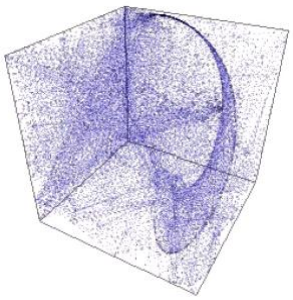
PRINCIPLES OF AUTONOMOUS NEURODYNAMICS 2010
Toronto, Canada
August 23-25, 2010



7th Annual Meeting of the Society for Autonomous Neurodynamics (SAND)

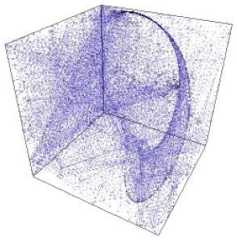
In collaboration with the
University of Toronto Epilepsy Research Program's (UTERP)
Annual Meeting

Location:

University of Toronto, Medical Sciences Building (MSB)
Monday August 23 - Room 2172
Tuesday August 24 - Room 2172
Wednesday August 25 - Room 4227

Supporting Institutes and Programs:
University of Toronto Epilepsy Research Program (UTERP)
Stichting Epilepsie Instellingen Nederland (SEIN)
Society for Comprehensive Epilepsy Care (SCEC), University of Saskatchewan
Institute of Experimental Physics, Warsaw University

www.utoronto.ca/sand/PAND2010/



PRINCIPLES OF AUTONOMOUS NEURODYNAMICS 2010
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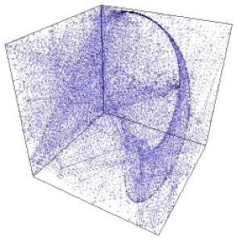
Monday, August 23rd - U of T, Medical Sciences Building, Room 2172

	Registration	8:30 - 9:00	
Melanie Jeffrey & McIntyre Burnham	Welcome and Introduction to UTERP	9:00 - 9:05	
Elan Liss Ohayon	A brief introduction to autonomous neurodynamics and SAND	9:05 - 9:10	
UTERP Epilepsy Session I		**Chair: McIntyre Burnham**	
Marc Trepanier	Effects of polyunsaturated fatty acids on pentylenetetrazole seizures	9:10 - 9:30	*p.1*
Miguel Cortez	Human and murine succinic semialdehyde dehydrogenase deficiency	9:30 - 9:50	*p.2*
Amjad BaniHani	Association between HLA-B*1502 in Han with correlation to hyper sensitivity for aromatic anti-epileptic drugs	9:50 - 10:10	*p.3*
Michael Sumner	Are epilepsy and pseudoepilepsy essentially the same disorder?	10:10 - 10:30	*p.4*
	Group discussion & Coffee break	10:30 - 10:50	
UTERP Epilepsy Session II		**Chair: Melanie Jeffrey**	
Miles Thompson	Delineation of a novel seizure disorder, Mabry syndrome: Identification of the inherited deficiency in alkaline phosphatase metabolism	10:50 - 11:10	*p.5*
Brian Scott	Adult hippocampal neurogenesis: Implications for epilepsy	11:10 - 11:30	*p.6*
Liang Zhang	A mouse model for studying post-ischemic seizures	11:30 - 11:50	*p.6*
Chao Du	Telemetry EEG recordings of seizure activities in mice	11:50 - 12:10	*p.7*
	Group discussion over lunch	12:10 - 1:30	
SAND History & UTERP Epilepsy Session III		**Chair: Paul Hwang**	
Stiliyan Kalitzin	A brief history of SAND	1:30 - 1:40	
James Eubanks	Mechanisms of epileptiform activity in MeCP2-deficient mice	1:40 - 2:00	*p.8*
Manuela Neuman	Hypersensitivity syndrome to aromatic anti-epileptic drugs and In-vitro predictors	2:00 - 2:20	*p.9*
Igor Spigelman	$GABA_A$ receptor plasticity in alcohol withdrawal	2:20 - 2:40	*p.10*
	Group discussion & coffee break	2:40 - 3:00	
THEME: Noise and Networks		**Chair: Peter Carlen**	
Andrea Protzner	Hippocampal signal complexity in mesial temporal lobe epilepsy: A noisy brain is a healthy brain	3:00 - 3:20	*p.11*
Ernest Ho	Slow population activities in noise-driven biological networks	3:20 - 3:40	*p.12*
	Group discussion	3:40 - 3:50	
THEME: Epilepsy - Social Policy		**Chair: Ann Lam**	
McIntyre Burnham Alex Dolan Thomas Drag	Cost/benefit analysis of epilepsy care in Ontario	3:50 - 4:10	*p.13*
NARRATIVES: Journeys in epilepsy research and autonomy		**Chair: McIntyre Burnham**	
Paul Hwang	A Journal of 30 years in epilepsy research: From molecules to mind.	4:10 - 4:30	*p.14*
Melanie A. Jeffrey	Autonomy and relationality: Living epilepsy research	4:30 - 4:50	*p.15*
Round Table I	*What's wrong with epilepsy care - and how to fix It?*	4:50 - 5:10	



PRINCIPLES OF AUTONOMOUS NEURODYNAMICS 2010
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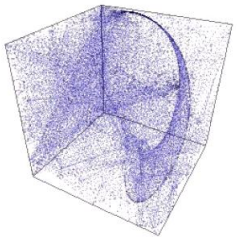
Tuesday, August 24th - U of T, Medical Sciences Building, Room 2172

Melanie Jeffrey	Introduction to SAND Day 2	9:00 - 9:05	
THEME: Rhythms		Chair: Stiliyan Kalitzin	
Harshit Sam Talasila	Low frequency calcium-dependent subthreshold fluctuations in membrane potential; a modeling study	9:05-9:25	*p.16*
Katie Ferguson	Mathematical network models of theta rhythms in the hippocampus	9:25-9:45	*p.17*
Muhammad Dur-e-Ahmad	Computational model of CA3 pyramidal cells: From an adapting neuron to network bursting	9:45-10:05	*p.18*
Piotr Suffczynski	The fast and the curious: mechanisms of 60 - 200 Hz oscillations in the brain	10:05-10:25	*p.19*
	Group discussion & Coffee break	10:25-10:40	
THEME: Neuromodulation		Chair: Marija Cotic	
Sinisa Colic	RBF based stimulators to control epilepsy	10:40-11:00	*p.19*
Berj L. Bardakjian	Seizure-like events in populations of coupled oscillators	11:00-11:20	*p.20*
Osbert Zalay	Complex rhythmic waveform generation for feedback neuromodulation of epileptiform dynamics	11:20-11:40	*p.21*
Ariel S. Garten	Brainwave based control paradigms	11:40-12:00	*p.21*
Joshua A. Dian	Field programmable gate array (FPGA) based responsive neurostimulators.	12:00-12:20	*p.22*
	Group discussion over lunch	12:20 - 1:30	
FEATURED SPEAKER: Cat Criger			
	Introduction by Melanie A. Jeffrey	1:30 - 1:40	
Mark "Cat" Criger, Helper	Stories, thoughts, and teachings: A First Nations perspective on healing	1:40 - 2:00	*p.23*
THEME: Social Dimensions		Chair: Elan Ohayon	
Ann Lam	Can x-rays illuminate a neuroanatomical and social cognitive connection in Williams Syndrome?	2:00 - 2:20	*p.24*
Tarek Abd El Halim	Women with epilepsy (WWE) in Ontario: Knowledge gaps and information needs	2:20 - 2:40	*p.25*
Kirk Nylen	Shifting away from the postal code lottery of health care - Ensuring access to safe, accurate, high quality care for all through organized chronic disease management systems	2:40 - 3:00	*p.26*
Trish Lenz	The effects of Toronto police services' tactics on the ability of homeless, illegal-drug consuming individuals to practice harm reduction: A mixed methods study	3:00 - 3:20	*p.27*
	Group discussion	3:20 - 3:30	
	Coffee break	3:30 - 3:40	
THEME: Time, Space and Embodiment		Chair: Piotr Suffczynski	
Marija Cotic	Spatiotemporal investigation of gamma activity in the human epileptic brain	3:40 - 4:00	*p.28*
Eunji E. Kang	Time varying spectral features during anesthesia	4:00 - 4:20	*p.29*
Don S. Borrett	Autonomous agents and the pathophysiology of Parkinson's disease	4:20 - 4:40	*p.30*
Elan Liss Ohayon	Routes and roadblocks to autonomous neurodynamics in time, space and social contexts	4:40 - 5:00	*p.31*
	Group discussion and announcements	5:00 - 5:10	
SAND DINNER			



PRINCIPLES OF AUTONOMOUS NEURODYNAMICS 2010
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Wednesday, August 25th - U of T, Medical Sciences Building, Room 4227

Peter Carlen	Introduction to SAND - Day 3	9:00 - 9:10

THEME: Neurodynamics: Mechanisms, Classification, Pitfalls and Perception — Chair: Eunji E. Kang

