Neuroimaging

Abstract #1

In Vivo Mapping of Tauopathy in Temporal Lobe Epilepsy

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Rationale

Temporal lobe epilepsy (TLE), the most common drug-resistant epilepsy in adults, is associated with atrophy beyond the primary mesiotemporal substrate. Although TLE is traditionally not considered a neurodegenerative disorder, emerging evidence from ex vivo specimens have shown elevated levels of misfolded tau protein, a hallmark of neurodegeneration (Tai et al. 2016, Brain). In this study, we assessed the in-vivo presence of tau-aggregates in TLE using F18-MK6240, a recently validated in vivo positron emission tomography (PET) tracer and examined its associations to structural atrophy.

Methods

We included 14 drug-resistant TLE patients (median ± IQR age 33.0±4.0 years, 3 females; 3/14 had two scans available), and 15 age-and sex matched healthy controls (30.5±8.8; 4 females, 1/15 had two scans available). F18-MK6240 PET uptake was partial volume corrected, normalized for cerebellar gray matter uptake to obtain a standardized uptake value ratio, and registered to cortical/subcortical surfaces derived from T1-weighted 3T MRI. This resulted in vertex-wise cortical, hippocampal, and subcortical maps of tau uptake, and grey matter thickness/volume. We compared TLE and controls at the level of F18-MK6240 uptake and thickness/volume using a mixed effects model, controlling for age and sex, and corrected for multiple comparisons with random field theory ($p<0.05$). To assess associations between atrophy and tau-uptake, we re-ran the mixed effects model controlling for regional grey matter thickness/volume estimates.

Results

Comparing groups, we observed increased F18-MK6240-uptake in patients in lateral temporal, parietal, and occipital regions (Fig 1A). This pattern differed qualitatively from cortical thinning in TLE, which was mainly visible in ipsilateral frontal lobe areas, together with trends for grey matter reductions in ipsilateral mesial and anterior temporal cortical as well as posterior regions (Fig. 1B). Indeed, rerunning tau group comparisons after controlling for cortical thickness changes locally resulted in a rather similar spatial distribution of increased tau uptake in patients (Fig. 1C). No significant increase was found in any model in the subcortical structures including hippocampus.

Conclusion

Our findings show elevated F18-MK6240-uptake in TLE patients in a bilateral temporo-posterior distribution, which may provide in vivo confirmation that the condition implicates an elevated risk for neurodegenerative cascades. Additional confirmation in larger samples is warranted, to also verify the hypothesized role of tau as a modulator of disease progression and cognitive decline in TLE.

Clinical Epilepsy / EEG / Antiepileptics

Abstract #2

Magnetoencephalography Spectral Abnormalities Delineate the Epileptogenic Zone

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Rationale
Successful surgery for focal epilepsy requires accurate presurgical delineation of the epileptogenic zone (EZ), which remains extremely challenging for poorly-defined cases (i.e., the lesion and/or its borders are not seen on MRI). Magnetoencephalography (MEG) has become a well-established component of the presurgical evaluation but marking interictal epileptiform discharges (IEDs) is time-consuming, prone to human errors, and of debated clinical value. Here we explore the potential of detecting abnormal variants of source spectral power density (PSD) in pediatric focal epilepsy cases relative to a large normative database, as a novel marker for EZ delineation.

Methods
We used MEG rest recordings of 97 pediatric epilepsy patients and obtained maps of delta- to gamma-band brain activity. We applied the same procedure to create a normative distribution of PSD brain maps in healthy controls from the Open MEG Archive (n=200). Each patient was contrasted against this normative distribution to identify deviations from healthy variants.

Results
Preliminary results from 20 pediatric cases show a concordance between PSD maps and IED localizations in 85% of cases, with delta being the most consistent (75% of cases). We will present the full results and discuss the prediction of surgical outcomes from spectral deviation maps.

Conclusion
PSD mapping is efficient, reproducible, and allows for faster MEG analyses in epilepsy. Relating these findings to individual surgical resection zones, patient outcomes, and histopathology will advance our understanding of aberrant neural dynamics in epilepsy and potentially provide a novel marker to improve surgical outcomes in these complex cases.

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Pediatric Epilepsy

Abstract #3

Online Calculator for Seizure Freedom Following Pediatric Hemispherectomy: A Post Hoc Analysis of the HOPS Study

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Rationale
Hemispherectomies are effective procedures for medically intractable pediatric epilepsy, although large variability in outcomes remains. Identifying ideal candidates is imperative to maximize the potential for seizure freedom. The objective is to develop an online tool that accurately predicts and reports the probability of seizure freedom post-hemispherectomy to provide clinicians accessible and reliable prognostic information to complement their clinical judgement.

Methods
Retrospective data for 1276 pediatric patients from 30 centers internationally was analyzed to determine predictors of seizure freedom following hemispherectomy. The primary outcome was the time-to-seizure recurrence. A multivariate Cox proportional-hazards regression model was developed to predict the likelihood of seizure freedom post-hemispherectomy from combination of statistical analysis and clinical judgement. The final model from this study was developed into a free publicly accessible online calculator displayed on the (iNEST) website.

Results
The final model includes the 5 original HOPS variables (age at seizure onset, etiologic substrate, seizure semiology, previous non-hemispheric resective surgery, and FDG-PET hypometabolism) and 2 additional variables (MRI lesions and ictal EEG findings). Significant predictors of shorter time-to-seizure recurrence include younger age of seizure onset, PET hypometabolism contralateral to side of surgery, contralateral MRI lesion, non-lesional MRI, and non-stroke etiologies. The AUC of the final model is 72.7%.

Conclusion
Online calculators are efficient, cost-free tools that can facilitate physicians in risk-estimation, inform joint decision-making with families and potentially lead to better long-term seizure freedom in pediatric epilepsy patients. Although the HOPS data was previously validated in the first analysis, the authors encourage further research to prospectively validate this new tool.

Pediatric Epilepsy

Abstract #4

Seizure Outcome of Pediatric MR-guided Laser Interstitial Thermal Therapy versus Open Surgery: A Matched Non-Inferiority Cohort Study

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Rationale

Minimally invasive MR-guided laser interstitial thermal therapy (MRgLITT) has been proposed as a safer alternative to open epilepsy surgery, to addresses some of the risks associated with open surgery. This study evaluated the effectiveness of MRgLITT compared to open surgery in children with drug-resistant epilepsy.

Methods

This retrospective multi-center cohort study included children treated with MRgLITT or open surgery from thirteen North American epilepsy centers. Exclusion criteria were corpus callosotomy, neurostimulation, hemispheric or multilobar surgery, and lesion with maximal dimension greater than 60 mm. MRgLITT patients were matched to open surgery patients using propensity score. The primary outcome was seizure freedom at one-year post treatment. The difference in seizure freedom was

compared using noninferiority test, with a noninferiority margin of -10%. The secondary outcomes were complications and length of stay.

Results

184 MRgLITT patients were matched to 184 open surgery patients. Seizure freedom at one-year follow-up was achieved in 89/184 (48.4%) MRgLITT and 103/184 (56.0%) open surgery patients (difference = -7.6%, one-sided 97.5%CI: -18.2% to ∞, P-Noninferiority=0.36). Complication rates were lower in MRgLITT compared to open surgery (15 [8.2%] vs. 51 [27.7%] respectively, $p<0.001$). The mean hospital stay was shorter for MRgLITT than open surgery (3.1±2.9 vs. 7.0±5.7 days respectively, $p<0.001$).

Conclusion

MRgLITT was associated with lower seizure freedom compared to open surgery in children with drug-resistant epilepsy. However, MRgLITT demonstrated better safety profile and shorter hospitalization. The findings will help counsel families on the benefits and risks of MRgLITT, and contribute to informed decision making on treatment options.

Neuroimaging

Abstract #5

WITHDRAWN

Neuroimaging

Abstract #6

Homotopic Coupling in Persons with Epilepsy using Movie-Driven and Resting-State fMRI

Caroline Chadwick[1], Mark O'Reilly[1], Hana Abbas[1], Daniella Ladowski[1], Nargess Ghazaleh[1], Ali Khan, Jorge G. Burneo[2], David A. Steven[2], Seyed M. Mirsattari[2], Ingrid Johnsrude[1]

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Rationale
Temporal lobe epilepsy can be considered a network disorder (Pittau & Vulliemoz, 2015), which can manifest as abnormal functional coupling. The strongest coupling is typically observed between homologous areas in the two hemispheres, and the corollary of strong coupling is high sensitivity to abnormality. In persons with refractory temporal lobe epilepsy (TLE), we evaluated functional homotopic coupling activity in resting-state and movie-driven fMRI.

Methods
22 persons with TLE (PWE) and 24 healthy controls were scanned using fMRI at rest and while movie-viewing. Registration and surface-based parcellation (Glasser et al., 2016), was used to identify 180 cortical regions and 22 functionally distinct sections. Homotopic coupling activity between pairs of regions and sections in a subset of controls was used as a set of normative distributions. Activity in PWE and controls that fell outside 2 SD of the mean for each region/section was considered abnormal. The number of abnormalities and the strength of coupling activity was compared between groups and scanning paradigms.

Results
PWE displayed more abnormal homotopic coupling activity than controls ($p = .006$), reflecting the combined effects from resting-state and movie-driven fMRI. PWE displayed unique patterns of abnormal coupling within and outside of the temporal lobe. Differences in the strength of coupling activity between scanning paradigms were identified in the inferior parietal, medial temporal, early auditory, and visual cortices.

Conclusion
Variation in the degree and location of homotopic coupling abnormalities between scanning paradigms demonstrates the combined utility of movie-driven and resting-state fMRI for evaluating functional connectivity in epilepsy.

Neuroimaging

Abstract #7

Establishing Standardized Clinical fMRI Paradigms to Lateralize Language in Patients with Epilepsy

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Rationale
Language lateralization is the extent to which an individual's language functioning demonstrates a hemispheric specialization within the brain. Identifying a patient's dominant language hemisphere is a critical evaluation performed prior to epilepsy surgery. Despite the clinical relevance and growing acceptance of functional magnetic resonance imaging (fMRI) for language lateralization, this technique is not standardized. The heterogeneity of fMRI paradigms used in clinical practice is an inherent limitation to its efficacy and reproducibility in determining accurate language laterality. This study aimed to evaluate whether there is a set series of fMRI paradigms that can maximize the therapeutic potential of language lateralization for patients with epilepsy.

Methods
Using information collected from supporting literature and Canadian Epilepsy Centres, two paradigms that demonstrated reliability in lateralizing both receptive and expressive language areas were implemented: the Sentence Completion (SC) and Word Generation (WG) Tasks. Four healthy volunteers were recruited as participants to pilot these fMRI paradigms.

Results
We found significant lateralizing activity in primary and secondary language areas. While the SC task demonstrated significant lateralizing patterns in Wernicke's Area and the Middle Frontal Gyrus, the WG task significantly lateralized activations in Broca's Area and the Middle Frontal Gyrus. The WG also elicited activations in the cerebellum in the contralateral hemisphere.

Conclusion
These results establish the feasibility of these paradigms in healthy volunteers. For future directions of study, this paradigm series will be evaluated in patients with epilepsy. Only then can we recommend the standardization of these paradigms into Canadian fMRI language lateralization practices to minimize the extent of clinical heterogeneity.

Neuroimaging

Abstract #8

Cortical Microstructural Gradients Capture Memory Network Reorganization in Temporal Lobe Epilepsy

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Rationale

Temporal lobe epilepsy (TLE) is associated with variable degrees of mesiotemporal damage and memory impairment. To explore associations between atypical brain structure and function, we mapped cortical gradients of microstructural differentiation and examined how microstructural changes relate to episodic memory function in TLE.

Methods

A cohort of 21 drug-resistant TLE patients (9 women; mean±S.D. 36.14±11.59 years) and 35 healthy controls (HCs; 17 women; 34.51±9.27 years) underwent microstructural imaging at 3T. We sampled intracortical quantitative T1 intensities between pial and white matter boundaries, resulting in cortex-wide microstructural intensity profiles. Cross-correlating profiles yielded microstructural similarity matrices between all vertex pairs, which were used to derive the principal gradient of microstructural similarity with diffusion map embedding. Participants also completed a functional MRI episodic memory task, enabling us to study how regions showing atypical microstructural differentiation were embedded within functional memory networks and related to recall accuracy.

Results

Comparing gradient of cortical microstructure between groups, differentiation between sensory/motor and paralimbic anchors was reduced in TLE. Gradient reductions targeted anterior temporal regions and lateral prefrontal cortices ipsilateral to the seizure focus ($pFWE<0.001$). Seed-based functional connectivity analysis from regions of gradient reductions during encoding showed reduced connectivity between temporal and prefrontal regions ($pFWE<0.05$). Moreover, individual recall performance was correlated with microstructural gradient changes in temporal ($r=0.406$; $p=0.004$), but not prefrontal regions ($r=0.111$; $p=0.457$).

