junction of the brainstem. Knowing that brainstem stimulations can be viewed throughout the scalp presents the drawback of volume conduction. The connectivity calculations will begin with specific regions lying at the top of the brain such as the motor cortex, sensory cortex and others. The Health Sciences Center has taken high-density EEG recordings of 17 seizure patients in all states of consciousness from wakefulness to REM sleep. These data sets will be tailored and run through different connectivity algorithms between different areas of the brain to find patterns to indicate why REM sleep protects from seizures.

Conclusions
Ultimately create a framework that depicts the oscillatory coupling between every state of sleep to better understand leading or lagging propagations at explicit frequencies. This framework would be beneficial in creating a device that could mimic identical frequencies that would protect against seizures.

Epilepsy Surgery

Abstract #53

Stimulation of the Anterior Nuclei of the Thalami for the Treatment of Focal Therapy-resistant Epilepsy

Ana Suller Marti, Andrew Parrent, Keith MacDougall, David Steven, Jorge Burneo

CNS Department, Western University

Rationale
Deep-brain stimulation of the Anterior Nuclei of the Thalami (DBS-AN) is a type of neuromodulation used as a treatment in those with therapy-resistant epilepsy. It has been used in Europe and has been approved in Canada. We present the experience of our centre.

Method
We interrogated the database of the Epilepsy program at Western University and identified those patients with multifocal DRE epilepsy, who underwent DBS-AN implantation, since this treatment became available in Canada, until November 2018.

Results
Seven patients were implanted with DBS-AN. The median age of DBS-AN implantation was 30.5 years of age (IQR:17.8-28.5) and 5 were males. The median number of antiseizure medications (ASM) was 3(IQR:3-4) at the time of the implantation and the median ASM failure number before surgery was 6.5 (IQR:5-8.5). Vagus nerve stimulation failed to control seizures previously in all of the patients. There were no complications with the DBS implantation. The median follow up time after implantation was 36.5 months(IQR:24-55.8m) and the therapeutic output current was 6.216mA (IQR:5.314-9.5mA) in the right and 6.67mA (IQR:5.1445-11.65mA) on the left-sided electrode. The median reduction of seizures rate at the last follow up was -13.9%(IQR:(-72.2)-(86)) and 33.3%(n=2) had more than a 50% seizure reduction. The best response in seizure reduction was seen after 12 months following implantation. The most common side effect was short memory complaints in 50%(n=6), starting at 12 months (IQR:10-18m).

Conclusions
DBS-AN is another therapeutic strategy in the management of patients with therapy-resistant focal epilepsy. It is a safe procedure and is well tolerated by patients.

Epilepsy Surgery

Abstract #54

Improving Access to Surgical Therapies for Children Diagnosed with Drug Resistant Epilepsy: A Comprehensive Epilepsy Clinic Model in Ontario, Canada

Michelle Gratton[1], Maryam Nabavi Nouri[2], Asuri Narayan Prasad[2], Margo DeVries-Rizzo[1], Sandrine deRibaupierre[2], Andrea Andrade[2]

[1]Children's Hospital, London Health Sciences Centre
[2]Schulich School of Medicine & Dentistry, Western University

Rationale
The only cure for drug resistant epilepsy (DRE) is surgery. There is an 80% chance of achieving seizure freedom, plus the benefit of reducing psychosocial comorbidities (Bowen et al., 2012). However, despite its effectiveness surgery is underutilized, with only a fraction of the population who may be eligible for surgery assessed every year (Critical Care Services Ontario Guidelines, 2016).

Method
In 2008, Children's Hospital, London Health Sciences Centre was designated one of two paediatric regional epilepsy surgical centers in Ontario. In 2017 a multi-disciplinary Comprehensive Epilepsy Clinic (CEC) was created with the goal to improve the well-being and facilitate surgical interventions for children with DRE. Referrals from healthcare providers are made to the CEC where new consults are assessed and streamlined advanced treatment options are provided.

Results
The total number of patients evaluated for surgery in the last 5 years from 2014-2019 was 123; pre-CEC was 27 (22%) vs 96 post (78%). Of those evaluated, 61 (50%) had surgical therapy; pre-CEC 15 (12%) vs post 46 (38%). The CEC has grown from 1 clinic per month in 2017 to 3 a month in 2019. With 25 new consults and 88 follow-ups the 1st year to 58 new consults and 176 follow-ups the 2nd year. Overall, evaluations, surgeries and CEC growth has more than tripled.

Conclusions
A CEC model improves access to surgical therapies in children with DRE through a streamlined referral process and facilitation of pre-surgical work ups for continued evaluation of potential candidates via a multi-disciplinary team.