Stiliyan Kalitzin	Dynamics of synchrony and plasticity	9:10-9:30	*p.32*
Angela Lee	Brain state classification in epilepsy and anaesthesia	9:30-9:50	*p.33*
Peter L. Carlen	Fetal ethanol exposure and postnatal brain hyperexcitability: "the tip of the neurobehavioural nightmare"	9:50-10:10	*p.34*
Uziel Awret	How long is 'Now'?	10:10-10:30	*p.35*
	Group Discussion and coffee break	10:30-10:45	

ROUNDTABLE DISCUSSION: — Chairs: Ann Lam and Stiliyan Kalitzin

Round Table II	The Social Context and Autonomous Neurodynamics	10:45-11:30

Society for Autonomous Neurodynamics Planning Session: — Chairs: Peter Carlen & Piotr Suffczynski

Round Table III	Future Directions: Science, Narratives and Locations	11:30-11:50
Melanie Jeffrey	Closing Remarks and Announcements	11:50-12:00
	Departure to Parry Sound for Boat and Canoe Journeys	Noon

POST-PRESENTATION EVENTS
SAND Scientific Retreat: Wednesday August 25th - Sunday, August 29, 2010

EFFECTS OF POLYUNSATURATED FATTY ACIDS ON PENTYLENETETRAZOLE SEIZURES

Marc Trepanier

University of Toronto Epilepsy Research Program

BACKGROUND: Epilepsy is a neurological disorder defined as spontaneous and recurrent seizures. It affects approximately 1% of the population. Anticonvulsant drugs are the first line therapy for epilepsy. However, these drugs come with side effects and are ineffective in 20-40% of patients. Therefore, there is a need for improved treatments. Growing evidence suggests omega-3 polyunsaturated fatty acids (n3-PUFA) have antiepileptic properties. However, our laboratory has had difficulties replicating the strong anticonvulsive effects of PUFA reported by other groups and have reported smaller anticonvulsant effects.

OBJECTIVE: We originally tried to replicate a study which demonstrated the anticonvulsant properties of 3 weeks of daily i.p injections of 40mg/kg dose of linoleic acid (LA) and alpha linolenic acid (ALA) in a 4:1 ratio (SR-3 mixture) in the maximal pentylenetetrazole (PTZ) model. We then tried to replicate a second study which was released demonstrating the effects of 2 weeks of daily i.p. injections of 50mg/kg of docosahexaenoic acid (DHA) ethyl ester in both the maximal PTZ model and repeated subconvulsive PTZ model.

PROCEDURE: Two month old male Wistar rats were injected i.p. for 3 weeks daily with 40 and 200mg/kg SR-3 mixture. On day 22, animals received an intraperitoneal (i.p.) injection of 100 mg/kg of PTZ. Latency to tonic-clonic seizure was measured. In another group of animals, animals were injected with DHA or DHA ethyl ester for two weeks. On day 15, animals were either tested with 105 mg/kg PTZ or small repeated subconvulsive dose of 15 mg/kg of PTZ every 15 minutes.

RESULTS: The 200mg/kg dose of SR-3 mixture was able to increase seizure latency 3 folds compared to the saline control ($p < 0.05$). However, the 40mg/kg dose was not significantly different from the saline control ($p > 0.05$). In experiment 2, DHA and DHA ethyl ester were not significantly different from one another ($p > 0.05$) in both PTZ models. However, both were significantly different from the saline control ($p < 0.05$).

CONCLUSION: These results suggest that PUFAs may have antiepileptic properties, providing a potentially cheap therapy for epilepsy. However, we were not able to report the same strong anticonvulsant effects of PUFAs reported by other groups.

HUMAN AND MURINE SUCCINIC SEMIALDEHYDE DEHYDROGENASE DEFICIENCY

Miguel Cortez

Cortez MA, Shen L, Wu Y, Stewart L and Snead OC III
The Hospital for Sick Children, Toronto, Ontario

Succinic semialdehyde dehydrogenase (SSADH) deficiency, a disorder of gamma-aminobutyric acid (GABA) degradation, elevations of GABA and γ-Hydroxybutyric acid (GHB) in brain. Human SSADH deficiency is a neurometabolic disorder with multiple comorbidities including intellectual disability, epilepsy, hypotonia, ataxia, associated with cerebral and cerebellar atrophy (Hogema et al. Nat Genet. 2001 Oct;29(2):212-6). EEG abnormalities are consistent with absence epilepsy with a characteristic gradual transition to tonic-clonic seizures (Cortez et al. Pharmacol Biochem Behav. 2004 Nov;79(3):547-53) and a parallel developmental failure-to-thrive, progressive ataxia and lethal convulsive status epilepticus (Stewart et al. Epilepsy Behav. 2008 Aug;13(2):290-4). Binding and electrophysiological studies demonstrate use-dependent downregulation of GABA (A) and (B) receptors in the mutant mouse (Buzzi et al. Brain Res. 2006 May 23; 1090(1):15-22; Wu et al. Ann Neurol. 2006 Jan; 59(1):42-52). Ketogenic diet is effective for seizure control in the mouse model (Nylen et al. Exp Neurol. 2008 Apr; 210(2):449-57) but no clinical trials have been attempted to date. The effects of a ketogenic diet on ATP concentrations and the number of hippocampal mitochondria in Aldh5a1 (-/-) mice (Nylen et al. Biochim Biophys Acta. 2009 Mar; 1790(3):208-12). Experimental treatment with SGS-742, a GABA (B) antagonist eliminates the epileptiform activity and may be effective in clinical trials (Pearl et al. J Inherit Metab Dis. 2009Jun; 32(3):343-52).

ASSOCIATION BETWEEN HLA-B*1502 IN HAN WITH CORRELATION TO HYPER SENSITIVITY FOR AROMATIC ANTI-EPILEPTIC DRUGS

Amjad BaniHani

Amjad BaniHani[1], Manuela Neuman[2], Pauline Arditi, Paul A. Hwang[4]
[1]Department of Neurology, RMS, Amman, Jordan,
[2]In Vitro Drug Safety and Biotechnology and Department of Pharmacology & Toxicology, University of Toronto;
[3]Faculty of Pharmacy, University of Toulouse; [4]NYGH & UTERP, University of Toronto, ON, Canada

OBJECTIVE: To study *in-vitro* lymphocyte toxicity assay (LTA) and HLA-B*1502 as predictors to severe hypersensitivity reactions (HSRs) to aromatic anti-epileptic drugs (AEDs) in Han compared to other races.

MATERIALS AND METHODS:A prospective cohort study of patients with severe HSRs to AEDs is performed. A total of 26 patients were enrolled in this study. 20 suffered from hypersensitivity (14 Han, 6 non-Han) to AEDs. 6 (4 Han, 2 non-Han) patients who tolerated the drugs were selected as controls. HLA-B*1502 genotyping and *in-vitro* LTA were performed against different aromatic anti-epileptic drugs including carpamazepine, phenytoin, phenobarbitol and lamotrigine to all patients.

RESULTS: LTA was positive to AED in 100% (14/14) in Han patients, who suffered from hypersensitivity reaction and positive HLA-B*1502. Other 4 Han control patients had negative in-vitro LTA results as well as negative for HLA-B*1502 with one exception, one control Han subject had positive LTA to lamotrogine, but negative to other AED. In non-Han patients who suffered from hypersensitivity reaction; LTA was positive to drug in 100% (6/6). Other 2 non-Han control patients had negative in-vitro LTA. All non-HAN patients had negative HLA-B*1502.

CONCLUSION: In vitro LTA is more sensitive than genetic study, because it detected severe in-vitro LTA sensitivity to lamotrigine in one of the control patients from Hans's origin. LTA showed to have higher specificity and sensitivity than genetic study, because the strong association to hyper sensitivity and HLA-B*1502 is related to Han population only.

ARE EPILEPSY AND PSEUDOEPILEPSY ESSENTIALLY THE SAME DISORDER?

Michael G. Sumner

Michael G Sumner & Paul A Hwang
University of Toronto Epilepsy Research Program

OBJECTIVE: To determine the overlap between epilepsy and pseudoepilepsey

MATERIAL AND METHODS: There is significant difficulty in making the diagnosis of epilepsy, in some patients, and the risk factors for non-epileptic seizures are also risk factors for seizures. Anticonvulsants are very frequently used outside neurology to treat mood disorders, anxiety disorders, and impulse control disorders as well as chronic pain. The literature of seizures and pseudosiezures is reviewed.

RESULTS: The diagnosis of seizures vs. non epileptic seizures is often academic, depending on the intervention that is proposed to treat the patient and the benefit verses risk. This was demonstrated with a patients who was diagnosed as having epilepsy but responded well to anticonvulsants. Pseudosiezures are caused by brain dysfunction and can be treated.