Conclusion

We found atypical cortical microstructural organization in TLE extending beyond a mesio-temporal epicentre towards anterior temporal and lateral prefrontal cortices, offering a microarchitectural framework to understand cognitive dysfunction in TLE.

Neuroimaging

Abstract #9

Repeated Intracranial EEG-Fmri Studies Colocalize Regions Important for Postsurgical Seizure Freedom in Epilepsy

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Rationale

EEG-fMRI may be used to identify regions for resection in patients with epilepsy. Scalp EEG-fMRI studies report reasonable spatial overlap of BOLD responses related to interictal epileptiform discharges at two or more time points. No similar evidence exists for intracranial EEG-fMRI (iEEG-fMRI). We hypothesized moderate spatial concordance of the BOLD responses at two time points, and resection of these areas would be associated with seizure freedom.

Methods

Four patients each underwent two separate iEEG-fMRI studies. Patients then underwent surgical resection. Post-surgical outcome was determined >1 year after surgery using the Engel Scale. For each patient at each time point we compared: i) the distance between the electrode contacts where epileptiform discharges were observed, ii) the distance between the maximum BOLD responses, and iii) the spatial overlap between the resection area and maximum BOLD response.

Results

Between studies, the average distance between active electrode contacts was 26mm (+/-16mm). The corresponding BOLD responses had a mean separation of 49mm (+/-42mm). Three patients achieved post-surgical seizure freedom (Engel I) whereas one patient has recurrent seizures (Engel III). Cases in which the maximum BOLD responses from both time points were ultimately resected were associated with seizure freedom whereas failure to resect the maximum BOLD responses was associated with seizure recurrence (% overlap = 71% +/-0.4% and 1% +/-0.1%, respectively).

Conclusion

Our iEEG-fMRI findings are consistent with scalp EEG-fMRI studies assessing reproducibility of the BOLD activation to discharges. This series supports the use of spike-associated BOLD activation as an important target for resection.

Research generously supported by CIHR and Alberta Innovates.

Clinical Epilepsy / EEG / Antiepileptics

Abstract #10

WITHDRAWN

Clinical Epilepsy / EEG / Antiepileptics

Abstract #11

Outcome in Bilateral Temporal Lobe Epilepsy after Treatment with Vagus Nerve Stimulation

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Rationale

The most common type of therapy-resistant epilepsy is temporal lobe epilepsy (TLE). Unilateral TLE usually has a favourable prognosis with resective surgery. However, surgery is usually not considered in cases of bilateral temporal lobe epilepsy (bi-TLE) which occurs in 10–20% of patients with TLE. Vagus nerve stimulation (VNS) is approved as a palliative therapeutic option. The outcome of treating bi-TLE with VNS is unknown. Our study evaluates the effect of VNS on the reduction of seizure frequency in therapy-resistant epilepsy patients with bi-TLE.

Methods

retrospective study include bi-TLE patients who underwent VNS implantation at Western University Hospital from 1997 to 2019. Main outcome was reduction in seizure frequency.

Results

Our study included 17 patients (11 women). The mean seizure onset age was 19.4 years (SD=12.99). Bi-TLE was confirmed by scalp EEG in 8 cases (47%) and invasive recording in 9 (52.9%). The mean follow-up was 48.11 months (SD=59.49). The mean seizure frequency per month before VNS was 8.75/m, and after VNS stimulation was 2.64/m. Compared to the baseline, 11 individuals (64.7%) achieved at least 60% reduction in seizure frequency. None of our patients became seizure-free. Six patients (35.3%) experienced either no or minimal reduction in seizure frequency. The responder rate was 87.5% in those who underwent scalp EEG only and 55.5% in those who underwent invasive EEG. Side effects were reported in 10 patients (58.8%). Side effects included mild coughing and hoarseness. In one case, post-surgical wound infection was documented and managed with a brief course of antibiotics.

Conclusion

In therapy-resistant BI-TLE therapeutic choices are restricted. VNS shown to be safe and beneficial as an additional treatment in this group of patients.

Clinical Epilepsy / EEG / Antiepileptics

Abstract #12

Epilepsy Surgery in Adult Stroke Survivors with New-Onset Drug-Resistant Epilepsy

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Rationale
Despite its effectiveness, surgery for drug-resistant epilepsy is underutilized. However, whether epilepsy surgery is also underutilized among patients with stroke-related drug-resistant epilepsy is unclear. Therefore, our objectives were to estimate the rates of epilepsy surgery assessment and receipt among patients with stroke-related drug-resistant epilepsy and to identify factors associated with these outcomes.

Methods
We used linked health administrative databases to conduct a population-based retrospective cohort study of adult Ontario, Canada residents discharged from an Ontario acute care institution following the treatment of a stroke between January 1, 1997, and December 31, 2020, without prior evidence of seizures. We excluded patients who did not subsequently develop drug-resistant epilepsy and those with other epilepsy risk factors. We estimated the rates of epilepsy surgery assessment and receipt by March 31, 2021. We planned to use Fine-Gray subdistribution hazard models to identify covariates independently associated with our outcomes, controlling for the competing risk of death.

Results
We identified 265,081 patients who survived until discharge following inpatient stroke treatment, 1,902 (0.7%) of whom subsequently developed drug-resistant epilepsy (805 women; mean age: 67.0 ± 13.1 years). Fewer than six (≤0.3%) of these patients were assessed for or received epilepsy surgery before the end of follow-up (≤55.5 per 100,000 person-years). Given that few outcomes were identified, we could not proceed with the multivariable analyses.

Conclusion
Despite a lack of evidence indicating that stroke-related etiology is a contraindication for epilepsy surgery, patients with stroke-related drug-resistant epilepsy are rarely considered for the procedure in Ontario.

Clinical Epilepsy / EEG / Antiepileptics

Abstract #13

Characterizing the Effects of Vagus Nerve Stimulation on the Amygdala: A Gene Expression Profiling Study

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Rationale
Vagus nerve stimulation (VNS) is one of the neuromodulation therapies offered to patients with refractory epilepsy. It is reported that VNS has near 50% reduction in seizure rates and a protective effect on mitigating sudden unexpected death in epilepsy (SUDEP). However, the molecular and structural changes induced by VNS therapy remain poorly understood. This study offers a focus on understanding gene expression level and morphological characteristics on the limbic system, specifically the amygdala, in response to VNS in patients with refractory epilepsy.

Methods
Six autopsy cases with a history of refractory epilepsy were included [three cases with VNS treatment (VNS), three without VNS treatment (non-VNS)]. Both clinical and post-mortem data were assessed to mitigate confounding factors. Total RNA was extracted from post-mortem amygdala of each group. Gene expression analysis was performed using NanoString human Neuroinflammatory and glial subtyping panel (1500 genes), and analyzed using nSolver software.

Results
Patients across both cohorts died of SUDEP, except for one in the VNS group.

From the data collected, 9 genes showed significantly differential expression, with 7 downregulated and 2 upregulated in the VNS cohort relative to the non-VNS control. Structural changes induced by VNS are currently being assessed through histology and immunohistochemistry.

Conclusion
This is the first study delineating histopathological long-term effects of VNS therapy on the amygdala. Identification of these 9 genes may suggest VNS therapy's contribution to alterations within the amygdala, although the role these specific genes have in mediating VNS therapy has yet to be deduced.

Funding: This research was conducted with support of the Lawson's Internal Research Fund.

Clinical Epilepsy / EEG / Antiepileptics

Abstract #14

Efficacy and Safety of Adjunctive Perampanel for Myoclonic and Absence Seizures: Post Hoc Pooled Analysis of Adult, Adolescent, and Pediatric Patients in Studies 332, 311, and 232

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Rationale

We performed a post hoc pooled analysis of Phase II/III studies to assess the efficacy and safety of adjunctive perampanel for myoclonic and absence seizures in adult, adolescent, and pediatric patients.

Methods

In Study 332 (NCT01393743), patients aged ≥12 years with idiopathic generalized epilepsy and generalized tonic-clonic seizures (GTCS) received placebo/adjunctive perampanel 8 mg/day. In Study 311 (NCT02849626), patients aged 4 to <12 years with focal-onset seizures or GTCS received open-label perampanel ≤16 mg/day. In Study 232 (NCT01527006), patients aged 2 to <12 years with epilepsy received open-label perampanel ≤0.18 mg/kg/day. Data from patients with baseline myoclonic and/or absence seizures were pooled. Assessments included: median percent change in seizure frequency/28 days, 90% responder rates, and treatment-emergent adverse events (TEAEs).

Results

At baseline, 66/393 patients had myoclonic seizures (placebo, n=23; perampanel, n=43) and 72/393 had absence seizures (placebo, n=33; perampanel, n=39); patients with both seizure types were counted twice. Median percent reductions in seizure frequency/28 days were observed with placebo and perampanel: myoclonic, 52.5% and 24.6%; absence, 7.6% and 25.1%, respectively. Corresponding 90% responder rates were: myoclonic, 26.1% (n=6/23) and 14.0% (n=6/43); absence, 18.2% (n=6/33) and 25.6% (n=10/39), respectively. TEAEs with placebo and perampanel occurred in 18 (78.3%) and 36 (83.7%) patients with myoclonic seizures, and 25 (75.8%) and 34 (87.2%) patients with absence seizures, respectively. With perampanel, the most common TEAEs were dizziness and fatigue.

Conclusion

Despite small patient numbers, these data suggest adjunctive perampanel does not worsen myoclonic or absence seizures in adult, adolescent, and pediatric patients.

Funding: Eisai Inc.

Clinical Epilepsy / EEG / Antiepileptics

Abstract #15

Multimodal Machine Learning Can Predict Persistent Depression in Adults with Epilepsy: A Pilot Study

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Rationale
Depression is common in people with epilepsy and is associated with poor health outcomes. Accurate prediction of depression may mitigate adverse outcomes through early treatment. Our aim was to develop a multimodal machine learning (ML) approach for predicting depression in epilepsy.

Methods
We randomly selected 200 patients from the Calgary Comprehensive Epilepsy Program registry and linked their baseline clinical data to their first available clinical EEG and MRI. Two analyses were performed: (i) predicting incident depression following the baseline clinic visit and (ii) predicting a combination of incident and prevalent depression that was persistent across all follow-up visits. We applied the ReliefF algorithm on clinical, EEG, and MRI features, and tested and trained seven ML algorithms. F1 score (F1) and Matthew's correlation coefficient (MCC) were reported.

Results
Of 200 patients, 150 had EEG and MRI data of sufficient quality for feature extraction (50% female). Median age was 36 years, 14% were 1-year seizure-free, 21% had baseline depression, and 18% developed incident depression during follow-up. A total of 46 and 32 features were selected, respectively, but no quantitative MRI or EEG variables were selected for the final models. Four ML algorithms performed well (F1: 0.70-0.75; MCC: 0.39-0.48) for predicting persistent depression. Model performance was less reliable when predicting incident depression (F1: 0.71-0.75; MCC: 0.05-0.09).

Conclusion
Multimodal ML can predict the course of depression in epilepsy. These pilot models to predict persistent depression demonstrated good discrimination and calibration, but future efforts are needed to refine performance before they can be deployed in routine clinical practice.

This work was supported by Epilepsy Canada.

Clinical Epilepsy / EEG / Antiepileptics

Abstract #16

Examining Vaporized and Edible THC/CBD Products for Treating Seizure-Induced Changes in Emotional Behaviour

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Rationale

Up to half of people with epilepsy have emotional comorbidities, including depression and anxiety disorders, which can severely impair quality of life. Reduced endocannabinoid signaling following repeated seizures has been shown to drive these emotional behaviours. Pharmacologically boosting cannabinoid receptor 1 (CB1) signaling by inhibiting enzymes which break down molecules that bind to CB1 has previously been shown to reverse the behavioural impairments caused by repeated seizures. The objective of this project was to determine if vaporized and edible phytocannabinoids are effective given that this is a more ecologically valid method for the treatment of seizure-induced behavioural changes.

Methods

Young adult Long-Evans rats were stereotaxically implanted with bipolar stimulating electrodes in the right basolateral amygdala (BLA) and an electrical kindling protocol was used to model temporal lobe epilepsy. Rats received either tetrahydrocannabinol (THC) or cannabidiol (CBD), in either vaporized or edible form prior to behavioural testing. Performance on behavioural assays including auditory fear conditioning, and the elevated plus maze was assessed to determine if the compound and method of administration was effective in restoring typical behavioural responses.