Epilepsy Surgery

Abstract #55

Beyond Memory: Episodic Simulation and Prosocial Intentions in Individuals with Anterior Temporal Lobe Resections for Epilepsy

Mary Pat McAndrews[1,2], Caspian Sawczak[3], Morris Moscovitch[3]

[1]*University Health Network*
[2]*Krembil Research Institute*
[3]*University of Toronto*

Rationale
Imagining helping others in situations of need (episodic simulation; ES) increases willingness to help in laboratory studies. Recent research indicates that ES relies on the medial temporal lobe and thus we predicted that people who had anterior temporal lobe (ATL) resections for epilepsy would show a reduced effect of ES on prosocial intentions.

Method
We tested 16 individuals post ATL surgery and 16 controls. Participants read vignettes describing people in situations of need and after each, either imagined themselves helping the person or performed an unrelated verbal task. Later, they rated each scenario on several scales. Two scales captured prosocial intentions: willingness to help ('instrumental' intentions) and empathic concern ('emotional' attributes). For the imagine condition, participants also rated the vividness of their imagined scenarios and described the situation to quantify the number of episodic details; both measures reflect the quality of the simulation.

Results
As expected, patient simulations were rated as poorer than controls by themselves (self-reported vividness) and by external raters (episodic details). Furthermore, the effect of simulation on the two prosocial variables was greater in controls than in patients. Finally, this effect was entirely mediated by vividness whereas the number of details was not correlated with prosocial intent in either group.

Conclusions
These findings provide evidence that the effect of episodic simulation on prosocial intent relies on the medial temporal lobe. Observed here in an experimental task, our findings have broader implications for social cognition in individuals with damage to the medial temporal lobe.

Funding: Canadian Institutes of Health Research

Epilepsy Surgery

Abstract #56

Role of Resective Surgery in the Patients over 60 Years Old with Drug-resistant Epilepsy

Juan Santiago Bottan, Ana Suller Marti, Andrew Parrent, Keith MacDougall, Richard McLachlan, Jorge Burneo, David Steven

Western University

Rationale
Epilepsy surgery in the elderly population has been controversial. The concern for patients with long-lasting epilepsy as well as higher surgical risk has rendered this group of patients as non-candidates for surgery. Literature suggests that this group of patients can benefit from surgery. Our objective was to analyze the role of resective surgery in patients over 60 years old, assessing outcomes and safety.

Method
We conducted a retrospective analysis of 595 patients who underwent resective epilepsy surgery at our center from 1999-2019 (20 years). 31 patients who were 60 years of age or older were identified. 60 patients of 59 years of age or younger were randomly selected as control group. Population characteristics, presurgical evaluations, postoperative outcome and complications were analyzed.

Results
No significant differences were found between both groups in terms of hemisphere dominance, side of surgery, lesional/non-lesional ratio and incidence of TLE over extratemporal epilepsy. Age, duration of epilepsy, and the need for invasive recording in younger patients were statistically significant. Engel I at 6 months, 1 year and 2 years were 92.9%, 88% and 94.4% for the Old group and 75%, 64.7% and 78.1% for the Young group, respectively. The subgroup of TLE exhibited a better seizure outcome for both groups but was higher in the Old group. Complication rates were higher in the Old group but not significant.

Conclusions
Epilepsy surgery in older patients has comparable or better outcomes than in general population. A tendency towards lesional TLE may explain this bias. Although surgical risk might be higher, decision to operate should be individualized on patient's inherent risk and not due to age.

Epilepsy Surgery

Abstract #57

Development and Validation of a Seizure-freedom Prediction Tool Based on Differentially-weighted Preoperative Predictors

Alireza Mansouri

Toronto Western Hospital

Rationale
A clinical tool for prediction of postoperative seizure-freedom was developed, separately for paediatric and adult populations, based on preoperative clinical parameters.

Method
Adults (07/2004-01/2017) and paediatric (07/2003-07/2014) individuals undergoing surgery for medically-refractory epilepsy were retrospectively reviewed. The primary outcome was 5-year seizure freedom (Engel). The model was developed based on a random selection of 70% of the cohort and validated with 30% of the cohort. The proportion for the odds ratio obtained from the regression model was used to construct whole number coefficients for each significant variable. Receiver operating characteristic curves were used to evaluate model utility.

Results
194 adult and 316 paediatric subjects (N = 510) were included. For adults, lack of generalized tonic-clonic seizures (score = 3), family history of epilepsy (score = 2), MRI abnormality (score = 2), and lack of need for invasive EEG (score = 2) were significant predictors; the total score range was 0-9). For paediatric patients, lack of generalized tonic-clonic seizure (score = 3), monthly seizure frequency < 20 (score =3), and lack of need for invasive EEG (score = 2) were significant predictors; the total score range was 0-8. The AUC of the predicted 5-year seizure-freedom for each score compared to the actual rate was >0.79, performing better than published models when applied to our internal dataset.

Conclusions
Clinical prediction tools, developed separately for paediatric and adult patients, can be used for patient selection and counseling. Further multi-center studies are needed to validate this score while comparing its performance to other available scores and nomograms.