CONCLUSION: We need to look for epilepsy. However if cause of the disturbance cannot be diagnosed the patient should still be treated to the best of our ability. There are large numbers of patients who are not treated by neurologists because they are felt to have non epileptic seizures, and are further not treated by psychiatrists because they have real seizures leaving them in a limbo. These patients in the borderland between neurology and psychiatry deserve better care.

RELEVANCE: Our diagnostic categories constrain our therapeutics to the detriment of our patients

DELINEATION OF A NOVEL SEIZURE DISORDER, MABRY SYNDROME: IDENTIFICATION OF THE INHERITED DEFICIENCY IN ALKALINE PHOSPHATASE METABOLISM

Miles D. Thompson

Miles D. Thompson,[1-4] Marjan M. Nezarati,[5] Paul A. Hwang,[5], Arnold Munnich[6], Denise Horn[7], Charleton C. Mabry[8], Han Brunner[9], Peter M. Krawitz[7], David E C Cole,[1, 3]
[1]Lab Medicine, Banting Inst & [2]Dept. Laboratory Medicine & Pathobiology, University of Toronto
[3]University of Toronto Epilepsy Research Program
[4]Division of Clinical and Metabolic Genetics, Hospital for Sick Children & [5]North York General Hospital, Toronto
[6]INSERM U781-Université Paris Descartes-Hôpital Necker-Enfants Malades, Paris, France
[7]Institut für Medizinische Genetik, Charité Universitätsmedizin, Berlin, German
[8]University of Kentucky College of Medicine, Lexington;
[9]Department of Human Genetics, University Medical Centre St. Radboud, Nijmegen, The Netherlands.

The impact of seizures associated with childhood onset metabolic disorders is considerable even though they account for less than 1% of live births. Like many infantile metabolic storage disorders, hyperphosphatasia with neurologic deficit, Mabry syndrome, has its onset starting in the first year of life – commencing with seizures followed by developmental disability (DD). At first considered rare, the disorder was described by Mabry et al. in 1970 a single family (OMIM#239300) [1970]. Both the frequency and nosology of this condition, however, remained uncertain until the present study. Patient recruitment has been conducted globally in order to delineate this distinctive, autosomal recessive disorder. Common to all patients is facial dysmorphism, particularly hypertelorism, a broad nasal bridge and a tented mouth. All patients have some degree of middle and distal phalangeal shortening that varies in position and degree. The persistent elevation of alkaline phosphatase (ALP) activity without any evidence for active bone or liver disease also varies considerably among patients (from ~1.3 to ~20 times the upper age-adjusted reference limit), but remains constant in any one individual. We have identified mutations in the type V phosphatidylinositol glycan (PIG) anchor biosynthesis (PIGV) gene in less than half of all probands – particularly those with high ALP levels. Consistent with this observation is the fact that the PIGV defect results in complete failure of PIG anchoring of ALP at the membrane – resulting in the extreme elevation of serum ALP. We speculate that seizures result from lysosmal storage of portions of the malformed PIG anchor. Interestingly, patients with low ALP over-secretion have been found to accumulate glycolipid storage material in a wide range of cell types including Schwann cells. This suggests that a mutation in another gene in the PIG synthesis pathway may result in a partially active PIG anchor that may not be retained in the cytoplasm and not integrated into the cell membrane. The genetic heterogeneity of the disorder supports this hypothesis. The possibility that other genes in the PIG anchor biosynthesis pathway might be involved is likely, since the PIG anchor is a major modulator of ALP expression on the cell surface. Substantial phenotypic variability, including variable degrees and extent of lysosomal storage in probands, also argues for genetic heterogeneity in Mabry syndrome. We will elucidate the disruptions to the PIG anchor pathway, identifying the molecular basis of the disorder on a case by case basis and tracing the biochemical consequences to a pathway only recently linked to seizures in humans.

ADULT HIPPOCAMPAL NEUROGENESIS: IMPLICATIONS FOR EPILEPSY

Brian Scott

Institute of Medical Sciences, University of Toronto Epilepsy Research Program

The production of new neurons (neurogenesis) continues to occur throughout adulthood in the dentate gyrus of the hippocampus of mammals, including humans. Neurogenesis is believed to be involved in some forms of hippocampal dependent learning and memory. Traumatic brain injury, stroke and seizures have been found to greatly increase neurogenesis in adult rodents. Seizures have also been shown to alter several aspects of young neuron development. Young neurons migrate to abnormal locations, as well as have altered morphology following seizures. They have been found to make unusual connections with other parts of the hippocampus and may contribute to the formation of epileptic foci. Newly born neurons may also contribute to the abnormal functioning of the hippocampus between seizure episodes. Aberrant neurogenesis is now being considered as a contributor to spontaneous seizures and co-morbid conditions associated with epilepsy, and may provide a novel target for anti-epileptic treatments.

A MOUSE MODEL FOR STUDYING POST-ISCHEMIC SEIZURES

Liang Zhang

Liang Zhang, Youssef Hanna El-Hayek, Chiping Wu, Rick Chen, Abdel Rahman Al-Sharif, Shelley Huang, Nisarg Patel, Peter L Carlen
Toronto Western Research Institute, University Health Network

Stroke is a major cause of seizures in adult and aging population. These seizures can be classified as early-onset (within 2 weeks) and late-onset (months to years after the initial stroke event). The early-onset seizures, which occur largely within the first 24 hours post stroke, are correlated with worsened outcome and mortality. The mechanisms of post-stroke seizures are presently unclear. We thus explored whether hypoxic-ischemic (HI) episodes service a useful model to study post-ischemic seizures. Adult C57 black mice (4-9 months) were used in our experiments. The animal received a unilateral occlusion of common carotid artery and then exposed to systemic hypoxia (8% O2 for 30 min). To characterize the HI model, we measured brain blood flow using a laser Doppler system and monitored hippocampal and cortical EEG via chronically implanted electrodes. In addition, we examine EEG, ECG and core body temperature via telemetry (wireless) recordings. We found that the HI was effective of causing lateralized brain ischemia in about 50% of mice tested, which were verified by great decreases in blood flow and EEG activity and infarcts in the hemisphere ipsilateral to the carotid artery occlusion. The animals with ipsilateral ischemia had a high propensity of exhibiting generalized seizures. Similar post-HI seizures were also observed in aging/aged (18-22 months) mice. We thus suggest that the HI is a convenient model for studying post-ischemic seizures in adult and aged mice.

RELEVANCE: EEG activities associated with behavioral seizures in this model may be of wide interest to both clinicians and basic researchers. Further investigation of this model may help to understand the origin and genesis of post-ischemic seizures.

TELEMETRY EEG RECORDINGS OF SEIZURE ACTIVITIES IN MICE

Chao Du

Chao Du, Nisarg Patel, Chiping Wu, James Eubank, Liang Zhang
Toronto Western Research Institute, University Health Network

ABSTRACT: We found recently that hypoxic-ischemic (HI) episodes are effective of inducing seizures in adult mice. The objective of these pilot experiments was to examine EEG features of these seizures using a telemetry system. C57 black mice (4-9 months) were used. A transmitter/thermal sensor (total weight of 1.6g) was placed into the peritoneal cavity and the EEG electrode was implanted in the hippocampus CA1 or neocortical region. After 9-10 days of post-implantation recovery, the animal received a permanent occlusion of the right common carotid artery and then a subsequent exposure to global hypoxia (8% oxygen for 40 min). Telemetry recordings were conducted continuously before and following the hypoxic episode, together with simultaneous video monitoring. Of 11 mice examined, no seizure was observed prior to the HI challenge and baseline temperature, heart rate and EEG activity (such as hippocampal theta and sharp waves) appeared to be "physiological". Vigorous motor seizures, such as jumping, fast running, barrel rolling and/or falling with loss of righting reflex, were observed in 3 of 11 mice following the HI challenge. Unlike our previous wired recordings, telemetry EEG signals were not interrupted by movement-relate artifacts, thus revealing no electrographic discharges that correlated with the motor seizures. In contrast, spike wave discharges (6-8 Hz) were observed from the MeCP2+/- mice during immobility. Based on these preliminary observations, we suggest that chronic telemetry EEG recordings (together temperature/activity monitoring) are of great value for examining EEG activity in mouse models and that the post-HI seizures may arise from sub-cortical structures.

RELEVANCE: We found recently that hypoxic-ischemic (HI) episodes are effective of inducing seizures in adult mice. The objective of these pilot experiments was to examine EEG features of these seizures using a telemetry system.