Results

Orally administered THC increased the time spent in open arms of the elevated plus maze. There were no differences between any experimental measures when either THC or CBD were vaporized. Rats that were administered vehicle and had seizures showed impaired fear memory retention, seen as decreased freezing in response to the conditioned tone, 24 and 48 hours after auditory fear conditioning relative to no seizure controls. At both 24 and 48 hours, seizure rats that were exposed to vaporized THC exhibited an improvement in fear memory, seen as freezing behaviour similar to no seizure controls, at earlier tones but no difference at later tones.

Conclusion

These experiments illustrate that an exogenous vaporized or oral THC/CBD can modulate fear processing, memory, and anxiety-like behaviors and could be utilized in future treatments of comorbid psychiatric conditions in people with epilepsy.

Clinical Epilepsy / EEG / Antiepileptics

Abstract #17

Transition Needs of Caregivers of Patients with Epilepsy and Moderate-Severe Cognitive Impairment

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Rationale

Transition from pediatric to adult care is often a time of turmoil and stress for patients and families. Much research has discussed the importance of preparing patients with epilepsy for their transition. However, very little research has looked at the needs of caregivers of adolescents with epilepsy and moderate-severe cognitive impairment going through the transition process. This is important because the caregiver's well-being and understanding of their adolescent's condition is directly associated with the care they provide.

Methods

Baseline data were analyzed in 16 caregivers with transition-aged adolescents with epilepsy and moderate-severe cognitive impairment, enrolled in a transition clinic.

Results

Results showed that caregivers scored high on all transition readiness items; scoring, on average, 46/50. This suggests that caregivers have a thorough understanding of their adolescent's condition and how best to care for it. When looking at caregiver QoL, almost all caregivers reported high levels of money stress. Many caregivers reported that they had little support as a caregiver and felt they had few life choices. This is important as these factors are potentially a precursor to depression. Lack of seizure control was associated with significantly lower perceived ability to care (p=.012), as well as higher levels of caregiver stress.

Conclusion

Findings suggest that it is insufficient to focus solely on the patient's condition in patients with moderate-to-severe cognitive impairments. Instead it may be important to take a family-centered approach to transition to ensure that caregivers are able to provide the best care possible for their loved one.

Clinical Epilepsy / EEG / Antiepileptics

Abstract #18

The MitoRead Platform for the Identification of New Drug Targets for Refractory Epilepsy

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Rationale

Despite the advent of newer medications, 30-40% of epileptic patients are refractory to any known drugs and continue to have unremitting recurrent seizures and attendant life-long cognitive, behavioral and mental health problems. The continued persistence of this refractory population suggests that novel approaches to anti-seizure drug discovery are needed to uncover new drugs with unexpected mechanisms of action.

Methods

Previously, we established a metabolism-based drug-screening platform (termed MitoRead) that harnesses the power of zebrafish genetics and the measurement of whole animal bioenergetics to uncover new druggable targets that might confer anti-seizure properties based on the improvement in mitochondrial function. Over the years, we have screened nearly 2,000 repurposed compounds for which the drug target is already known and identified dozens of new anti-seizure pathways. We have validated several of these targets using pharmacological and knockdown approaches in Scn1a-mutant zebrafish and mice, including assaying hyperthermia-induced seizures and video-EEG. Our lead program is in hit-to-lead optimization for a novel compound that displays a unique mechanism of action for Dravet syndrome.

Results

At the same time, we have transitioned the MitoRead platform from zebrafish to brain organoids and can now measure metabolic changes in Dravet patient-derived organoids. For the first time we show that brain organoids from Dravet individuals possess unique metabolic signatures that can be used for a personalized medicine drug screen. Currently, a bench-to-beside validation of the brain organoid MitoREAD approach is ongoing whereby antiseizure drugs efficacious in the donor Dravet patient is being confirmed in the corresponding brain organoid.

Conclusion

Combined, our metabolism-based approach to identifying unexpected druggable pathways represents a new direction for the discovery of novel therapeutics for intractable epilepsy.

Clinical Epilepsy / EEG / Antiepileptics

Abstract #19

Interictal Epileptiform Discharges on Routine EEG Follow-Up Predict Seizure Recurrence Risk

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Rationale
Interictal epileptiform discharges (IEDs) on routine EEG predict seizure recurrence risk following a first seizure, before antiseizure medication tampering, or after epilepsy surgery. However, their prognostic quantitative value during epilepsy follow-up is controversial.

Methods
We included PWE who underwent a routine EEG at the Centre Hospitalier de l'Université de Montréal between January 2018 and June 2020. Exclusion criteria were lack of follow-up after the EEG and electrical seizure(s) on EEG. Medical charts were reviewed for time to seizure recurrence after the EEG, IEDs on EEG, and potential confounders: epilepsy type, age, gender, focal brain lesion, epilepsy duration, history of febrile seizures, and relative(s) with epilepsy. We estimated the hazard ratio (HR) of seizure recurrence after EEG for patients with and without IEDs using a Cox proportional hazard model. We stratified the analysis by epilepsy type.

Results
We included 448 PWE. Median follow-up after EEG was 113.5 weeks (IQR 79 – 137). During follow-up, 211 patients (47.1 %) had seizure recurrence. After adjusting for confounders, the presence of IEDs was associated with a 1.52-fold increased rate of seizure recurrence (1.12–2.07, p = 0.008). In subgroup analysis, the HR was significantly increased in generalized epilepsy (n = 116, HR = 1.97 [1.13–3.41], p = 0.016), but not in focal epilepsy.

Conclusion
The presence of IEDs on routine EEG during follow-up is independently associated with an increased rate of seizure recurrence. These findings support a potential benefit of adjusting treatment based on the follow-up EEG, particularly in patients with generalized epilepsy.

Clinical Epilepsy / EEG / Antiepileptics

Abstract #20

ELEVATE Study 410: Phase IV Study of Perampanel as Monotherapy or First Adjunctive Therapy in Patients Aged ≥4 Years with Focal-Onset Seizures or Generalized Tonic-Clonic Seizures

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Rationale
During ELEVATE (NCT03288129), patients aged ≥4 years with focal-onset seizures (FOS), with/without focal to bilateral tonic-clonic seizures (FBTCS), or generalized tonic-clonic seizures (GTCS), received perampanel as monotherapy/first adjunctive therapy. We present the final efficacy and safety results by seizure type.

Methods
ELEVATE consisted of Screening, Titration (≤13 weeks), Maintenance (39 weeks), and Follow-up (4 weeks) Periods. Patients received perampanel 2 mg/day, titrated to a maximum of 12 mg/day. Primary endpoint: retention rate at 3, 6, 9, and 12 months. Secondary endpoints: seizure freedom (Maintenance Period) and safety. Exploratory endpoints (Maintenance Period): median percent reduction in seizure frequency/28 days; 50% responder rate.

Results
The Safety Analysis Set included 54 patients (FOS, n=38 [including FBTCS, n=9]; GTCS, n=11; FOS+GTCS, n=5). Full Analysis Set: 52 patients (FOS, n=37 [including FBTCS, n=9]; GTCS, n=11; FOS+GTCS, n=4). Mean (standard deviation) daily perampanel dose (mg) (Maintenance) was: 6.4 (2.1) (FOS, 6.5 [2.2]; FBTCS, 6.0 [1.7]; GTCS, 6.0 [1.9]). Retention rates at Months 3, 6, 9, and 12, respectively: 92.1%, 73.7%, 68.4%, and 68.4% (patients with FOS); 88.9%, 66.7%, 55.6%, and 55.6% (patients with FBTCS); 72.7%, 54.5%, 54.5%, and 54.5% (patients with GTCS). In patients with FOS, 11 (29.7%) achieved seizure freedom; 27 patients (81.8%) achieved ≥50% reduction in seizure frequency; median percent reduction/28 days in FOS frequency was 76.1% (n=33). Low incidences of serious treatment-emergent adverse events (TEAEs) and TEAEs leading to perampanel discontinuation (7.4% and 18.5%, respectively) were reported overall.

Conclusion
Perampanel as monotherapy/first adjunctive therapy was well tolerated with no unexpected safety concerns.

Funding: Eisai Inc.

Clinical Epilepsy / EEG / Antiepileptics

Abstract #21

Does REM Mark the Spot? Understanding Sleep-Wake Effects on Epileptic Source Localization from Literature Review to Experimental Evidence

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Rationale
Epilepsy surgery requires spatially triangulating epileptic source generators inside of brain tissue that is continuously cycling through sleep-wake states (SWS). SWS greatly alter cortical electrodynamics, with known effects on epilepsy. Recent work evaluates how SWS affect spatial localizations of epileptic source generators.

Methods
A systematic literature review was conducted regarding SWS effects on epileptic source localization, with quantitative analysis performed on studies reporting per-patient SWS localization and post-operative seizure burden. Next, amongst n=16 prospectively-recruited focal epilepsy patients, electrical source localization (of candidate epileptic generators, using individualized brain models) was compared and contrasted across interictal spikes in the 5 canonical SWS: wakefulness, rapid-eye-movement sleep (REM), and non-REM-1,2,3. Results: mean±SD.

Results
In literature review of 4 epilepsy surgery studies, a pooled n=27/46 subjects experienced post-operative seizure freedom. Among n=27, REM correctly localized the epileptogenic zone 84% of the time: of that, 64% was agreement with other SWS, but 20% of the time REM alone among SWS correctly localized the epileptogenic zone. In a prospective n=16 clinical experiment using electrical source localization, SWS unanimously spatially “agree” on an epileptic source localization comprising 17.0±15.5% cortical grey matter. Interestingly, REM relatively “disagrees” with other SWS regarding localization of epileptic source generators; 20±19.0% of the REM source localization activates unique cortical voxels untouched by any other SWS localization.

Conclusion
In literature review, REM amongst sleep-wake states accurately localizes the epileptogenic zone. In a prospective clinical experiment of electrical source localization, SWS – especially REM – influenced results. Future studies should prospectively compare seizure-free epilepsy surgery resection cavities against SWS source localizations.

Clinical Epilepsy / EEG / Antiepileptics

Abstract #22

Mental Health in Epilepsy Patients After Neuromodulation Therapy

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Rationale

Epilepsy has direct consequences on psychological wellbeing with about 20-30% of patients with epilepsy experiencing symptoms of depression. Although vagus nerve stimulation (VNS) is used for medically resistant epilepsy (MRE) and deep brain stimulation (DBS) for different psychiatric diseases, the real effect remains unknown. The potential beneficial mental health effect in patients with MRE implanted with these devices also remains unknown. The goal of this study is to analyze the effect on mood in patients who receive VNS or DBS.

Methods

A prospective study collecting patients with MRE who underwent VNS or DBS. NDDI-E questionnaires are completed before implantation and at 6 months. The inclusion criteria is to be implanted with VNS/DBS in our Epilepsy Program at Western University since January 2020.

Results

A total of 32 patients were implanted with the mean age of 35 and 50% were females. From those patients, 26 were implanted with VNS and 6 with DBS. 21 patients were diagnosed with depression in the VNS group and 5 in the DBS group. The average baseline NDDI-E score in the VNS group was 16 and 18 in the DBS. The 6-month NDDI-E score in the VNS group was 15 and 14 in the DBS. Although the DBS group was smaller, the NDDI-E results were better in the DBS compared to the VNS.

Conclusion

Depression is a concern among patients with epilepsy. DBS is associated with better depression results at follow-ups. Longer follow-ups and larger data sets are needed to further understand the impact of neuromodulation devices in mental health.

Clinical Epilepsy / EEG / Antiepileptics

Abstract #23

Long-Term Efficacy and Safety of Perampanel Monotherapy in Patients with Newly Diagnosed/Currently Untreated Recurrent Focal-Onset Seizures: FREEDOM Study 342 Extension Phase

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Rationale
FREEDOM (NCT03201900; Japan/South Korea) showed perampanel 4–8 mg/day monotherapy was efficacious and generally well tolerated in patients aged ≥12 years with newly diagnosed/currently untreated recurrent focal-onset seizures, with/without focal to bilateral tonic-clonic seizures. We report long-term efficacy and safety from the Extension Phase.

Methods
During the Core Study, patients received perampanel 4 mg/day (4-week Pretreatment; 32-week Treatment [6-week Titration; 26-week Maintenance], with titration up to 8 mg/day). Patients could enter the Extension Phase for an additional 26 weeks (52 weeks). 52-week and 24-month seizure-freedom rates and treatment-emergent adverse events (TEAEs) were monitored.