MECHANISMS OF EPILEPTIFORM ACTIVITY IN MECP2-DEFICIENT MICE

James H. Eubanks

James H. Eubanks and Liang Zhang.
Toronto Western Research Institute, Toronto, Canada

Rett syndrome is an autism-spectrum disorder caused by loss of function mutations within the gene encoding methyl CpG-binding protein 2 (MeCP2). Although MeCP2 is expressed throughout the body, the primary deficits of Rett syndrome arise from alterations of nervous system function. Although subtle decreases in synaptic plasticity have been detected within cortical and hippocampal neurons of Mecp2-null mice, relatively little information exists on how the loss of MeCP2 affects neuronal network activity in the brain. Using the isolated hippocampal circuit as a model network system, we tested whether the intrinsic network activities of symptomatic Mecp2-null mice would differ from wild-type. Extracellular and whole-cell patch recordings revealed that although spontaneous IPSP-based rhythmic activity is presen in Mecp2-null slices, its frequency is significantly reduced from wild-type. This reduction was not associated with alterations in the gross electrophysiological properties of hippocampal neurons, but was associated with a diminished level of basal excitatory drive within this recurrent circuit. In addition to showing this network alteration, we also show that the Mecp2-null hippocampal network is paradoxically over-responsive to excitatory stimuli, and that it possesses a high propensity for generating sharp waves – an excitation-dominant and self-sustained population event that arises from subtle alterations in the basal excitatory / inhibitory balance in the CA3 circuitry. Taken together, these results indicate that the Mecp2-null hippocampal network has a diminished basal inhibitory rhythmic activity, but that the circuitry is inherently prone to becoming hyper-excitable.

HYPERSENSITIVITY SYNDROME TO AROMATIC ANTI-EPILEPTIC DRUGS AND IN-VITRO PREDICTORS

Manuela G. Neuman

Manuela G. Neuman[1], Izabella M. Malkiewicz[1], Amjad BaniHani[2,3], Paul A. Hwang[2]
[1]In Vitro Drug Safety and Biotechnology and Department of Pharmacology & Toxicology, University of Toronto,
[2]Department of Neurology, RMS, Amman, Jordan,
[3]Departments of Medicine & Pediatrics, NYGH & UTERP, University of Toronto, ON, Canada

Some anti-epileptic drugs (AEDs) cause a syndrome of rash, fever and organ involvement that leads to hypersensitivity syndrome (HSR). Using lymphocyte toxicity assay (LTA) we diagnosed and predict AED-HSR.

We aimed to study interleukins 5 and 6 in sera of patients that presented with clinical HSR. All patients had LTA and HLA B*1502 performed. Correlation between clinical severity of the reaction, with the in vitro LTA and with genetic marker and interleukin was performed.

Individuals from an epilepsy clinic (PAH) were referred for diagnostic testing. Patients (16) manifested fever, cutaneous eruptions ± hepatic involvement within 8 weeks of exposure to AED. Patients (16) that used the same drugs without presenting a reaction volunteered as controls. HLA B*1502 genotyping and in-vitro LTA were performed against carbamazepine, phenytoin, phenobarbitol and lamotrigine.

LTA was positive (>12.5±2.5%) for the incriminated drugs in HSR patients, while all controls had negative LTA (<12.5±2.5%). Interleukine 5 in patients that presented only rash were significantly higher ($p<0.05$) when compared to the levels of controls. Interleukin 6 have been significantly higher in patients that presented an additional organ involvement when compared to patients that presented only rash or to the control ($p<0.05$). The level of IL6 correlated with the severity of the AED and with the LTA. IL5 did not correlate with the LTA. There was no correlation between ILs and HLA B*1502. This study concluded that a combination of LTA and HLA B*1502 offers the possibility of avoiding high-risk AEDs. Also LTA correlates with IL6 showing that AED have a strong immune component.

$GABA_A$ RECEPTOR PLASTICITY IN ALCOHOL WITHDRAWAL

Igor Spigelman

Division of Oral Biology & Medicine, UCLA School of Dentistry, USA

Chronic intermittent ethanol (CIE) treatment and withdrawal in rats produces behavioral changes modeling human alcohol dependence including increased seizure susceptibility, and can be explained by plastic changes in inhibitory neurotransmission involving γ-aminobutyric acid type A receptors (GABARs). The withdrawal syndrome includes hyperactivity and hyperexcitability, increased anxiety, sleep disorders, including tolerance to sedative actions of ethanol and other sleep aids, and increased seizure susceptibility. Using the rat CIE model of alcohol dependence, we deduced that multiple withdrawals produce a critical kindling-like phenomenon due at least partially to aberrant changes in subunit composition, subcellular location, and pharmaco-physiology of GABARs. CIE treatment (>30 doses) in rats leads to a persistent down-regulation of EtOH-sensitive extrasynaptic α4/δ-containing GABAR-mediated tonic currents in hippocampal and other cells. BZ-sensitive α1/γ2-mediated synaptic currents are also down-regulated and compensatory α4/γ2 synaptic GABARs are elevated in parallel with increased sensitivity to low mM EtOH. Likewise, we found that a single intoxicating EtOH dose (5 g/kg, gavage) produces rapid (<1 hr) down-regulation of cell surface α4βδ-GABARs, tolerance to EtOH enhancement of tonic current, and reduced basal tonic currents in hippocampus. This is followed by slower decreases in synaptic BZ-sensitive γ2-containing GABARs, an increase in α4βγ2 GABARs, and increased EtOH enhancement of synaptic GABAR currents. However, the changes are fully reversible by 2 weeks or less after EtOH exposure, unlike the persistent alterations induced by CIE treatment. We conclude that GABAR plasticity is essential to development of EtOH dependence including seizure susceptibility, a possible model of epileptogenesis in mammalian brain.

HIPPOCAMPAL SIGNAL COMPLEXITY IN MESIAL TEMPORAL LOBE EPILEPSY: A NOISY BRAIN IS A HEALTHY BRAIN

Andrea B. Protzner

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Patients with mesial temporal lobe epilepsy show structural and functional abnormalities in hippocampus and surrounding mesial temporal structures. Brain signal complexity appears to be a marker of functional integrity or capacity. We examined complexity in 8 patients with intracranial hippocampal electrodes during performance of memory tasks (scene encoding and recognition) known to be sensitive to mesial temporal integrity. Our patients were shown to have right mesial temporal seizure onsets, permitting us to evaluate both epileptogenic (right) and healthy (left) hippocampi. Using multiscale entropy as a measure of complexity, we found that iEEG from the epileptogenic hippocampus showed less complexity than iEEG from the healthy hippocampus. This difference was reliable for encoding but not for recognition. Our results indicate that both functional integrity and cognitive demands influence hippocampal signal complexity.

RELEVANCE: Recent computational modelling suggests that variability or "noise" in physiological signals may be an important parameter reflecting both the processing capacity and the functional integrity of biological systems. We examined variability as a potential marker of functional integrity of the hippocampus in patients with mesial temporal lobe epilepsy.

SLOW POPULATION ACTIVITIES IN NOISE-DRIVEN BIOLOGICAL NETWORKS

Ernest C. Ho

Ernest C. Y. Ho[1,2], Liang Zhang[1,3] and Frances K Skinner[1,2,3,4]
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OBJECTIVE: Slow population activities (SPAs) are population activities of frequencies smaller than 5 Hz. SPAs occur in many brain areas. Examples of SPAs include the cortical EEG K-complex during NREM sleep and the large irregular activities in the hippocampus. Despite their prevalence, mechanisms underlying SPAs are currently poorly understood. We develop mathematical network models constrained by data extracted from an in vitro preparation expressing SPAs. Our goal is to achieve a mechanistic understanding of SPAs in general through the analyses of these mathematical network models.

METHODS: We use a combination of data extraction, simulation and mathematical analyses to understand how SPAs are generated. We first extract relevant synaptic quantities from experiments using thick hippocampal slices from mice in which spontaneous inhibitory-based SPAs occur. We use these quantities in our inhibitory network simulations. We vary the input-output characteristics (i.e. f-i curve) of the constituent inhibitory neurons, the inhibitory coupling conductance (gsyn), and excitatory conductance noise level as parameters of simulation. Finally, in order to explain the trends and make predictions from our simulation results, we approximate the network with mean field equations and perform mathematical analysis via these equations.

RESULTS: Simulated networks with differing f-i characteristics of constituent neurons have diverging behaviours of SPAs. We see strong SPAs in networks with a more linear f-I curve for their constituent neurons. A network with its neurons having a high curvature f-I curve has weaker SPAs, but that which can be observed for a larger set of gsyn values. Mathematical analyses (via mean field theory) conclude that solutions for SPAs tend to "clump" together in a narrow region of gsyn values for a more linear f-I curve of constituent neurons. Solutions of SPAs tend to "spread out" for networks with a high curvature f-I curve for their neurons.

Conclusion: Intrinsic properties of individual neurons are critical in determining the overall characteristics of SOs. For robust SPAs, a tradeoff has to be made between a strong response and a weaker response that can be observed for a wider range of gsyn values. This tradeoff is facilitated by the curvature of f-I curves. We have successfully quantified how individual neuronal characteristics can affect collective network behaviours. Our results may generalize to SPAs occurring in other brain areas.

RELEVANCE: Using an in vitro hippocampal experiment as a backdrop, we develop computational and mathematical models to quantify how individual properties of neurons can affect various aspects of global network behaviours.