Results
Eighty-nine patients received ≥1 perampanel dose (Safety Analysis Set) and 73 entered the 4-mg/day Maintenance Period (modified Intent-to-Treat Analysis Set); 21 patients entered the 8-mg/day Treatment Phase. Overall, 46/67 (68.7%) eligible patients entered the Extension (39 who completed the 4- or 8-mg/day Treatment Phase [4 mg/day, n=32; 8 mg/day, n=7] and seven who discontinued the 8-mg/day Treatment Phase); 38 patients completed the Extension and eight discontinued, most commonly due to withdrawal of consent (n=3 [6.5%]). Overall, 24/32 (75.0%) and 20/32 (62.5%) patients who entered the Extension from the 4-mg/day Treatment Phase while seizure free had sustained seizure

freedom for 52 weeks and 24 months, respectively; corresponding values from those who entered from the 4- and/or 8-mg/day Treatment Phase were 31/39 (79.5%) and 22/39 (56.4%), respectively. TEAEs occurred in 74/89 (83.1%) patients, most commonly dizziness (38.2%).

Conclusion

Seizure freedom was sustained during long-term (≤24 months) treatment with perampanel 4–8 mg/day monotherapy and was well tolerated.

Funding: Eisai Co., Ltd.

Clinical Epilepsy / EEG / Antiepileptics

Abstract #24

The Phenotypic Spectrum of Epilepsy in Periventricular Nodular Heterotopia

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Rationale
Periventricular nodular heterotopia (PVNH) is a common congenital brain malformation, often associated with seizures. We aimed to clarify the spectrum of epilepsy phenotypes in PVNH, and the significance of more specific patterns of brain malformation.

Methods
We recruited people with PVNH and a history of seizures, and collected clinical data via medical record reviews, patient interviews, and a standardized questionnaire.

Results
One hundred individuals were included, aged 1 month to 61 years. Mean age of seizure onset was 7.9 years. Ten patients had self-limited epilepsy and 35 pharmacoresponsive epilepsy. Fifty-five had ongoing seizures, of whom 23 were defined as drug-resistant. Patients were subdivided as follows: PVNH-Only with a single nodule (18) or with multiple nodules (21), PVNH-Plus with a single nodule (8) or multiple nodules (53) with additional brain malformations. Of patients with isolated single nodule PVNH, none had drug-resistant seizures. Amongst PVNH-Plus patients, 55% with multiple unilateral nodules were pharmacoresponsive, compared to only 21% of those with bilateral nodules. PVNH-Plus patients with multiple bilateral nodules demonstrated the highest proportion of drug-resistant epilepsy (39%) across all groups.

Conclusion
The spectrum of epilepsy phenotypes in PVNH is broad, and seizure patterns are highly variable between patients; however, epilepsy course may be predicted to an extent by the precise pattern of malformation. Overall, drug-resistant epilepsy occurs in only a minority of individuals with PVNH.

Clinical Epilepsy / EEG / Antiepileptics

Abstract #25

Studying the Role of the Anterior Insula and the Ventromedial Prefrontal Cortex in Decision-Making Through Direct Electrical Stimulations in Epileptic Patients During Stereo-Electroencephalography

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Rationale
While the role of the anterior insula (aINS) and the ventromedial prefrontal cortex (vmPFC) in risky decision-making has been extensively studied in lesional and functional imaging studies, it has rarely been investigated in direct electrical stimulation (DES) studies. The aINS appears to increase perception and favor risk avoidance whereas the vmPFC seems to process rewards and enhance risk in decision-making.

Methods
We assessed the effect of DES of aINS or vmPFC on risky decision-making during a behavioral task involving a choice between a risky offer and a safe option, in patients explored with stereo-electroencephalography (SEEG) during presurgical evaluation for their focal drug-resistant epilepsy (DRE). Each session included 14 trials with DES of either aINS or vmPFC and 14 control trials without stimulation. Subjects were blinded to experimental conditions. 16 sessions with stimulation of aINS in 7 patients and 7 sessions with stimulation of vmPFC in 3 patients were recorded.

Results
Our results revealed that the probability of accepting the risky offer was significantly decreased in easy trials when applying DES to aINS compared to non-stimulation trials. In contrast, the probability of accepting the offer in trials of medium difficulty with DES of vmPFC was significantly increased compared to non-stimulation trials.

Conclusion
These preliminary findings support the hypothesis of a functional dissociation between aINS and vmPFC in risky decision-making and are in line with data from functional imaging and lesional studies.

Clinical Epilepsy / EEG / Antiepileptics

Abstract #26

Intracranial EEG Patient Analysis: Seizure Reduction in Refractory Epilepsy Following Depth Electrode Insertion

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Rationale
The implantation effect describes an immediate reduction in seizure frequency following the insertion of intracranial electrodes. There is limited information regarding which patients will experience a reduction of seizures and the reason for the implantation effect. This study focuses on describing predictor factors for the reduction in seizure frequency in patients with medically resistant epilepsy implanted with depth electrodes.

Methods
We conducted a retrospective chart review of 89 patients who underwent intracranial electroencephalography (iEEG) monitoring with depth electrodes. Sixty-five of these patients had no subsequent therapeutic interventions and had a 3-6 month follow-up. Patients were grouped as either responders (>50% seizure reduction at the 3-6 month follow-up) or non-responders.

Results
The median age of the patients included in this study was 34.0 years (interquartile range [IQR]: 27.0-45.0), and 60% were female (n = 39). We report a 31% response rate (20/65) with 6 patients achieving complete seizure freedom at the 3-6 month follow-up. Among responders, 80% (16/20) were classified with temporal lobe epilepsy. No significant differences between the demographic factors of responders and non-responders were identified. The antiseizure medications did not influence the delay of seizures. The reduction in seizure frequency was independent of the number of electrodes implanted. Moreover, 90% (18/20) of the responders received cortical stimulation during iEEG monitoring compared to 58% (26/45) of the non-responders.

Conclusion
Our data shows that one-third of patients will have a temporary reduction in seizure frequency, and this phenomenon is frequently seen in patients who received cortical stimulation.

Clinical Epilepsy / EEG / Antiepileptics

Abstract #27

Validating the Odds Ratio Product in an Epilepsy Monitoring Unit

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Rationale
The odds ratio product (ORP) is a novel quantitative electroencephalographic (EEG) measure of sleep depth. In subjects without pathology, ORP during non-rapid eye movement sleep (NREM) increases between the first and second halves of the night. This project assessed whether ORP behaves similarly in patients from the epilepsy monitoring unit (EMU).

Methods
The ORP is based on a four-digit permutation of relative powers in four frequency bands represented by a single value from 0 (deep sleep) to 2.5 (awake). ORP was calculated from the C3-A2 and C4-A1 electrodes in 29 event-free nights of video-EEG telemetry from 12 epilepsy and 3 PNES patients in the adult Winnipeg EMU. We used the Shapiro-Wilks test to assess for normality, and compared halves of the night using the corresponding paired-t or Wilcoxon test.

Results
We analyzed a total of 216556 and 203831 NREM ORP values in C3-A2 and C4-A1 respectively. Distributions did not deviate from normality (C3-A2: p=0.598, C4-A1: 0.602). There was a significant mean ORP increase of 0.137 (0.946 vs. 1.083, p <0.001) and 0.116 (0.908 vs. 1.024, p<0.001) between the first and second halves of the night in C3-A2 and C4-A1 respectively.

Conclusion
Like subjects without pathology, ORP also increases across halves of the night in the EMU. This finding supports extending use of ORP into both the epilepsy and PNES populations during times of event-freedom. This also opens up the possibility of routinely tracking sleep depth and quality in a quantitative way as part of a comprehensive EMU evaluation.

Clinical Epilepsy / EEG / Antiepileptics

Abstract #28

WITHDRAWN

Clinical Epilepsy / EEG / Antiepileptics

Abstract #29

WITHDRAWN

Clinical Epilepsy / EEG / Antiepileptics

Abstract #30

WITHDRAWN

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Abstract #31

Memantine Improves Seizure Frequency and Encephalopathy in Children with Epileptic Encephalopathy: A Randomized Double-Blind Placebo-Controlled Crossover Trial

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Rationale

Memantine is an NMDA receptor antagonist, approved for dementia treatment. There is limited evidence of memantine showing benefit for pediatric neurodevelopmental phenotypes, but no randomized placebo-controlled trials in children with epileptic encephalopathy (EE).

Methods

In this randomized double-blind placebo-controlled crossover trial, patients with EE received memantine and placebo, each for a 6-week period separated by a 2-week washout phase. EEG, seizure diary, patient caregivers' global impression, serum inflammatory markers, and neuropsychological evaluation were performed at baseline and after each treatment phase. The primary outcome measure was classification as a "responder," defined as ≥ 2 of: > 50% seizure frequency reduction, EEG improvement, caregiver clinical impression improvement, or clear neuropsychological testing improvement.

Results

Thirty-one patients (13 females) enrolled. Two patients withdrew prior to initiating medication and two (twins) had to be removed from analysis. Of the remaining 27 patients, nine (33%) were classified as responders to memantine versus two (7%) in the placebo group ($p < 0.02$). EEG improvement was seen in eight patients on memantine compared to two on placebo ($p < 0.04$). Seizure improvement was observed in eight patients on memantine and two on placebo ($p < 0.04$). Caregivers reported overall clinical improvement in 10 patients on memantine compared to seven on placebo (not significant). Statistical analysis of neuropsychological evaluation indicated improvements in symptoms of attention deficit hyperactivity disorder and autism.

Conclusion

Memantine is a safe and effective treatment for children with EE, having the potential to improve both seizure control and cognitive function.

Clinical Epilepsy / EEG / Antiepileptics

Abstract #32

Sleep Quality and Quality of Life Among People with Drug-Refractory Epilepsy who use Cannabis versus those who do not – A Cross Sectional Study

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Rationale

Comprehensive evaluation of sleep and quality of life among people with drug-refractory epilepsy (PWDRE) who use cannabis versus those who don't, would generate important knowledge guiding management to improve seizure and comorbidity-related-outcomes.

Methods

Consecutive consenting PWDRE, admitted to our epilepsy-monitoring-unit were included, following ethics approval.

Sleep, mood and quality-of-life were assessed using Pittsburg sleep quality index (PSQI) and Epworth sleepiness scale (ESS); Beck depression (BDI) and anxiety (BAI) inventories and QOLIE-31 respectively. Cannabis use was assessed using validated questionnaires.

Results

Complete data was available for 35 (23F)/56 PWDRE [17 using cannabis (group-1, age 32+27) and 18 denying use (group-2, age 46+20). Mean PSQI scores were similar, however PSQI>5 was found in 59% group-1 patients vs 85% group-2 patients. Daytime naps were reported by more patients, 9/17(53%) in group-1 compared to 5/18(27.8%) in group-2, however, all patients in both groups reported excessive sleepiness (ESS>10). QOLIE-31, BAI and BDI scores trended to be better in group-1, however, overall scores among most PWDRE suggested moderate to severe mood disturbances.

Conclusion

Subjective sleep quality appears to be better among PWDRE who used cannabis compared to those who did not, however severe daytime sleepiness, mood disturbances and poor quality of life were observed similarly in both groups.

Clinical Epilepsy / EEG / Antiepileptics

Abstract #33

Cognitive and Behavioural Features of Insular Epilepsy: A Scoping Review

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Rationale
Insular epilepsy is increasingly recognized as an important type of drug-resistant epilepsy. Although the insula is involved in various functions, the cognitive and behavioural characteristics in individuals with insular epilepsy has not been established.

Methods
A systematic search of MEDLINE, Embase, PsycINFO and Web of Science was completed. Eligible studies included original research reporting behavioural and/or neuropsychological outcomes in individuals with insular epilepsy and in a comparison group (i.e., individuals without epilepsy, non-insular epilepsy, or normative data). Studies reporting outcomes following a hemispherectomy were not included. Data were extracted and analyzed using a narrative synthesis.

Results
The systematic search yielded 1887 articles, of which 40 met inclusion criteria. 30 studies focused on adults (25 surgical and 5 non-surgical), 7 on paediatric (6 surgical and 1 non-surgical), and 3 contained both paediatric and adult surgical cases. In most studies, seizures and/or resections included the insula, frontal and temporal regions. Cognitive functioning was heterogenous with frequent impairments noted in intellectual functioning, memory/learning, and language. Following insular resections, improvements and declines were noted across a variety of outcomes; however, follow-up periods were variable. Generally, insular and non-insular groups exhibited similar psychiatric symptoms.

Conclusion
Insular epilepsy is associated with variable cognitive and behavioural profiles. This heterogeneity may be partly attributed to the diverse reciprocal connections between the insula and other brain regions. Critically, the cognitive and behavioural characteristics of insular epilepsy, especially in paediatric cases, remains understudied. More research is needed to evaluate these domains of functioning in non-surgical and surgical cases.

Funding Source: SickKids's Foundation & SickKids Restracomp Fellowship

Clinical Epilepsy / EEG / Antiepileptics

Abstract #34

Optimal Vagus Nerve Stimulation and Titration for Patients with Drug-Resistant Epilepsy

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Rationale
Titration of VNS requires selection of multiple parameters and has been fundamentally empiric. However, evidence accrued over the past 25 years can be used to assess trends of clinical effectiveness for VNS dosing.

Methods
A database was compiled for patients implanted with VNS prior to 2018. A subset of these subjects (n=1,178) have detailed programming history information available during the first 12 months post-implantation and were selected for analysis. A generalized linear mixed model (GLMM) assessed the programming settings associated with clinical response (≥50% reduction from baseline in seizure frequency). Time to the VNS output current associated with clinical response and the time to clinical response were evaluated via Cox regression.

Results
An output current of 1.63mA was associated with the highest rate of clinical response. In a subset of patients that achieved this dose prior to being lost follow-up (n=995), a small proportion of patients (n=105, %=10.5) were titrated to this VNS intensity within 3 months of VNS implantation. Most patients (n=793, %=79.6) were titrated over 6 or more months to reach a similar level. Titration within 3 months was associated with a significantly increased likelihood of response and faster time-to-response than titration that occurred over 6 or more months.

Conclusion
Using GLMM, VNS output current near 1.625 mA is associated with the highest patient response to VNS for drug-resistant epilepsy. Completing titration to this VNS intensity within 3 months was associated with a significantly faster time-to-response than titration completed over 6 or more months.

This work was funded by LivaNova USA Inc.

Clinical Epilepsy / EEG / Antiepileptics

Abstract #35

Association Between Multiple Sclerosis and Epilepsy: A Systematic Review and Meta-Analysis

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Rationale
Previous reports have described a relationship between multiple sclerosis (MS) and seizures; however, the risk of epilepsy in adults with MS remains poorly defined.

Methods
We performed a systematic review and meta-analysis to evaluate the incidence and prevalence of epilepsy in adults (aged 18 years and over) with MS compared to those without. We searched MEDLINE and EMBASE from inception to January 1, 2022. We included observational studies that reported the prevalence or incidence of epilepsy in both adults with MS and a comparator group consisting of adults without MS or the general population. We used the Newcastle Ottawa Scale to evaluate quality of the included studies. We subsequently performed random-effects meta-analyses to determine the prevalence and incidence of epilepsy in adults with MS compared to the non-MS group.

Results
We identified 17 studies consisting of 4,589,111 participants, including 207,093 adults with MS, across nine countries. Of these, 10 reported prevalence of epilepsy, 3 reported incidence of epilepsy, and 4 reported both metrics. Our meta-analysis showed that adults with MS had a higher prevalence (pooled odds ratio 2.04, 95% CI 1.59 to 2.63, I2 = 95.4%) and incidence (pooled risk ratio 3.34, 95% CI 3.17 to 3.52, I2 = 4.6%) of epilepsy than the non-MS group. Subgroup analyses across different comparator groups showed similar findings.

Conclusion
MS is independently associated with a higher risk of epilepsy. Further research is required to identify individuals with MS at risk of epilepsy to reduce the burden of disease and prevent future complications.

Clinical Epilepsy / EEG / Antiepileptics

Abstract #36

Automated Detection of Interictal Epileptiform Discharges on Electro- and Magneto-encephalogram Recordings Using Deep Learning

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Rationale
Clinical evaluation of epilepsy involves epileptologists identifying interictal epileptiform discharges (IEDs) from electroencephalograms (EEGs). Automatic detection of IEDs from magnetoencephalograms (MEGs), however, remains a relatively unexplored area. Since MEG is complementary to EEG, identifying IEDs using both modalities would decrease the probability of missed IED detections and maximise the amount of valuable information from each patient.

Methods
Simultaneously recorded EEG and MEG recordings from a single patient were preprocessed using the open-source Brainstorm neuroimaging application. The patient had 1692 IEDs labelled by an epileptologist across four runs (with a combined length of ~3650 seconds). Using the marked IED labels, the EEG and MEG recordings were segmented into one-second epochs such that each epoch was either centered around an IED or IED-negative. Two two-dimensional convolutional neural networks (2D CNNs) were trained to identify IEDs from these EEG and MEG epochs, respectively.

Results
The proposed EEG CNN and MEG CNN both achieved high-performances in detecting IEDs. The EEG CNN achieved an accuracy of 0.975 and an AUROC (area under the receiver operating characteristic curve) of 0.997 and the MEG CNN achieved an accuracy of 0.969 and AUROC of 0.989.

Conclusion
Our study is one of the first to attempt to automatically detect IEDs from MEG recordings using CNNs. Our results show that the same strengths CNNs demonstrate in identifying IEDs from EEGs are transferable to MEG. Future work demonstrating this proof of concept in a larger patient cohort could lead to a new practical approach for identifying IEDs.

Pediatric Epilepsy

Abstract #37

Clinical, Radiologic and Genetic Characterization of a Focal Cortical Dysplasia Type I Cohort

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Rationale
Focal cortical dysplasia (FCD), a malformation of cortical development, is the most common cause of refractory epilepsy, often requiring surgical resection for seizure control. FCDI is less well-characterized, with a limited number of series published. Our study aims to delineate the clinical, radiologic, and genetic characteristics of FCDI.

Methods
We enrolled 21 patients who underwent epilepsy surgery and had a histological diagnosis of FCDI. Clinical and neuroimaging data were systematically reviewed. Screening for somatic pathogenic variants in SLC35A2, the only gene associated with FCDI, was performed in brain-derived DNA.

Results
The average age of seizure onset was 3.3 years. All individuals had drug-resistant focal seizures and 85% were on anti-seizure polytherapy. Brain MRI revealed cortical dysplasia in 19% and non-specific features in 28.5%. Global developmental delay was noted prior to epilepsy onset in 47%. Intellectual disability was noted in 23%, neurodevelopmental disorder (such as learning disability, attention deficit and hyperactivity disorder and autism) in 48.5% and neuropsychiatric disorder in 81%. FCDI involved the temporal lobe in 81%. 71.5% patients underwent a single surgery and 28.5% underwent two surgeries. Post-surgical outcomes according to Engel classification were I/II in 67%, and III/IV in 33%. Screening for somatic pathogenic variants in SLC35A2 is ongoing.

Conclusion
Children with FCDI present with early-onset refractory focal epilepsy and have high prevalence of developmental impairment, often observed prior to seizure onset. Radiologic features are heterogeneous, making diagnosis based on neuroimaging challenging. The temporal lobe was the mostly involved, and 2/3 of children achieved favourable post-surgical outcome according to Engel classification.

Funding resources: Myriam Srour holds salary award from the Fonds de Recherche en Santé du Quebec.

Pediatric Epilepsy

Abstract #38

WITHDRAWN

Pediatric Epilepsy

Abstract #39

WITHDRAWN

Pediatric Epilepsy

Abstract #40

WITHDRAWN

Pediatric Epilepsy

Abstract #41

The Epileptology of Wiedemann-Steiner Syndrome: Electroclinical Findings in Six Patients with KMT2A Pathogenic Variants

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Rationale
Wiedemann-Steiner Syndrome (WSS) is a rare chromatinopathy caused by pathogenic variants in KMT2A. WSS is characterized by neurodevelopmental disorders (NDD) and distinct dysmorphic features. Epilepsy has been reported in only 27 individuals with WSS, with limited electroclinical description. We report six new patients with pathogenic variants in KMT2A, five of whom presented with developmental and epileptic encephalopathy (DEE).

Methods
Case-Series.

Results
Patients 1 and 2 exhibited Lennox-Gastaut syndrome (LGS). Patients 3 and 4 exhibited infantile epileptic-spasms syndrome (IEES). Patient-5 exhibited DEE with spike-and-wave activation in sleep (SWAS). Patient-6 exhibited generalized paroxysmal fast activity and an absent posterior-dominant rhythm, without electroclinical seizures. All six patients had severe global developmental delay. Patient-4 had bilateral perisylvian polymicrogyria, Patient-5 a Chiari-1 malformation, and Patient-6 a thin corpus-callosum. Patients 1 and 2 were drug-resistant. Patients 1, 2, and 5 had CXXC-domain variants.

Conclusion
Epilepsy in WSS occurs in early childhood, and includes: LGS, IEES and DEE-SWAS. Although severe WSS phenotypes occur with CXXC-domain variants, the severity of epilepsy in relation to CXXC-domain variants or brain-malformations remains unclear. Additionally, the pathogenesis of KMT2A-related epilepsy is, at this point, unknown.

KMT2A regulates neurogenesis in the subventricular zone, with knockout mice exhibiting neurocognitive impairment. Patients with WSS present with NDD-related non-epileptic behaviours, which may delay the diagnosis of subtle seizures in early childhood.

Studies aimed at understanding the epileptology and epigenetic pathways associated with KMT2A variants would guide management options, as well as refine the threshold for seizure suspicion in patients with near-universal NDD and the potential to develop DEE.

Pediatric Epilepsy

Abstract #42

Growing up Without a Right Hemisphere

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Rationale
Research on the neuropsychological outcomes of hemispherectomy in childhood has focused on the preservation of language development after surgery to the left hemisphere. That work has highlighted the positive aspects of neural plasticity and the crowding effect, where language functioning is transferred to the right hemisphere and aspects of visual-spatial processing may suffer. Less is known about the effects of right hemispherectomy on cognitive development, with existing studies including samples that vary considerably in etiology, age of seizure onset, duration of epilepsy, and age at surgery. Here we present a case of a right hemispherectomy very early in life, allowing for an extended period of seizure-free development of the left hemisphere.

Methods
A comprehensive neuropsychological assessment was administered to a 6-year-old boy who underwent a right hemispherectomy at 6 months of age in the context of right-sided hemimegaloencephaly and seizures.

Results
Testing revealed average language and verbal intellectual skills in contrast to significant difficulty with visual-spatial skills, non-verbal reasoning, visuomotor processing speed and visuomotor integration. Working memory, verbal and visual recall, and ratings of adaptive behaviour were intact. Academic skills were in the low average range. Parents reported inattention and academic struggles.

Conclusion
These results illustrate that the isolated left hemisphere can capably support the development of language and verbal reasoning abilities. There is little evidence for plasticity of the left hemisphere to take on the visual-spatial skills typically associated with the right hemisphere. This case illustrates the prioritization and limitations of plasticity for cognitive development.

Pediatric Epilepsy

Abstract #43

Process Evaluation of the Making Mindfulness Matter© in Children with Epilepsy Study, a Live-online Mindfulness-based Intervention for Children with Epilepsy and their Families

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Rationale
Children with epilepsy (CWE) and their caregivers can experience reduced health-related quality of life (HRQOL). The Making Mindfulness Matter© in Children with Epilepsy (M3-E) study assesses the feasibility of a mindfulness-based program (M3©) proposed to improve HRQOL in CWE and parents. A process evaluation, essential to interpreting outcomes observed, was conducted to determine whether the intervention was delivered as proposed.

Methods
The M3-E study is a parallel, 1:1 randomized controlled trial comparing the 8-week M3© intervention to waitlist control. M3© is delivered online by non-clinician staff of a local epilepsy agency to CWE ages 4-10 and parents. Mixed methods assessed key indicators of implementation: reach, recruitment, fidelity, dose delivered, and dose received. For the process evaluation, results from study arms were combined.

Results
Of 273 parent-child dyads assessed for eligibility, 70 have been randomized - 32 to the intervention and 38 to waitlist control. Session attendance was higher among children than parents (43% versus 24% attending all 8 sessions). Session quality was high; 87-100% of curriculum units were delivered fully by facilitators. Most participants (ranging 58% to 93%) were engaged in sessions and most (ranging 51% to 72%) reported practicing M3© skills the previous week. Over 95% were satisfied with M3©, but 24% of satisfaction data were missing.

Conclusion
Preliminary results indicate M3© is being delivered as proposed with high satisfaction. Areas for improvement include expanding recruitment and improving attrition and adherence. This research will guide a multi-centered trial to evaluate whether M3© improves HRQOL in CWE and parents.

Funding: Project Grant from the Canadian Institutes of Health Research (PJT 159504).

Pediatric Epilepsy

Abstract #44

The Scope of Paediatric Tuberous Sclerosis Complex (TSC) Neurological Care: Results from a National Survey

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Rationale
Epilepsy associated with Tuberous Sclerosis Complex (TSC) can be challenging to treat and is associated with significant disease burden. Our objective was to better understand the state of neurological care delivery of TSC amongst paediatric neurologists in Canada (with an emphasis on epilepsy care), identify gaps in care and determine whether access to a dedicated TSC clinic has an impact on neurological/epilepsy management.

Methods
A survey was developed after literature review and discussion amongst two paediatric epileptologists and one nurse practitioner with expertise in TSC. Canadian paediatric neurologists participated via an anonymous web-based survey through the Canadian League Against Epilepsy (CLAE) and Canadian Neurological Sciences Federation (CNSF).