COST/BENEFIT ANALYSIS OF EPILEPSY CARE IN ONTARIO

McIntyre Burnham
Alex Dolan
Thomas Drag

University of Toronto Epilepsy Research Program

The purpose of the present research was to develop a plan for improving the treatment of epilepsy in Ontario. It involved an assessment of the literature currently available on epilepsy care in North America and Ontario. Our thesis was that improved care could be provided at no increased cost.

Our research began by establishing the basic facts relevant to epilepsy health care, such as the prevalence and incidence of epilepsy, its types, its duration and causes. We also assessed the therapies for epilepsy, including therapy with antiepileptic drugs (AEDs) and the treatments that are used when AEDs fail, such as surgery, dietary therapies, vagus nerve stimulation, etc.

Finally, an economic analysis of epilepsy care was done, comparing current and potential expenditures, and particularly focused on the medical costs of controlled and uncontrolled epilepsy. We concluded that improved health care that converted people with uncontrolled epilepsy into people with controlled epilepsy would be cost effective. The present talk will focus on the cost effectiveness of dietary and surgical care.

RELEVANCE: This presentation relates to autonomy in that it shows how at no extra cost, or at a potential savings to the people, epilepsy health care could be improved, both for the patient and the province of Ontario.

A JOURNAL OF 30 YEARS IN EPILEPSY RESEARCH: FROM MOLECULES TO MIND

Paul A. Hwang

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Beginning in the late 1970's the author began studying this paroxysmal disorder at the Montreal Neurological Institute under Frederick Andermann, Pierre Gloor et al: the clinical semiology of seizures, EEG correlates and impact on higher cognitive functions and psychosocial development and behavior.

On return from Colorado to Toronto, PAH explored neurotransmitter-receptor interactions in human brain and in experimental models, and found exciting changes in benzodiazepine-receptors, coupled to GABA-A receptor activity. Free radical scavengers seem to ameliorate some aspects of epilepstogenesis. In the developing brain of the newborn and the child, a number of congenital anomalies with epilepsy were encountered, revealed by structural neuroimaging, confirmed by functional imaging closely coupled to EEG changes during long-term monitoring with video-EEG telemetry at the Hospital for Sick Children, leading to excisional surgery even in young children with refractory epilepsies, who have failed control with adequate AEDs, impacting on their cognitive development and behavior.

Close collaboration with the experimental laboratories of Dr. Burnham studied animal modela especially in amygdaloid kindling but also PTZ and MES, exploring pathways of propagation of motor seizures, the roles of apoptosis and neurogenesis, the channelopathies in genetic syndromes, including mutations.

As his patients mature into adolescents and young adults, PAH expanded his studies into epilepsy in the transitional years: higher cognitive functions in development, sex hormones and higher-resolution neuroimaging of the brain , and multichannel digital EEG recording , including sleep studies in PSG. Clinical trials of novel antiepileptic drugs were undertaken: levertiracetam, brivaracetam, perampanel (AMPA-receptor antagonist) and polyunsaturated fatty acids, and assessment of the quality of life affected by epilepsy.

The challenge of the future lies in facing the growing needs of persons with epilepsy in the health-care section with diminishing resources when the exploding neurosciences offer tremendous potential for therapy, rehabilitation and long-term care, possibly even a cure for epilepsy.

AUTONOMY AND RELATIONALITY: LIVING EPILEPSY RESEARCH

Melanie A. Jeffrey

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University of Toronto Epilepsy Research Program

In 2007, I presented a personal narrative to SAND in Quebec City. It was a transformative experience. I am now pursuing my PhD in Pharmacology & Toxicology, researching neurosteroids and epilepsy, where the integration of whole human being is manifest, belying Cartesian mind-body dualism. But that is not what I want to tell you.

In epilepsy health care and advocacy, autonomy of the individual is often an unstated goal. As a person living with epilepsy, I am keenly aware of how much seizures impinge on my life. Living with seizures has been a challenge, and there is a network of people who support me. They worry, they watch, they wait for the next "little earthquake" In the wake of my brother's suicide, my mental health is constantly examined. My own autonomy is cradled in this network of relationality.

If I care for my mental, emotional, physical and spiritual wellbeing, I have fewer seizures (don't tell anyone, graduate students aren't supposed to have life balance). This involves many layers of relationality with my family & partner, communities, and ecosphere. This is a balance I constantly struggle to maintain. It is particularly difficult in the realm known as science, which denotes primacy to the physical under the pretext of objectivity.

My relationships are inherent to my autonomy. How does this inform my research? This is what I want to tell you.

RELEVANCE: Examining the underpinnings of "autonomy" in epilepsy and epilepsy research.

LOW FREQUENCY CALCIUM-DEPENDENT SUBTHRESHOLD FLUCTUATIONS IN MEMBRANE POTENTIAL; A MODELING STUDY

Harshit Sam Talasila

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Subthreshold fluctuations in membrane potential have long been implicated in limiting the transfer of useful information between neurons. Recent studies have shown that subthreshold fluctuations contain useful information pertaining to changes in the state of the neuronal network. Previous work by Diba et al [2004] has implicated Calcium-dependent potassium (K_{ca}) channels as playing a central role in producing subthreshold voltage noise. While most channels generate noise through their inherent thermal fluctuations, we hypothesize that K_{ca} channels also generate low-frequency subthreshold oscillations by transmitting the stochastic fluctuations of intracellular calcium.

We constructed a detailed computational model of a CA3 pyramidal cell based on the biophysical model developed by Traub [1994]. Channel noise was introduced by replacing all Hodgkin-Huxley type channels with their equivalent Markovian kinetic models. We also implemented an intracellular calcium pool with Ca2+ levels that fluctuate stochastically, due to the influence of Markovian calcium channels.

Preliminary results show that, there exists a relationship between intracellular calcium and membrane potential fluctuations. This suggests that stochastic calcium fluctuations may partially drive low-frequency voltage noise-like activity. Further modeling has implicated Ca^2+ dependent afterhyperpolarization current (I_{AHP}) as being the primary link between these two signals, as power spectrum analysis of I_{AHP} shows that the contribution of intracellular calcium fluctuations is dominant at low frequencies, below the natural cutoff for I_{AHP} noise. We believe that this link between membrane potential noise and intracellular calcium could regulate many of the well-documented roles of noise in the nervous system.

MATHEMATICAL NETWORK MODELS OF THETA RHYTHMS IN THE HIPPOCAMPUS

Katie A. Ferguson

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One of the most prominent clocking mechanisms detected in the mammalian brain is the theta rhythm - a network rhythm oscillating between 3-12 Hz. Theta rhythms are recorded in the hippocampus during exploratory behaviour and R.E.M. sleep, and can induce long-term potentiation (LTP) and long-term depression (LTD) - the basis for synaptic plasticity. Recently, using an intact hippocampus in vitro, the hippocampal CA1 region was shown to possess the minimum circuitry to generate its own intrinsic theta rhythm (Goutagny R, Jackson J, Williams S (2009). Nature Neuroscience 12:1491-1493). Unfortunately, the mechanism(s) responsible for the generation of the hippocampal theta rhythm is unclear. In an attempt to understand the underlying dynamics of this rhythm, a mathematical network model has been developed. The network model is composed of four cell types: pyramidal cells, O-LM interneurons, fast-firing parvalbumin (PV) basket cells, and slow-firing cholecystokinin (CCK) basket cells. By using experimental data of known connectivities to create the network configuration, the model successfully produces oscillatory behaviour in the theta frequency range. Previous research has focused on the influence of basket cells on the faster gamma rhythm (20-100 Hz.). Interestingly, our model suggests that the pyramidal cell - basket cell interaction may play a key role in the generation of hippocampal theta rhythms, whereas the O-LM interneuron - pyramidal cell connections were less influential.

RELEVANCE: Hippocampal theta rhythms are thought to be involved in both the encoding and retrieval of memories. Thus the rhythm can be altered by the environment, or it can be generated independently. We create a mathematical network model to determine the underlying dynamics behind the creation of these theta rhythms.

COMPUTATIONAL MODEL OF CA3 PYRAMIDAL CELLS: FROM AN ADAPTING NEURON TO NETWORK BURSTING

Muhammad Dur-e-Ahmad

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The hippocampus is an essential brain structure, playing a key role in the formation of long term memory and spatial navigation in mammals. The CA3 region with its highly recurrent circuitry holds a strategic position in the hippocampus and is believed to be important in the rapid acquisition of novel information. It has been suggested that that excitatory CA3 pyramidal neurons mainly communicate through bursts of spikes instead of regular firing of action potentials. Two distinct patterns of intrinsic activities of individual CA3 neurons have been observed using slice preparations from hippocampus. The first category of cells exhibit a regular firing pattern with a short latency spiking behaviour in the presence of rheobase current and a high frequency of spikes with strong adaptation with an increased current intensity. The second category of cells shows a delayed onset of spiking at the rheobase and a weakly adapting firing pattern in the presence of high intensity current.