Results
Fifty-seven responses were received. Access to a dedicated TSC clinic was reported by 25% (n=14). Sixty percent (n= 34) reported performing serial EEG monitoring in infants with TSC and 57% (n= 33) started prophylactic antiseizure therapy when EEG abnormalities were detected, regardless of access to a TSC clinic. While 52% (n=29) did not feel comfortable prescribing mTORi for epilepsy, 65% (n=36) indicated they would consider it with additional training. Epilepsy surgery was offered in 93% (n=13) of centers with a dedicated TSC clinic, but only 45% of centers without a TSC clinic (n=19) (p=.002).

Conclusion
Our findings demonstrate the variability in neurological care of paediatric patients with TSC as it pertains to epilepsy management. There is a need for the establishment of epilepsy practice guidelines, and a national network to support clinical practice, research, and education.

Status Epileptics / Critical Care

Abstract #45

WITHDRAWN

Status Epileptics / Critical Care

Abstract #46

Rapid Titration of VNS in Status Epilepticus

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Rationale
Status epilepticus (SE) remains refractory (RSE) in 20-40% of patients and becomes super-refractory (SRSE) in 5-10%. The early management of SE is well defined, but the treatment of SRSE remains variable. Neuromodulation has been used as an adjunctive treatment strategy in SE in children and adults; however, there is considerable variability in its use. The following research provides further evidence for early use of VNS with a rapid titration schedule.

Methods
A single centre, retrospective case series of 3 adult patients with SRSE and literature review.

Results
VNS was employed successfully in 3 adult patients in the acute setting (day 16, day 32, and day 55) of SRSE. A rapid titration schedule starting with an output current of 0.5mA twice daily, followed by increasing increments of 0.25mA BID to a target of 2.0mA at day 4 post implantation was achieved. Auto-stimulation and magnet output current remained 0.25mA and 0.5mA above the output current at each step, respectively. Pulse width was 250ms and duty cycle was 10% (on-time 30s, off-time 5min). Each patient achieved cessation of SRSE. The main side effects experienced in our patients were cough and hoarseness.

Conclusion
Here we describe the safety and tolerability of a rapid titration schedule for VNS in the acute setting of SRSE to provide a framework for the use of VNS as an adjunctive treatment in SRSE.

Funding sources: None.

Status Epileptics / Critical Care

Abstract #47

Positive Prognostic Value of Sleep Architecture in Patients with Status Epilepticus in the ICU

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Rationale
Status epilepticus (SE) is associated with increased morbidity and mortality. Altered sleep architecture is a poor prognostic factor following posttraumatic coma, intracranial hemorrhage, cardiac arrest, and in critically ill ventilated. The aim of this study is to investigate the prognostic value of sleep architecture on continuous EEG (cEEG) in patients with SE as measured by 3- and 6-month mortality, survival time and duration of hospitalization.

Methods
This retrospective cohort study at Kingston Health Sciences Centre included patients ≥18 years

(2015-2019) with electrographic SE on cEEG. Sleep architecture (any combination of N2, slow wave sleep or REM sleep in at least one 30-second epoch) was marked by epileptologists blinded to patient outcomes. Association between presence of sleep architecture and mortality (2-tailed Fisher's exact test), total survival time (Kaplan Meier Survival Curve), and duration of hospitalization (2-tailed Mann Whitney U test) were analyzed.

Results
Of a total of 223 cEEGs, 25 were adult patients with electrographic SE identified during cEEG (mean duration 2.23±0.4 days). Patients without sleep architecture displayed increased mortality rate at 3- and 6-months (P=0.041 for both, 62% without sleep architecture died, 17% with sleep architecture died), and reduced total survival time (P=0.021; effect size of 1.20). There was no effect on hospitalization time (P=0.57).

Conclusion
Identification of even a single 30-second epoch of sleep is identified on cEEG following electrographic SE decreases mortality at 3- and 6-months. The presence of sleep architecture may represent limited brain injury, or it may serve as a protective mechanism following neurological insults.

Status Epileptics / Critical Care

Abstract #48

StatNet Electroencephalogram is Reliable Compared to Conventional EEG in the Intensive Care Setting

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Rationale

An electroencephalogram (EEG) is a useful tool in evaluating patients with decreased sensorium in the critical care setting. However, it requires a trained technician for electrode placement, which limits the access afterhours and in resource-limited settings. This problem may be addressed by using StatNet EEG, a disposable peel-and-stick headpiece with 18 electrodes that can be easily applied even by untrained personnel. In this study, we evaluate the use of StatNet EEG in critically ill patients suspected of having non-convulsive status epilepticus.

Methods

Critically ill adults were evaluated using both conventional EEG and StatNet EEG, and recordings were read by 2 independent epileptologists. The EEGs were blinded for reading using the same StatNet montage. Findings were compared in terms of presence or absence of epileptiform discharges or seizures, generalized or focal slowing, type of coma, as well as inter-rater agreement.

Results

Thirteen patients were included in the study and 26 EEG recordings were reviewed. There is 92.3% agreement in terms of whether studies were normal or abnormal for both conventional and StatNet EEGs. None of the recordings had captured seizures (100% agreement). There is substantial agreement (0.63 for StatNet, vs 0.75 for Conventional EEG) between readers for presence or absence of epileptiform discharges.

Conclusion

There are some limitations in this study, including limited montage for review, and time interval between conventional EEG and STATnet recording, however, STATnet EEG is a viable option for evaluation of critically ill patients in settings where conventional EEG is not readily available.

This study was supported by the research fund from Division of Neurology of the University of British Columbia.

Basic Science / Engineering

Abstract #49

An Ex Vivo Model to Study Fast Ripple High-Frequency Oscillations Detected by SEEG Using Dedicated Surgical Specimens from Pediatric Focal Epilepsy Patients

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Rationale

High-frequency oscillations (HFOs, 80-500 Hz), specifically fast ripples (FRs, >250Hz), are recorded from ictogenic brain areas and are commonly observed in pediatric patients with drug-resistant epilepsy during stereoelectroencephalography (SEEG) evaluation. Detection of FRs helps to delineate the seizure onset zone for surgical resection increasing seizure freedom rates. Here, we investigate single neuron activity from dedicated pediatric epilepsy surgery specimens containing FRs during pre-surgical evaluation in order to establish an ex vivo model to study these important electrophyiological biomarkers toward a better understand of their epileptogenesis and potential pharmacological treatment.

Methods

Electrophysiological recordings were performed in acute slices from pediatric epilepsy surgery specimens containing high FRs rates (> 6 per minute), as detected by pre-surgical SEEG evaluation. Cell attached and whole-cell patch clamp recordings in voltage and/or- current-clamp modes were obtained from neurons located in cortical layers II to V. Spontaneous excitatory post-synaptic currents (sEPSCs) and ictal seizures-like events (SLEs) were analyzed.

Results

Twenty-five cells were recorded from 62 slices obtained from 6 patients. Thirteen spontaneous SLEs were recorded and high frequency of sEPSCs were identified in 8 neurons within the FRs resection areas. Pharmacology showed strong AMPA and Kainate component in cells recorded within FRs areas since most of EPSCs were blocked by NBQX.

Conclusion

Surgical specimens taken from areas of SEEG-detected FRs can be used as an ex vivo model to study FRs and to assess the impact of pharmacological interventions on these epileptogenic pertubations. This may allow for new insights aiming glutamate in the treatment of pharmaco-resistant epilepsy in pediatric patients.

Basic Science / Engineering

Abstract #50

Determining the Effects of Early Life Seizures on Hippocampal CA2 Pyramidal Neurons

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Rationale

Neurons in the immature brain are hyperexcitable due to their elevated ratio of excitation to inhibition, which can lead to excessive excitability and vulnerability to seizures. Early life seizures (ELS) pose a significant threat to developing neurons and often result in later-life epilepsy and cognitive deficits. Sitting between CA3 and CA1, hippocampal CA2 has recently emerged as a critical region in processing hippocampal-dependent memory, including social recognition memory. Mature hippocampal CA2 has been shown to be more resistant to temporal lobe epilepsy-induced pyramidal neuron loss seen in CA1 and CA3. However, little is known about the effects of ELS on CA2 pyramidal neurons in the developing hippocampus. Here, we hypothesize that ELS can regulate the excitability of immature CA2 pyramidal neurons during the critical period of development.

Methods

ELS was induced by pentylenetetrazol (50mg/kg, i.p.) in P10 mouse pups. Using electrophysiological techniques to investigate AMPA receptor function.

Results

We found that ELS significantly increased the frequency of AMPA receptor-mediated sEPSCs, but not sEPSC amplitude in CA2 pyramidal neurons in hippocampal slices from one-hour post-ELS mice, through increasing the probability of neurotransmitter release as evidenced by increased paired-pulse ratio of evoked AMPAR EPSCs.

Conclusion

These data strongly support an ELS-induced dysregulation of hippocampal CA2 pyramidal neurons in the developing hippocampus. Identifying the potential effects of ELS on the function of CA2 neurons could help determine a novel target for intervention while reversing the long-term effects of ELS.

Basic Science / Engineering

Abstract #51

Towards a Human Cell Co-Culture Model of Epileptic Foci

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Rationale
Tuberous sclerosis (TS) is an autosomal dominant disorder, caused by mutations in the TSC1 or TSC2 genes. Benign, tumorlike brain malformations called cortical tubers, which contain hyperactive neurons and glia and atypical neural stem-like (NSC) “giant cells,” cause severe epilepsy in TS patients. Our lab and others have shown that TSC2-/- neuro-glial cultures are hyperactive; we will now determine, using a co-culture approach, if aberrant TSC2-/- NSCs also contribute to synaptic dysfunction.

Methods
We are creating a novel human cell model of cortical tubers that contains not only atypical neurons and glia, but also NSCs that resemble giant cells. Human pluripotent stem cell-derived NSCs carrying a TSC2 loss of function mutation (TSC2-/-) are used to generate 1) hyperactive neuro-glia cultures, and 2) stem-like giant cells. NSCs exhibiting giant cell phenotypes will be introduced into established neuronal cultures and effects on synaptic activity will be measured by: live cell Ca2+ imaging, patch-clamp electrophysiology, and immunostaining for cell type-specific and synaptic markers.

Results
Forebrain neurons produced from TSC2-/- NSCs show heightened electrical activity. TSC2-/- NSCs develop giant cell-like phenotypes when maintained in culture under growth conditions. These include progressive accumulation of organelles (e.g., mitochondria, lysosomes), stem cell identity markers, enlarged vesicles, and altered morphologies

Conclusion
A lack of appropriate human cell models has limited our understanding of how giant cells contribute to epilepsy in TS. We have generated a culture model reflective of giant cells and can now investigate their contribution to neuronal hyperactivity in a human TS model.

Funding sources: This work is supported by Epilepsy Canada, with additional support from the Cancer Research Society, and the CIHR-Canada Research Chairs program

Basic Science / Engineering

Abstract #52

Characterization of Neurogenic Fate Decisions in TSC2-/- Induced Pluripotent Stem Cell-Derived Model

Lisa Lin, Shama Nazir, George Allen, Lisa Julian

Simon Fraser University

Rationale

Dysregulation of cell fate decisions in the brain is implicated in many neurological disorders. The multisystem disorder tuberous sclerosis (TS) is caused by germline mutations in the TSC1 or TSC2 gene and exhibits substantial neurological involvement including development of cortical tubers. These low-grade tumors are a collection of hyperactive neurons, hypertrophic glial cells, and stem-like giant cells, and are epileptic foci. We have observed elevated ER stress and lysosome biogenesis in neural stem cells (NSCs) lacking TSC2, which we hypothesize lead to aberrant neurogenic fate decisions that underly the development of heterogenous epileptic foci in TS.

Methods

To determine the effects of ER stress and lysosome biogenesis on aberrant neurogenesis in TS, compounds that regulate these pathways are introduced into human pluripotent stem cell-derived NSCs that carry inactivating mutations in TSC2 (TSC2-/-) or their isogenic wild-type (WT) counterparts, while undergoing directed neuronal differentiation. Key experimental measurements are neurite morphology, live cell Ca2+ activity, functional metabolic signatures, and gene and protein expression of cell type-specific markers.

Results

Hyperactivity of TSC2-/- cells is clearly evident by early and increased Ca2+ activity in neuronal cultures, and pre-mature development of longer and thicker neurites. TSC2-/- NSCs show increased oxygen consumption rate, indicating an advanced metabolic shift to oxidative phosphorylation.

Conclusion

We have established a phenotypic platform to measure early metabolic, morphological and neuronal activity alterations during neurogenic fate decisions of TSC2-/- cells. We are harnessing this platform to assess the impacts of ER stress and lysosome activation in development of hyperactive TSC2-/- neurons.