We propose a simple model of spike generation which segregates these different behaviour patterns of CA3 neurons. Our models capture the entire spike characteristics and the input-output relationship for both current injection and spiking output with remarkable accuracy. Further, due to the simplicity of the model, it requires only modest computational resources and enables us to explore rather thoroughly the network behaviour of CA3 neurons. Finally, I will discuss the bursting behaviour of small CA3 network, which is directly related to the intrinsic adaptation characteristics of the individual neuron.

THE FAST AND THE CURIOUS: MECHANISMS OF 60 - 200 HZ OSCILLATIONS IN THE BRAIN

Piotr Suffczynski

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High-gamma activity, HGA (~60-200 Hz) has been observed during task-related cortical activation in humans and in animals, and have been used to map normal brain function and to decode commands in brain-computer interfaces. Very fast oscillations in LFP and EEG, ranging in frequency between 80 Hz and 250 Hz, have been also observed in spatial and temporal patterns corresponding to the epileptogenic zone. To understand the role that HGA plays in both normal and pathological brain states, deeper insights into its generating mechanisms are essential. We developed a biologically based computational model of a cortical network to investigate the mechanisms generating HGA. The computational model included excitatory pyramidal regular-spiking (PY) and inhibitory fast-spiking (IN) neurons described by Hodgkin-Huxley dynamics. We compared activity generated by this model with HGA that was observed in LFP recorded in monkey somatosensory cortex during vibrotactile stimulation. Increase of firing rate and broadband HGA responses in LFP signals generated by the model were in agreement with experimental results. The HGA appear to be mediated mostly by an excited population of inhibitory fast-spiking interneurons firing at high-gamma frequencies and pacing excitatory regular-spiking pyramidal cells. HGA reflects local cortical activation under normal conditions and as such is a good candidate for mapping cortical areas engaged by a specific task. The mechanisms of HGA, appear to be similar to those proposed for hippocampal ripples generated by subset of interneurons that regulate discharge of principal cells.

RBF BASED STIMULATORS TO CONTROL EPILEPSY

Sinisa Colic

Sinisa Colic, Osbert C. Zalay, Berj L. Bardakjian
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Deep Brain Simulation (DBS) has been noted for its potential to suppress epileptic seizures. To date, DBS has achieved mixed results as a therapeutic approach to seizure control. We demonstrate that high complexity (HC) biologically inspired stimulation is superior to periodic forms of stimulation such as those implemented in DBS. Using Radial Basis Functions (RBFs), we modeled interictal and postictal time series based on electroencephalograms (EEGs) of rat hippocampal slices while under low Mg2+/high K+ perfusion. We then compared the seizure-control efficacy of RBF-based interictal and postictal stimulation and simple periodic bi-phasic waveform stimulation, using a Cognitive Rhythm Generator (CRG) model of spontaneous seizure-like events (SLEs). What resulted was a significant improvement in seizure suppression for the interictal and postictal stimulation cases versus the periodic case. This suggests that the use of biologically-inspired high complexity stimulators may achieve better results than periodic pulse stimulators for electrical control of seizures in a clinical setting.

RELEVANCE: Provides results in favour of using highly complex RBF trained stimulation to control epilepsy

SEIZURE-LIKE EVENTS IN POPULATIONS OF COUPLED OSCILLATORS

Berj L. Bardakjian

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Epileptiform activity involves abrupt changes in dynamic behaviour of neuronal ensembles, which alternates between higher complexity ‘interictal’ mode and lower-complexity ‘ictal’ mode characterized by dense, rhythmic firing of the seizing network. Three mechanisms for generating seizure-like events (SLEs) in populations of coupled oscillators will be highlighted as state transitions from higher to lower complexity modes. (i) Changes in a system parameter can cause transitions by way of bifurcations or changes in the stability of stationary points or orbits in state space. (ii) Transitions produced by noise fluctuations can occur in bistable systems. This is how paroxysmal transitions are explained in a bistable model of absence epilepsy, wherein it is hypothesized that random fluctuations introduced into the system by noise in cortical and sensory inputs are necessary for epileptiform transitions to occur (Lopes da Silva *et al*, 2003; Suffczynski *et al* 2004). (iii) The cognitive rhythm generator network model (Zalay *et al,* 2010) exhibits intermittency in the absence of either system parameter changes or noise fluctuations. Under simulated epileptogenic conditions, transitions occur unprovoked between the interictal and ictal modes of a chaotic attractor with the trajectory visiting the neighborhood of each mode intermittently. Network "excitability" effects both local and global bifurcations in the dynamics, and under hyperexcitable conditions a bimodal epileptiform attractor is exhibited.

RELEVANCE: A description of the etiology of epileptic seizures as state transitions from higher to lower complexity modes.

COMPLEX RHYTHMIC WAVEFORM GENERATION FOR FEEDBACK NEUROMODULATION OF EPILEPTIFORM DYNAMICS

Osbert Zalay

Osbert C. Zalay and Berj L. Bardakjian
Institute of Biomaterials and Biomedical Engineering, University of Toronto

Electrical stimulation has been studied as an alternative treatment to resection surgery or anti-epileptic drugs in cases of intractable epilepsy. Most methods of stimulation involve simple open-loop delivery of periodic current pulses, as is the case with deep brain stimulation (DBS) and vagal nerve stimulation (VNS). While many isolated studies of DBS and VNS for epilepsy have been favorable, the overall body of research indicates mixed outcomes depending on stimulation parameters, treatment duration and type of epilepsy. We hypothesize that certain varieties of epileptiform dynamics might be mitigated through continuous neuromodulation with complex, non-periodic waveforms generated in a feedback configuration. The cognitive rhythm generator (CRG) is an architecture we have developed that is suitable for dynamic generation of complex waveforms for stimulation purposes. In network form, coupled CRGs can be programmed to operate over a wide range of dynamic modalities. Using a computational model of spontaneous, recurrent seizure-like events (SLEs) and stimulator based on CRGs, we demonstrate that feedback neuromodulation with complex rhythmic waveforms can suppress SLE transitions and restore dynamical complexity in the epileptic network. The insights gained from this computational study may be relevant to biological models of epilepsy and potentially to clinical practice.

RELEVANCE: The presentation will discuss controllability of epileptiform dynamics and present one approach to feedback neuromodulation demonstrated in a computational model.

BRAINWAVE BASED CONTROL PARADIGMS

Ariel S. Garten

Ariel Garten, Chris Aimone, David Singh
InteraXon

We are looking at participant's brainwaves and the change in that signal when subject to the intentional action of increasing alpha waves or beta waves (usually by focussing or relaxing) in order to effect a target (lights, visuals, music, etc). We do this with the aim of creating systems that are controllable by or responsive to an individual's brainwave patterns. We have created a number of such interactions using single channel EEG inputs where up to 7000 users have had the opportunity to attempt to interact with or control the targets with their mind. We hope to begin to look at continuous monitoring of brainwaves, exploring how they change over time and what meaningful data we can extract from them when an individual is engaged in a variety of activities and environments- sleeping, walking, thinking, listening
to ipod, etc.

RELEVANCE: The topic of an individual exerting control over their brainwaves by actively using one's brain to change itself, as well as using ones brainwaves alone to exert direct control and agency over parts of the world speaks directly to the theme of the conference.

FIELD PROGRAMMABLE GATE ARRAY (FPGA) BASED RESPONSIVE NEUROSTIMULATORS

Joshua A. Dian

Joshua Dian[2], Osbert Zalay[1], Sinisa Colic[2] and Berj L Bardakjian[1,2]
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Electrical stimulation has long appeared to be an attractive method to control seizures in the epileptic brain. Much research has been conducted on electrical stimulation; however, the majority of work has concentrated on simple biphasic square pulses of varying frequency and duty cycle. Continuous stimulation has produced mixed results with no clear trend suggesting a particular frequency or duty cycle as most effective. Recently, responsive stimulators have been developed that integrate seizure detection with stimulation systems and have shown promise in being more effective; however, they also produce inconsistent results and a large set of tunable parameters.

Complex stimulation systems, including those based on neural networks and Cognitive Rhythm Generators (CRGs) have numerous advantages including the ability to naturally adapt to the underlying system dynamics and the application of biologically relevant stimuli. Complex stimulators have a much larger computational burden often precluding their use in real-time applications. We propose the use of the Xilinx System Generator toolkit to implement the stimulator on an FPGA and hardware co-simulation as an ideal method for testing and verification. FPGAs provide an ideal medium for implementing real time stimulators as an intermediary step prior to the complex and costly application specific integrated circuit (ASIC) design process.

Featured Speaker

STORIES, THOUGHTS, AND TEACHINGS: A FIRST NATIONS PERSPECTIVE ON HEALING

Mark "Cat" Criger

Helper

Elder-In-Residence

University of Toronto Mississauga

First Nations House

SPOKEN NARRATIVE

CAN X-RAYS ILLUMINATE A NEUROANATOMICAL AND SOCIAL COGNITIVE CONNECTION IN WILLIAMS SYNDROME?

Ann Lam

Ann Lam[1,2] and Elan Liss Ohayon[2,3]
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Salk Institute for Biological Studies

There is a complex array of characteristics observed in Williams Syndrome (WS) individuals, including: increased sociability, anxiety and phobias related to non-social contexts, distinctive use of expressive language as a social tool, affinity to faces and difficulty with non-social abstraction. These characteristics have been examined in a number of functional, neuroanatomical, and genetic studies.

One central question underlying the potential interaction between the complex behavior and genes is: what role does neural structure play in social cognition in WS? In this study we examine several brain structures in WS and typical developing individuals that may be involved in social cognition. These structures include: the orbital frontal cortex, fusiform cortex, basal ganglia, hippocampus and amygdala. Synchrotron-based x-ray fluorescence imaging was used to examine post-mortem brain samples. Rasterized images were generated based on intensity of fluorescence for elements selected for possible biological relevance. Qualitative analysis showed excellent resolution between grey and white matter, and distinction between brain structures based on their elemental composition. The imaging provides a non-destructive way to examine the possible relation between brain structures and activity. Further comparisons with histological techniques may be useful in correlating structural features with functional recordings and network models of cognition. X-ray fluorescence imaging thus presents a new way of looking at structures and factors that we may have forgotten to consider.

RELEVANCE: Williams Syndrome is a prime example of classifications we make using genes and behavior. The ever increasing focus on "what genes do" in current research may lead to a considerable loss of autonomy. In this presentation we strive to set the stage to pose the larger question of whether genetics and neural structure are independent players or interactive intermediaries in the social "phenotype" of WS.

WOMEN WITH EPILEPSY (WWE) IN ONTARIO: KNOWLEDGE GAPS AND INFORMATION NEEDS

Tarek Abd El Halim

Tarek Abd El Halim[1], Ms. Dianna Findlay[2], Eduard Bercovici[1], Dr. Taufik Valiante[1]
[1]University of Toronto, [2]Epilepsy Ontario

PURPOSE: The purpose of this study was to identify how adult women with epilepsy in

Ontario obtained information with regard to their health. We also wanted to identify the overall health literacy of our sample population using different surrogate measures.

METHODOLOGY: We used an ecological survey design with a mixture of quantitative and qualitative questions to gather the relevant data. The survey was administered online using SurveyMonkey.com

RESULTS: We recruited 50 participants with an average age of 38.3 (range 19 to 71). The participants had a self-reported diagnosis of epilepsy and were residents of Ontario. The results from this study illustrate that despite a population with a high degree of self-efficacy and health literacy, there were still significant gaps in knowledge with regards to the side effects of anti-seizure medications.

This was also found to be an area of great interest to our sample population through qualitative analysis. Moreover, there appears to be specific sources of information that our study sample was more likely to utilize to learn about epilepsy, such as a neurologist (96%), the internet (92%), and pamphlets or brochures (78%).

CONCLUSIONS: There is a need for more information from health care practitioners, and for more support in the form of community organizations such as Epilepsy Ontario and other advocacy groups.

SHIFTING AWAY FROM THE POSTAL CODE LOTTERY OF HEALTH CARE - ENSURING ACCESS TO SAFE, ACCURATE, HIGH QUALITY CARE FOR ALL THROUGH ORGANIZED CHRONIC DISEASE MANAGEMENT SYSTEMS

Kirk Nylen

Cancer Care Ontario; University of Toronto Epilepsy Research Program

Where are we? Where do we want to go? How will we get there? How will we know?

These are the basic tenants of strategic planning. In terms of chronic disease management, in most areas of the world, the answer to the first question does not paint a happy picture. For example, a study by McGlynn and colleagues in 2003 (NEJM) found that only 56% of patients were given the recommended treatment for their chronic disease. We would like to move toward a system where patient care is driven by evidence-based and experience-informed standards and guidelines for high quality care. This system should be organized in a way that ensures equitable access to care and empowers the individual to be an active player in their care. This talk will outline the role of chronic disease management systems as well as some simple innovations in ensuring access to safe, accurate and high quality care for those living with chronic disease.

RELEVANCE: This talk speaks specifically to the autonomy of individuals with chronic disease, the development of chronic disease management systems and then subsequent empowerment of patients to play an active role in their care.

THE EFFECTS OF TORONTO POLICE SERVICES' TACTICS ON THE ABILITY OF HOMELESS, ILLEGAL-DRUG CONSUMING INDIVIDUALS TO PRACTICE HARM REDUCTION: A MIXED METHODS STUDY

Trish Lenz

York University

This research study explores the ramifications of an intensive police effort to reduce public drug use and disorder via a policing tactic known as a "crackdown" upon homeless illegal-drug using individuals in Toronto. Specifically, this research study focused on the March 2009 crackdown in 14 Division labeled "Project Deuce." Narrative interviews were conducted with four participants who frequented a needle exchange in downtown Toronto. As well, statistics from the needle exchange were used to quantitatively analyze the impact that the crackdown had upon needle exchange attendance and supplies given out. Aggregate mean values from during the crackdown were compared with means from the post crackdown three week period. Data was also compared in the pre- and post-crackdown time periods of three months, six months, and nine months. Interview topics included the exploration of how crackdown tactics such as intensified officer presence on the street, heightened surveillance and under-cover operations affected participants' ability to employ harm reduction practices when using illegal-drugs. The data was analyzed using open, axial and selective coding and was categorized into themes exploring the health related impacts of the Toronto Police Services' policing tactics, as well as the impact of such actions upon the dignity and self-esteem of study participants. The analysis found that study participants were less willing to utilize the Needle Exchange and less willing to carry harm reduction paraphernalia during the crackdown. Study participants' dignity and self-respect was also implicated by the crackdown, as the internalization of neo-liberal norms and values pervasively coloured participants understanding of their rights and freedoms as homeless, illegal drug-using individuals. Given these findings, this study recommends the discontinuation of the tactic of police crackdowns and advocates for the adoption of policies and procedures that respect the individual health and humanness of illegal-drug users.

Keywords: Homelessness; Harm Reduction; Policing

RELEVANCE: Illegal drug use has been politicized, moralized and demonized in our society, due largely to the inception and continued policy of prohibition. This study is based upon harm reduction principles and philosophy and therefore supports a health-based approach to illegal drug use, as opposed to criminalization. This study is based on harm reduction principles and philosophy in that illegal drug use is not judged as being inherently good or bad, and instead takes a health perspective in which the practice of consuming illegal drugs as safely as possible for the individual, and the health and safety of the community at large, is supported. This study advocates for both a change in Toronto Police Services' Response to illegal drug use amongst homeless individuals and a change in policy/legislation regarding illegal drug consumption such that harm reduction practices may be practiced without fear of negative repercussions at the hands of law enforcement officers.

SPATIOTEMPORAL INVESTIGATION OF GAMMA ACTIVITY IN THE HUMAN EPILEPTIC BRAIN

Marija Cotic

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Gamma activity in the brain (30-100 Hz) has been proposed as a candidate mechanism for connecting or 'binding' spatially distributed brain activities. As a result, numerous studies have focused on the study of gamma 'locking'-within its respective frequency range-, with a particular emphasis placed on the 40 Hz band. The properties of gamma activity have also been closely examined in relation to epilepsy, as the pathological locking of seizure discharges indicates a disturbance in the integration of cortical activities. We have applied wavelet phase coherence analyses to study phase associations related to gamma-frequency activity between channels of multisite intracranial electroencephalographic (ICEEG) recordings from epilepsy patients. Our analysis also involved the study of phase difference distributions between ICEEG channel pairs at various frequencies. Gamma phase coherence profiles varied temporally across preictal, ictal and postictal epochs as well as spatially between recording electrodes positioned closer and farther from seizure discharge zones. Gamma phase coherence increased during the transition to seizure and appeared strongest postictally. In conclusion, spatiotemporal profiles of neural channel phase differences may provide further insights into the initiation, maintenance and spread of epileptic foci or activity by revealing distinctive patterns of frequency-specific phase coherence and/or decoherence associated with the pathological coupling observed in the epileptic brain.

TIME VARYING SPECTRAL FEATURES DURING ANESTHESIA

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The administration of the anesthetic agents is known to alter the electroencephalogram (EEG) signal significantly as the brain being their primary target. Thus incorporating some analysis of EEG in the assessment of the depth of anesthesia (DoA) have been an active research area for many years. Although there have been many promising results, their reliability and clinical utility are still debatable. In this study, we analyzed the EEG recorded from six ASA I/II patients undergoing 1-2 hour surgery. The EEG was collected before and during induction, maintenance and recovery of anesthesia using the 10/20 lead-system. A combination of fentanyl and propofol (rocuronium) was the inducing agents and sevoflurane in air/O2 mixture was administered through an endotracheal tube to achieve the steady minimum alveolar concentration (MAC) to maintain haemodynamic responses during surgical stimulation within 25% of baseline. The collected time series EEG signals were decomposed into the time-frequency domain using the wavelet packet transformation. The power of the EEG signal varied both in time and frequency as the DoA was changed. There were a number of identifiable rhythms, some of which persisted throughout the entire operation but altered their peak frequency with the change of DoA. On the other hand, some rhythms emerged and disappeared as the DoA was changed. In this case, the rhythm was distinct feature to a particular DoA. In addition, phase coherences between different electrodes were investigated using the wavelet coherence and showed that the anesthetics enhanced the phase coherence in the high frequency (60 to 200 hz). The time-varying spectral features add another dimension to the currently available monitoring techniques and can improve the reliability and accuracy of monitoring of DoA.