Funding sources: This work is supported by Epilepsy Canada, with additional support from the Natural Sciences and Engineering Research Council of Canada (NSERC) and the CIHR-Canada Research Chairs program.

Basic Science / Engineering

Abstract #53

WITHDRAWN

Basic Science / Engineering

Abstract #54

Impact of the Unfolded Protein Response on Neural Stem Cell Development

Shama Nazir, Amelinda Firdauzy, Nicole Vukasovic, Lisa Julian

Simon Fraser University

Rationale

Activation of endoplasmic reticulum (ER) stress, due to misfolded proteins, and a subsequent Unfolded Protein Response (UPR) is observed in many neurological disorders including epilepsy. UPR alters organelles and signaling pathways to restore protein homeostasis. The rare genetic disorder tuberous sclerosis (TS) is caused by inactivating mutations in TSC1 or TSC2 which cause low-grade tumours in multiple tissues including the brain, leading to epilepsy, autism, and cognitive disorders. The objective of my research is to determine the role of the UPR on neural stem cell (NSC) specification and how aberrant UPR signaling impacts brain development in epilepsy syndromes like TS.

Methods

Human induced pluripotent stem cells (hiPSCs) engineered to carry TSC2 inactivating mutations (TSC2-/-) are differentiated into NSCs using a dual SMAD inhibition approach. TSC2-/- and isogenic wild-type cells are treated with ER stress inducing agents during neural induction and observed at later stages to determine the effects on NSC fate decisions. Cultures are characterized morphologically and for expression of cell type identity proteins (SOX2, Nestin, PAX6, GFAP & β-tubulin).

Results

Preliminary results suggest that transient treatment with mild ER stress agents during neural induction yields altered cell morphologies, increased cellular heterogeneity, and aberrant neuro-glial differentiation of NSCs.

Conclusion

Transient activation of ER stress-UPR during early neural lineage induction, as in TSC2-/- or compound treated cells, has long-term impacts on NSC fate decisions. Our data suggests that elevated UPR signaling during NSC specification leads to premature and atypical differentiation which may contribute to the development of epileptic tissue in TS.

Funding sources: This work is supported by Epilepsy Canada, with additional support from the Natural Sciences and Engineering Research Council of Canada (NSERC) and the CIHR-Canada Research Chairs program.

Basic Science / Engineering

Abstract #55

Modeling Hyperexcitability in Cerebral Organoids

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

Methods
Cerebral organoids derived from human embryonic stem cells were provided by L. Attisano at 4 months. Electrophysiological recordings with two local field potentials were conducted: 5 minutes baseline, 15 minutes convulsant, and 15 minutes washout. Signals were processed in MATLAB to extract power spectral density. Quantitative PCR was done with Trizol RNA extraction, Superscript 3 cDNA synthesis, and the PCR done with QuantStudio5.

Results
The power spectral density, which measures overall network activity, was significantly greater than baseline during OGD, picrotoxin, and pentylenetetrazol, for all signal frequencies at 4 months. Pre-incubation with GABA in 4-month cerebral organoids resulted in a reduced excitability response to OGD, suggesting that these organoids contain functional GABAergic receptors, and that GABA plays a role in producing hyperexcitability in the cerebral organoids. Furthermore, qPCR revealed evidence of GABA-related genes including receptor subunits and converting enzyme GAD67.

Conclusion
These findings support the presence of hyperexcitability changes in the cerebral organoid tissue, that likely involves the GABAergic system. Further investigation of the GABA receptors expression over time, and anti-seizure drug responses is warranted to develop cerebral organoids as a high-throughput, drug testing platform.

Basic Science / Engineering

Abstract #56

Vimentin Distinguishes Acute Ongoing Gliosis from GFAP-Reactive Chronic Gliosis in Hippocampal Sclerosis

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Rationale

Though glial fibrillary acidic protein (GFAP) is the standard immunocytochemical marker of gliosis of the CNS, it demonstrates only stable, chronic gliosis because it is a mature intermediate filament protein of astrocytes. Vimentin is a transitory intermediate filament of immature or proliferating astrocytes, replaced by GFAP as the cell matures. Gliosis is a frequent secondary feature of hippocampal sclerosis and is found to variable degrees in focal cortical dysplasias (FCD). Comparing vimentin and GFAP immunoreactivities in brain resections for epilepsy might distinguish acute from chronic gliosis.

Methods

Six children and adolescents with hippocampal sclerosis type 2, four of whom had FCD IIIa, underwent surgical mesial temporal lobe resections for seizure control. Immunoreactivities were examined in sections of hippocampus and temporal neocortex, using antibodies against several neuronal protein, α-B-crystallin, vimentin and polyclonal GFAP. The ratio of vimentin/GFAP reactive astrocytes was estimated.

Results

In hippocampus, vimentin/GFAP ratios were 1:4, vimentin-reactive cells in both dentate gyrus and Ammon's horn, especially in regions of neuronal loss, usually CA2 sector; α-B-crystallin was expressed in all glial cells. In parahippocampal gyrus and other temporal neocortex, vimentin-reactive astrocytes were fewer than in hippocampus but many cells expressed GFAP. All exhibited α-B-crystallin expression.

Conclusion

Vimentin indicates ongoing active gliosis, whereas GFAP denotes old stable chronic gliosis. The use of both antibodies provides dynamic information that GFAP alone does not convey, hence we recommend that vimentin be used as routinely as GFAP, in hippocampus. Reactivity of α-B-crystallin indicates the site of or proximity to an epileptic focus.

Basic Science / Engineering

Abstract #57

WITHDRAWN

Basic Science / Engineering

Abstract #58

WITHDRAWN

Basic Science / Engineering

Abstract #59

WITHDRAWN

Basic Science / Engineering

Abstract #60

Molecular and Circuit Mechanisms of Developmental Epileptic Encephalopathies Associated with Gain of Function Mutations in CACNA1A

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Rationale
CACNA1A mutations causing a gain of function (GOF) of the CaV2.1 calcium channels are typically associated with familial hemiplegic migraine (FHM1). However, we recently described de novo GOF variants leading to Lennox-Gastaut syndrome, a severe early-onset epileptic encephalopathy. The mechanisms by which these novel variants induce epilepsy rather than FHM1 are unclear.

Methods
We generated a novel mouse model carrying an epilepsy-associated GOF mutation (Cacna1aA713T+/-) and combined behavioral assays, video-EEG recordings, histology and whole-cell patch clamp recordings to explore the underlying mechanisms.

Results
Cacna1aA713T+/- mutant mice display smaller body weight, diffuse tremors, ataxia, spontaneous seizures and an increased mortality (50%) before P21. Video-EEG recordings conducted in survivors at P21-P25 reveal a mixture of seizure types reminiscent of Lennox-Gastaut syndrome. Further, the mutant mice display impulsivity, hyperactivity and deficits in spatial learning and memory compared to control littermates. Electrophysiological slice recordings reveal an increase in the amplitude and frequency of both spontaneous excitatory postsynaptic currents (sEPSC) and spontaneous inhibitory postsynaptic currents(sIPSC) in cortical layer V pyramidal cells from somatosensory cortex of mutant mice at P19-P26. However, immunohistochemical assays reveal a loss of cortical parvalbumin-expressing INs, most strikingly in layers IV and V, and a reduction of layer V somatostatin-expressing interneurons, with no change in the density of other interneuron populations.

Conclusion
Alltogether, our data suggest that this new model of Cacna1a-associated epileptic encephalopathy faithfully recapitulates many aspects of the clinical phenotype observed in humans with Lennox-Gastaut syndrome. Furthemore, our preliminary results suggest that, contrary to what has been described in FHM1 models, the epilepsy-associated A713T mutation affects both pyramidal cells and GABAergic interneurons, with striking facilitation of synaptic release from both populations and a preferential impact on interneuron survival.

Basic Science / Engineering

Abstract #61

Investigating the Role of PIGB in the Migration of GABAergic Interneurons in a Mouse Model of Epileptic Encephalopathy

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Rationale
Autosomal-recessive pathogenic variants in PIGB were recently identified in children with epileptic encephalopathy, a neurological disorder characterized by refractory seizures with cognitive impairment.

The PIGB gene encodes mannosyltransferase III, an enzyme implicated in the GPI anchor biosynthesis pathway. These anchors are critical for the membrane attachment of a variety of proteins including cell adhesion and signaling proteins, both essential for neuronal migration. Although GPI anchor deficiency has been associated with epilepsy, little is known about its neurodevelopmental consequences.

Methods
Using Cre-loxP technology, we generated a novel conditional knock-out mouse model (Nkx2.1Cre;Pigbc/c;RCEEGFP), which was characterized using several behavioral tests and EEG recordings. At the cellular level, we quantified the number of medial ganglionic eminence (MGE)-derived interneurons at different postnatal ages (P0, P7, P21) using immunohistochemistry on brain slices. We also prepared MGE explants and used time-lapse microscopy to examine the impact of PIGB loss of function on interneuron migration and branching dynamics during embryonic development.

Results
Our mutant mice show spontaneous seizures and behavioral deficits, such as anxiety-like hyperactivity and altered spatial learning. In addition, we observed a reduction in the number of GABAergic interneurons in the postnatal somatosensory cortex, which suggested a migration deficit. Further analysis of different migration parameters (velocity, displacement, nucleokinesis), branching dynamics and morphological development of MGE-derived interneurons are being conducted to better characterize the impact on migration dynamics.

Conclusion
This study will clarify the pathophysiology underlying PIGB-associated epileptic encephalopathy as well as deepen our understanding of the role of GPI anchors in neurodevelopment and more specifically, in the migration of GABAergic interneurons.

Funding: CIHR

Basic Science / Engineering

Abstract #62

Mitochondrial Uncoupler 2,4-Dinitrophenol Ameliorates Postictal Hypoxia by Dampening Brain Reactive Oxygen Species Production

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Rationale
Reactive oxygen species (ROS) are an abundant by-product of the metabolic pathways involved in oxygen consumption. It is known that ROS production increases during seizures in experimental models of epilepsy and in drug-refractory human epilepsy. After a seizure, brain tissue oxygen levels drop below the severe hypoxic threshold (pO2 < 10 mmHg) for over an hour leading to detrimental pathological outcomes. The pharmacological agent 2,4-dinitrophenol (DNP) – a mitochondrial uncoupler – has recently demonstrated therapeutic potential in a broad spectrum of neurological diseases. This study investigated the effects of DNP on brain tissue oxygenation, postictal hypoxia and associated cognitive deficits. We further investigated whether DNP exerted its effects by dampening ROS generation.

Methods
The electrical kindling model of seizures and epilepsy was used in rats. Hippocampal oxygen profiles were recorded using a chronically implanted oxygen-sensing probe, before, during, and after an evoked electrographic seizure. Rats were continuously treated with DNP added to the drinking water for 24 days. Postictal cognitive impairment was tested using the novel object recognition task. ROS production from isolated mitochondria was measured using the amplex red assay.

Results
DNP raised tissue oxygenation and ameliorated severe postictal hypoxia. Mild mitochondrial uncoupling prevented postictal hypoxia-induced cognitive deficits. The uncoupling agent lowered ROS production, thereby protecting levels of free oxygen in the brain tissue.

Conclusion
Collectively, these findings provide evidence for a link between oxidative stress, mitochondria, and tissue oxygenation. Moreover, they establish DNP as a potential therapeutic strategy to attenuate the postictal state and prevent the associated pathological outcomes.

Epilepsy Surgery

Abstract #63

Surgical Time Reduction in Robot-assisted Depth-electrode Implantation and its Potential Cost-Benefit

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Rationale
Depth electrode implantation is a costly and time-consuming procedure that requires significant use of operating room time. Robot-assisted procedures have reduced surgical time. Faster procedures could have a positive economic impact. We sought to analyze time reduction and potential economic savings when introducing robot-assisted procedures.

Methods
A retrospective analysis of all SEEG cases performed between January 2013 and December 2018 was conducted. Conventional frame-based procedures were performed until April 2017 when the stereotactic robotic arm was introduced. Operative room (OR) time was registered in minutes. Time and costs data was retrieved from the institution's electronic medical records system. Direct costs for both, operative room and post-anesthesia care unit (PACU) were included.

Results
A total of 104 frame-based implantation cases vs. 54 robot-assisted procedures took place. Total OR time for the frame-based group was 223.6 (SD ± 55.53) vs. 180.7 (SD ± 59.70) minutes for the robot-assisted group ($p<0.0001$). Surgical time was 140.3 (SD ± 44.99) vs. 85.2 minutes (SD ± 30.96) ($p<0.0001$). Surgical time per electrode was 20.5 (SD ± 16.08) vs. 10.6 minutes (SD ± 7.35) ($p<0.0001$). Total number of electrodes per case was 9.3 and 10.5, respectively ($p=0.0197$) (Tables 1 and 2). A 10.1% ($p=0.0806$) cost reduction was found between frame-based and robot-assisted procedures. PACU costs did not show cost reductions (Table 3).

Conclusion
Robot-assisted SEEG reduced case time and thus OR usage significantly when compared to frame-based SEEG. A cost reduction, likely associated with time reduction, was found.

Epilepsy Surgery

Abstract #64

Long-term Outcomes of Pediatric Epilepsy Surgery: Individual Participant Data and Study Level Meta-Analyses

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Rationale
Long-term seizure outcomes of pediatric epilepsy surgery is understudied. A systematic review and independent patient data meta-analysis was performed to study seizure outcomes ≥ 10 years following pediatric resective epilepsy surgery.

Methods
Electronic literature searches of PubMed, Web of Science, and CINAHL were conducted for relevant articles from inception to April, 2020. Two reviewers (W.B.H., T.B.C.) performed title, abstract, and full-text screening. All relevant perioperative factors reported that may be associated with long-term seizure outcomes were recorded at a study or individual participant level. The primary outcome was long-term (≥ 10 year) seizure freedom measured by the Engel Classification scale.

Results
Twenty-five articles met criteria for inclusion in the study, which were analyzed for proportions of 10-year seizure freedom ranging from 57.6% at the study level to 64.8% at the individual patient level. At the study level, the proportion of patients remaining seizure free at least 10 years postoperatively (61.2%; 95% CI 52.5-69.3) was significantly less than at 1 year (74.2%; 95% CI 69.3-78.6; p = .008) but not at 2 years (67.9%; 95% CI 58.6-76.0) or 5 years (63.7%; 95% CI 55.4-71.2). No differences in long-term seizure freedom were detected by etiology or surgery type. At the individual patient level, univariate logistic regression analyses demonstrated that lobectomy (OR 0.280, 95% CI 0.117-0.651, p = 0.003) was associated with decreased long-term seizure freedom (41.9%) compared to lesionectomy (75.7%) and hemispherectomy (69.4%).

Conclusion
Resective surgery is a durable and potentially curative treatment option for select pediatric patients with refractory epilepsy. On a group level, two-thirds of children have long-term seizure freedom ≥ 10 years after resective epilepsy surgery. Given the greatest rate of change occurs in the first 2 years, this may serve as the best short-term follow-up period to predict long-term outcome.

Epilepsy Surgery

Abstract #65

Magnetic Resonance-guided Laser Interstitial Thermal Therapy for Drug-resistant Epilepsy: An Individual Participant Data Meta-analysis

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Rationale
Magnetic Resonance-guided laser interstitial thermal therapy (MRgLITT) is a popular minimally invasive alternative to open resective surgery for drug-resistant epilepsy (DRE). However, criteria for identifying optimal patients for MRgLITT remains unclear due to heterogeneity of outcomes and cohorts across existing studies.

Methods
Eleven databases were systematically searched from inception to 2/6/2021 using the terms: “MRgLITT”, “epilepsy”. Data from individual DRE patients treated with MRgLITT were collected. Multiple imputation by chained equations accounted for missing data. Multivariate mixed-effects Cox and logistic regression identified predictors of time-to-seizure recurrence, seizure freedom, operative complications, and postoperative neurological deficits.

Results
From 8,698 citations, 46 reporting on 450 patients were included. Median postoperative seizure freedom was 15.5 months. Generalized seizures (HR=1.78, p=0.027) and non-lesional MRI findings (HR=1.50, p=0.021) independently predicted faster time-to-seizure recurrence. Cerebral cavernous malformations (CCM) (OR=7.97, p<0.001) and mesial temporal sclerosis/atrophy (MTS/A) (OR=2.21, p=0.011) were independently associated with greater seizure freedom odds. Operative complications occurred in 8.5% and were independently associated with extratemporal ablations (OR=5.39, p=0.012) and targeting non-lesional tissue on MRI (OR=3.25, p=0.017). Postoperative neurological deficits were observed in 15.1% and were independently associated with hypothalamic hamartomas (OR=5.92, p=0.006) and invasive EEG monitoring (OR=4.83, p=0.003).

Conclusion
MRgLITT is particularly effective in treating select patients with lesional DRE, notably CCM and MTS/A. Conversely, MRgLITT has less efficacy for non-lesional cases or lesional cases with more diffuse epileptogenic zones. While generally safe, MRgLITT has non-negligible complication rates, particularly

when using invasive monitoring or ablating extratemporal and/or non-lesional targets. These results provide guidance on identifying optimal candidates for MRgLITT.

Epilepsy Surgery

Abstract #66

Depression and Suicide After Temporal Lobe Epilepsy Surgery: A Systematic Review

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Rationale
Psychiatric comorbidities, including depression and suicide, contribute substantially to the illness burden of patients with refractory temporal lobe epilepsy (TLE). The aim of this review was to synthesize the existing literature assessing the effect of TLE surgery on (1) depression prevalence and (2) severity and estimating the incidence of (3) de novo depression and (4) attempted and completed suicide following TLE surgery.

Methods
A literature search was performed using Ovid Medline, Embase, Clarivate Web of Science, Cochrane Library, and ProQuest Dissertations and Theses. Studies of patients who underwent TLE surgery and reported estimates of at least one of the following outcomes were included: pre- and post-operative depression prevalence or severity, incidence of post-operative de novo depression, or attempted or completed suicide. The search yielded 2,127 citations and after full-text review of 116 articles, 18 met the final eligibility criteria.

Results
Most studies reported a reduced or similar prevalence (n=12) and severity of depression (n=5) post-operatively, compared with the pre-operative period. Eleven studies reported the incidence of post-operative de novo depression, ranging from 0% to 38% over follow-up periods of three months to nine years. Four studies assessed the incidence of post-operative attempted or completed suicide, with completed suicide incidence ranging from 0% to 3% over periods of one to four years.

Conclusion
Overall, the effect of TLE surgery on depression and suicide remains unclear. Timely psychosocial follow-up for patients after TLE surgery should be considered. Future longitudinal studies with consistent measures are needed.

Epilepsy Surgery

Abstract #67

Patient Reported Quality of Life Before and After Insular Resection for Patients with Epilepsy

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Rationale

Advances in characterizing the semiology of seizures arising within the insula have provided the impetus for renewed interest in insular resections for patients with intractable epilepsy. Despite, the increasing frequency of these procedures, the impact on patient-reported quality of life is poorly studied.

Methods

Using an institutional database of patients undergoing surgery for epilepsy, we assessed the rate of seizure freedom and any post-operative deficits. We also collected pre- and post-operative patient reported quality of life (QoL) using validated questionnaire. The results of this cohort were compared with an age- and gender-matched cohort of patients who underwent temporal lobectomies.

Results

Between 2011 and 2021, 15 adult patients underwent insular resections of whom 13 had completed the QoL surveys before and after surgery. After a mean follow-up of 19 months, 62% achieved seizure freedom and 14% had persistent deficits. Improvements were reported across various domains of QoL, especially in social limitations. Patients also reported a high rate of depression before and after the surgery.

Conclusion

The improvements observed across various QoL domains after surgery are similar to those seen in patients undergoing temporal lobectomy for epilepsy.

Epilepsy Surgery

Abstract #68

Preoperative Epileptic Network Architecture Constrains Surgery-Induced Connectome Reorganization

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Rationale
Resection of the affected temporal lobe remains the most effective treatment to arrest refractory seizures in temporal lobe epilepsy (TLE). Here, we assessed structural connectome reconfigurations following surgery in individuals with drug-resistant TLE and examined associations with preoperative hippocampal atrophy and clinical variables.

Methods
Thirty-seven adults with drug-resistant TLE (18 males, mean age±SD=26.7±7.6 years) underwent T1w and diffusion MRI before and after anterior temporal lobectomy. Patients were compared to 31 age- and sex-matched healthy controls (14 males, mean age±SD=27.3±7.3 years).

Subject-specific structural connectome gradients were generated from preprocessed diffusion MRI. Univariate fixed effects (performed on each gradient) and multivariate mixed effects models (performed on the aggregate of the first four structural gradients) assessed (i) cross-sectional connectome changes between TLE (preoperatively) and controls, and (ii) pre- to postoperative connectome changes in TLE only. In a final integrative analysis, partial least squares analysis investigated the relationship between patient-specific surgery-induced deformations and standard clinical and neuroimaging variables.

Results
Relative to controls, individuals with TLE showed gradient changes in bilateral mesiotemporal and parietal cortices, particularly revealing a segregation of the ipsilateral anterior temporal lobe from the rest of the brain. Following surgery, individuals with TLE showed gradient alterations in contralateral temporo-parietal cortices, instead revealing predominant postoperative network integration of these areas with the connectome. Such pre- to postoperative connectome changes were found to be associated with ipsilateral hippocampal atrophy, low seizure frequency, and longer epilepsy duration.

Conclusion
We provide evidence that connectomics can bridge surgery-induced brain reorganization with inter-individual clinical variability, offering new avenues for stratification of individuals with refractory TLE.

Epilepsy Surgery

Abstract #69

Seizure and Cognitive Outcomes of Anterior Temporal Lobectomy versus Selective Amygdalohippocampectomy for Temporal Lobe Epilepsy

Sandra Wahby, Lisa Partlo, Neelan Pillay, Colin Josephson, Paolo Federico, Samuel Wiebe, Walter Hader

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Rationale

To compare seizure and cognitive outcomes between anterior temporal lobectomy (ATL) and selective amygdalohippocampectomy (SAH) in patients with temporal lobe epilepsy.

Methods

A single centre retrospective study of adult patients treated with ATL or SAH between 2000 and 2020 was conducted. Inclusion criteria were: at least one year surgical follow-up; pre- and post-operative neuropsychological assessment with scores on the California Verbal Learning Test-II, Rey Complex Figure Test, and Boston Naming Test to assess verbal and visual learning and memory, and naming ability, respectively. The Beck Depression Inventory-II assessed depressive symptoms at each neuropsychological assessment. Univariable comparisons were performed on seizure outcome (Engel classification), neuropsychological test scores, and anti-seizure medication (ASMs) use and driving status.

Results

We identified 137 patients (80 ATL, 57 SAH). Patients who underwent a SAH had a significantly longer duration of epilepsy before surgery [median (years) 19.5, IQR 8.4-34.2 vs. 13.6, IQR 6.7-22.0; p=0.03), were more likely to have an abnormal MRI (98% vs 76%, p<0.001) and mesial temporal sclerosis on pre-operative imaging (67% vs 29%, p<0.001), and had a longer follow-up [median (years) 6.9, IQR 2.9-10.5 vs. 4.4, IQR 2.6-6.7; p=0.03). There was no statistically significant difference between ATL and SAH on seizure outcome (Engel class I: 75% vs. 72%; Engel class II-IV: 25% vs. 28%), driving (39% vs. 54%) and use of ASMs at last follow-up (83% vs. 77%). Likewise, no significant differences were evidenced for any of the neuropsychological measures.

Conclusion

Seizure and cognitive outcomes did not differ for the two surgical approaches.

Epilepsy Surgery

Abstract #70

Seizure and Cognitive Outcomes of Temporal Lobe Epilepsy Surgery in Patients Older Than 50 Years

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Rationale

To assess seizure and cognitive outcomes of temporal lobe surgery in patients 50 years and older.

Methods

A single centre retrospective study of adult patients treated with temporal resections including mesial structures between 2000 and 2020 was conducted. Inclusion criteria were: ≥ 1 year surgical follow-up; pre- and post-operative neuropsychological assessment with scores on the California Verbal Learning Test-II, Rey Complex Figure Test, and Boston Naming Test to assess verbal and visual learning and memory, and naming ability. The Beck Depression Inventory-II assessed depressive symptoms at each neuropsychological assessment. Univariable comparisons between patients ≥ 50 years and < 50 years at surgery were performed on seizure outcome (Engel), neuropsychological test scores, and anti-seizure medication (ASMs) use and driving status.

Results

We identified 36 patients ≥ 50 years and 101 patients < 50 years. Older patients had a significantly longer duration of epilepsy [median (years) 21, IQR 11-42 vs. 14, IQR 7-22; p=0.02] and longer hospital stay [median (days) 5, IQR 4-7 vs. 4, IQR 3-5; p=0.002]. There was no statistically significant difference between older and younger patients on seizure outcome (Engel class I: 72% vs. 74%; Engel class II-IV: 28% vs. 26%), driving (42% vs. 47%) and use of ASMs at last follow-up (81% vs. 80%). Older patients had a significant decline in naming ability compared to younger patients (z-score change: -0.62 vs. -0.14; p=0.01).

Conclusion

Surgery is a similarly effective treatment option for older patients with temporal lobe epilepsy for seizure control, although the cognitive (naming) risks appear greater for older patients.