RELEVANCE: This study examines the changes in neurodynamics during the anesthesia by means of EEG signals and its various features to better classify the different states of the brain.

AUTONOMOUS AGENTS AND THE PATHOPHYSIOLOGY OF PARKINSON'S DISEASE

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In evolutionary autonomous agents that are capable of both visually guided, reactive and learned automatic movements, single lesions in their neural network controller resulted in the simultaneous occurrence of bradykinesia and the loss of the ability to perform learned automatic movements, deficits typical of Parkinson's disease. This suggests that these deficits occur as the result of generic network properties in systems with similar functional capabilities and are not necessarily the result of the idiosyncratic organization of the human nervous system. It points to an approach to movement disorders that emphasizes the identification of global dynamical patterns in the space of dynamics from the controller of systems that are embodied, contextual and normative, regardless of whether the system is naturally occurring or artificially synthesized. The use of evolutionary robots to model global motor properties provides a unique perspective in motor pathophysiology that complements that provided by either detailed computational models or experimental neurosciences.

RELEVANCE: The use of autonomous agents whose controller is a dynamical neural network allows the identification of global dynamical patterns in the controller that may serve as the basis for movement generation in all agents with similar functional capabilities regardless of whether the agent is human or synthetic.

ROUTES AND ROADBLOCKS TO AUTONOMOUS NEURODYNAMICS IN TIME, SPACE AND SOCIAL CONTEXTS

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Six years have passed since the first SAND meeting in Toronto. Computers have become considerably faster. Anatomical and physiological techniques are more precise. Modeling and mathematical approaches are increasing in complexity and sophistication. But are these apparent advancements in tools and scientific methodology bringing us closer to an understanding of autonomous neurodynamics?

I will review some findings presented in previous SAND meetings and will argue that some of these principles are indeed leading to a better understanding of the brain's ability to interact with the world in a free manner. These trends include the growing appreciation for the importance of the spatial and temporal features of brain structure and its ongoing embodied activity in a dynamical world.

However, I will also argue that many of our methodologies and paradigms are - paradoxically - undermining the very object of study. That is, approaches that focus on disembodied simulation, systems control and clinical categorization of individuals are increasingly raising roadblocks and eroding autonomy. At the core of this failure lies a disregard for the social context of the brain, including the social factors that define its development and growth. More acutely, this social context extends and applies to the very act of scientific investigation potentially resulting in entirely unintended negative consequences.

DYNAMICS OF SYNCHRONY AND PLASTICITY

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OBJECTIVES: We have shown earlier that lumped neuronal models can feature transitions between different patterns of dynamic behaviour. This phenomenon, called multi-stability, may be responsible for the clinical condition of epilepsy. Statistical analysis of the ictal and inter-ictal time intervals in both animal models of epilepsy and in a variety of clinical cases of this disease indicates that epileptic seizures might be due to fluctuation induced transitions to oscillatory states. Same analysis have shown however that seizure termination in some cases cannot be explained by the above mechanism alone. The central objective of this work is to expand the dynamic degrees of freedom of our models by introducing distributed and connected neuronal systems with synaptic plasticity. We investigate the effect of the connectivity and plasticity on the features of seizure generation.

METHODS: We use realistic models of neuronal dynamics that emulate known physiological facts. To extract the relevant analytical features of these models, metaphoric models of coupled bi-stable rotators are considered in parallel.

RESULTS: (1) Realistic models are indispensible in translating biological reality into abstract dynamic paradigm. Metaphoric analytical models, like the bi-stable rotator, can take over the description of large-scale phenomena. (2) A network of excitable (bi-stable) rotators is a natural extension of the Hopfield model of pattern retrieval. Phase-locked but otherwise autonomous states may provide the tool for designing resettable pattern recognition and unsupervised learning dynamics. (3) Simple models of plastic interactions can explain the deviation of the statistics of seizure durations from the model of random transitions.

BRAIN STATE CLASSIFICATION IN EPILEPSY AND ANAESTHESIA

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Transitions between normal and pathological brain states are manifested differently in the electroencephalogram (EEG). Traditional discrimination of these states is often subject to bias and strict definitions. A fuzzy logic-based analysis can permit the classification and tracking of brain states in a non-subjective and unsupervised manner. In this thesis, the combination of fuzzy c-means (FCM) clustering, wavelet, and information theory has revealed notable frequency features in epilepsy and anaesthetic-induced unconsciousness. It was shown that entropy changes in membership functions correlate to specific epileptiform activity and changes in anaesthetic dosages. Seizure episodes appeared in the 31-39 Hz band, suggesting changes in cortical functional organization. The induction of anaesthetics appeared in the 64-72 Hz band, while the return to consciousness appeared in the 32-40 Hz band. Changes in FCM activity were associated with the concentration of anaesthetics. These results can help with the treatment of epilepsy and the safe administration of anaesthesia.

RELEVANCE: My research attempts to extract features that demarcate brain state transitions in epilepsy and anaesthetic-induced unconsciousness.

FETAL ETHANOL EXPOSURE AND POSTNATAL BRAIN HYPEREXCITABILITY: "THE TIP OF THE NEUROBEHAVIOURAL NIGHTMARE"

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Individuals with the Fetal Alcohol Spectrum Disorder (FASD)are exposed to ethanol via their mothers during gestation. Our group hypothesized that this prenatal ethanol exposure could lead to a higher incidence than normal of epilepsy in this population. A retrospective chart review was conducted on all active charts (n=1063) at St. Michael's Hospital (Toronto, Ontario) and Glenrose Rehabilitation Hospital (Edmonton, Alberta) FASD clinics. Applying strict exclusion criteria left us with 425 subjects with a diagnosis of FASD. Twenty-five (5.9%) individuals had a confirmed diagnosis of epilepsy, and 50 (11.8%) had at least one documented seizure episode, yielding an overall prevalence of 17.7% in this population. When available, drinking histories indicated at least first trimester alcohol exposure.

We then turned to an animal model of the FASD. Guinea pigs prenatally exposed to 5% EtOH exhibit epileptiform activity in the hippocampal CA1 region if exposed at least in the first trimester, but not in the second and 3rd trimesters alone. Chemical synaptic transmission blockade (10 uM CNQX, 60 uM APV, and 10 uM gabazine), remarkably, did not stop the epileptiform activity, whereas gap junctional blockers (300 uM octanol, n = 9; 100 uM carbenoxolone, n = 5) did stop this intrinsic brain hyperexcitability. We suggest that this novel brain hyperexcitability, based on gap junctional communication, underlies, at least in part, the marked neurobehavioural abnormalities in the FASD population and deserves further study to understand the basic mechanisms, so as to devise appropriate treatment strategies.

RELEVANCE: A hyperexcitable brain state brought on by prenatal toxic exposure, leading to a lifelong neurobehavioural disability.

HOW LONG IS "NOW"?

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Can we design a computer with an artificial sense of "Now"? What would constitute an operational definition of "Now"? What are the neurological correlates of "Now"?

Philosophically the "Now" is a difficult concept. The concept of "Now" can only be had "now". While questions about the "Now" are closely related to questions about consciousness it is perhaps easier to come up with operational definitions of "now" than those of consciousness. Phenomenologically the "Now" has a certain thickness extending from that which happened to that which is about to happen. (Husserl's analysis of duration comes to mind.)

The relationship between a good "Now" and the whole time axis stretching from the past into the future is reminiscent of the way in which the unit sphere maps unto the whole plane in projective geometry. (A small circle not only maps onto the whole line but is also highly self-referential.)

The NCC (or the neural correlates of consciousness) is made of a spatial part and a dynamic part. While it's fair to say that we still can't pinpoint the neural geography of the "Now" and the multi-level dynamics that correlate with it, it is nevertheless instructive t to consider the relatively simple case of "place neurons".

Following Lisman's 2005 paper[1] on place neuron precession and recent work on Working Memory I will speculate on the length of the duration that harbors the "Now". I will argue that that duration itself constitutes a 150 ms (or so) dynamic recapitulation of much longer processes belonging both to the past and the future.

(1) The Theta/Gamma Discrete Phase Code Occuring During the Hippocampal Phase Precession May be a More General Brain Coding Scheme. John Lisman. HIPPOCAMPUS 15:913-922 (2005)

RELEVANCE: Can you have autonomy without a sense of now?

NOTES: