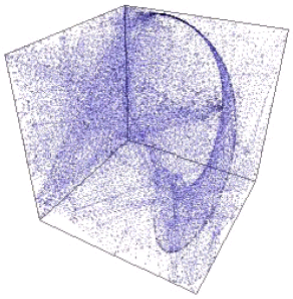
PRINCIPLES OF AUTONOMOUS NEURODYNAMICS 2007
Québec, Canada
August 20-22, 2007



4th Annual Meeting of the Society for Autonomous Neurodynamics (SAND)

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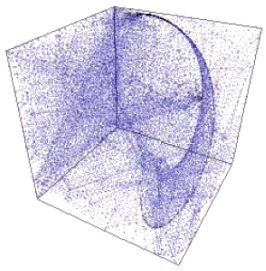

PRINCIPLES OF AUTONOMOUS NEURODYNAMICS 2007
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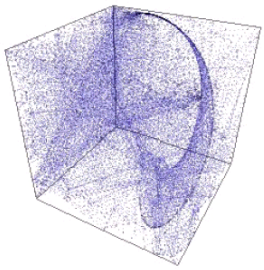
Monday, August 20 - Program Schedule

Registration		09:00 - 09:30	
THEME: Introduction, Theory and Embodiment	**Chair: Stiliyan Kalitzin**		
Kathryn Hum	Opening Remarks	09:30 - 09:35	
Igor Timofeev	Host Laboratory and CRULRG Welcome	09:35 - 09:45	
Elan Liss Ohayon	Open questions in autonomous neurodynamics	09:45 - 10:05	*p.1*
Miriam Madsen	Intermittent oscillations in simple cellular automata: Computational models of seizures and physiologic episodic oscillations	10:05 - 10:25	*p.2*
Ping Wang	When androids dream of electric sheep: neuromorphic engineering applications in neuroscience	10:25 - 10:45	*p.2*
	Group discussion	10:45 - 10:50	
	Coffee break	10:50 - 11:00	
THEME: Clinical Investigations and Autonomy	**Chair: Ameer Taha**		
Paul Hwang	Pathophysiological mechanisms in central perturbations of brain functions: An hypothesis	11:00 - 11:20	*p.3*
Steven Claus	Wave gazing by expanding the scope: see 'm all to find the one	11:20 - 11:40	*p.4*
Stiliyan Kalitzin	Does photosensitive epilepsy restrict patient's cognitive autonomy?	11:40 - 12:00	*p.5*
	Group discussion	12:00 - 12:10	
	Lunch	12:10 - 13:30	
THEME: Learning, Adaptation and Consciousness	**Chair: Piotr Suffczynski**		
Mohamed Abdelghani	Sensitivity Derivatives for Flexible Sensorimotor Learning	13:30 - 13:50	*p.6*
Kristen Fortney	Biological plausibility of kernel-based learning	13:50 - 14:10	*p.6*
Douglas Tweed	Optimal Sensorimotor control through generalized Hamilton-Jacobi-Bellman equations	14:10 - 14:30	*p.7*
Uziel Awret	Autonomous systems, peripheral self awareness and free will	14:30 - 14:50	*p.7*
	Group discussion	14:50 - 15:00	
	Coffee break	15:00 - 15:10	
THEME: Dynamics in Aging, Neurodegeneration & Epilepsy	**Chair: Liang Zhang**		
Marta Wais	Hypoxia-induced seizures in aged mice	15:10 - 15:30	*p.8*
Shun-ting Chang	The impact of 4-aminopyridine on aging-dependent hippocampal sharp waves	15:30 - 15:50	*p.9*
Wilson Yu	Hippocampal CA3 interneuronal responses to elevated [K+]e	15:50 - 16:10	*p.9*
	Group discussion	16:10 - 16:20	
Kathryn Hum	Closing remarks and announcements	16:20 - 16:30	



PRINCIPLES OF AUTONOMOUS NEURODYNAMICS 2007
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Tuesday, August 21 - Program Schedule

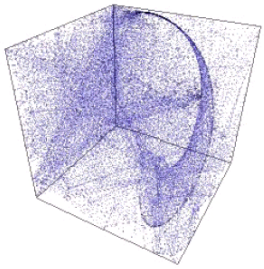
THEME: Analysis, Noise and Prediction		Chair: Eunji Kang	
Kathryn Hum	Opening Remarks and announcements	09:30 - 09:40	
Marija Cotic	Spatiotemporal investigation of hippocampal electrical activity using adaptive filters	09:40 - 10:00	*p.10*
Demitre Serletis	'Observable fluctuations' in the healthy mouse brain: A 'noisy' analysis	10:00 - 10:20	*p.10*
Piotr Suffczynski	Seizure prediction - do we have to stimulate?	10:20 - 10:40	*p.11*
	Group discussion	10:40 - 10:50	
	Coffee break	10:50 - 11:00	

THEME: Sleep and Neurodynamics		Chair: Igor Timofeev	
Sylvain Chauvette	Leading role of the deep intrinsically-bursting cells in the generation of active state during slow-wave sleep	11:00 - 11:20	*p.11*
Daniel Kroeger	Beyond the isoelectric line: Novel activity patterns in the anesthesia-induced comatose brain	11:20 - 11:40	*p.12*
Eunji Kang	Issues of EEG analysis and anesthesia	11:40 - 12:00	*p.12*
Liang Zhang	Adenosine: A local modulator of hippocampal sharp waves	12:00 - 12:20	*p.13*
	Group discussion	12:20 - 12:30	
	Lunch	12:30 - 13:30	

THEME: Neurodynamics - Physiology and Basic Mechanisms		Chair: Kristen Fortney	
Igor Timofeev	Postsynaptic impact of EPSPs and MINIs on neocortical neurons in vivo	13:30 - 13:50	*p.13*
Reza Zomorrodi	Small window of T-channel numbers influences the response of the thalamocortical cell	13:50 - 14:10	*p.14*
Éliane Proulx	A role for the thalamus in hippocampo-prefrontal interactions	14:10 - 14:30	*p.14*
	Group discussion	14:30 - 14:40	
	Coffee break	14:40 - 14:50	

THEME: Nutrition and Hormones		Chair: Ping Wang	
Elena Timofeeva	Neuronal dynamics linking food anticipation and feeding states	14:50 - 15:10	*p.15*
Ameer Taha	Evidence for the anticonvulsant effects of omega-3 polyunsaturated fatty acids in rats and mice	15:10 - 15:30	*p.15*
Kathryn Hum	The effects of right and left seizures on reproduction and feeding	15:30 - 15:50	*p.16*
	Group discussion	15:50 - 16:00	

THEME: Personal Narrative		Chair: Paul Hwang	
Melanie Jeffrey	The Journey So Far: My First Ten Year with Epilepsy	16:00 - 16:20	*p.17*
	Group discussion	16:20 - 16:30	
Kathryn Hum	Closing remarks and announcements	16:30 - 16:40	



PRINCIPLES OF AUTONOMOUS NEURODYNAMICS 2007
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Wednesday, August 22 - Program Schedule

FEATURED SPEAKER: Peter L. Carlen, Toronto Western Research Institute

Marija Cotic	Introduction	09:30 - 09:40	
Peter Carlen	Perception Is Not Reality: The Many Reasons For Our Misunderstandings Of Brain Dynamics And Epilepsy	09:40 - 10:10	p.19
	Group discussion	10:10 - 10:20	

ROUNDTABLE DISCUSSION I - Society for Autonomous Neurodynamics - The Next Step
Chairs: Peter Carlen & Stiliyan Kalitzin

Peter Carlen & Stiliyan Kalitzin	Overview of the upcoming special issue of the International Journal of Neural Systems (IJNS)	10:20 - 10:30	p.21
Round Table	Discussion of the IJNS issue and other publication, collaboration and organizational initiatives	10:30 - 10:50	
	Coffee break	10:50 - 11:00	

ROUNDTABLE DISCUSSION II - Autonomous Neurodynamics - What Are We Missing?
Chairs: Piotr Suffczynski & Elan Liss Ohayon

Round Table	Discussion of future directions in autonomous neurodynamics: questions, theory and research	11:00 - 11:50
Peter Carlen & Kathryn Hum	Closing remarks	11:50 - 12:00

Post Presentation Events: August 22 - August 25

OPEN QUESTIONS IN AUTONOMOUS NEURODYNAMICS

Elan Liss Ohayon
University of Toronto Epilepsy Research Program & Collaborative Program in Neuroscience, University of Toronto

This presentation will consist of an overview of some open questions in autonomous neurodynamics and review some research findings. I will suggest that answers to some of these questions might have profound implications to our understanding of behaviour, clinical practice and neuroscience as well as research in other fields. Some of the questions include:

- *What does "autonomous neurodynamics" mean? What would count as a principle of autonomous neurodynamics?*
- *How, where and when should we be looking? At what spatial scale and detail should the phenomena be studied? At what temporal scale?*
- *What are the appropriate forms or levels of description? Are these various forms/levels mutually exclusive? Supervenient? Interactive?*
- *What are the relevant categories of dynamics and what role does each play in cognition?*
- *What are the mechanisms of transition in brain activity and structure? How do these relate to autonomy?*
- *What is the relationship between structure and dynamics? Is it functional? Monotonic? Which architectures are most likely to generate a given type of dynamic? Conversely, how do dynamics shape brain structure? What is the nature of the interplay between structure and activity and how is this related to voluntary behaviour?*
- *What role do plasticity and adaptation play in autonomous dynamics? What are the types of plasticity that can avoid lock-up?*
- *What roles do entropy, determinism and noise play in autonomy? What are the disadvantages and advantages of relying on stochasticity?*
- *What is the relation of the study of autonomous neurodynamics to neuroscience research and other fields? For example, what problems in mathematics do we need to solve in order to understand autonomous neurodynamics? Can autonomous neurodynamics shed light on problems in mathematics?*
- *What can computational theory teach us about autonomous neurodynamics? What can autonomous neurodynamics teach us about computation? Do neural systems have computational limits? What computational limits do autonomous biological systems overcome and how?*
- *Can autonomous neurodynamics be statistically characterized? Can transitions be predicted? Should they be predicted?*
- *What are the clinical implications of autonomous neurodynamics research? What do clinical conditions teach us about autonomous neurodynamics? What can we learn from epilepsy, aging and neurodegeneration?*
- *What are we to make of sleep and hallucinations? Are these free modes of brain activity? If not, why not? If yes, what differentiates these from being awake?*
- *What is the relation of autonomous neurodynamics to consciousness? Is it simply a matter of complexity? For example, are autonomous neurodynamic zombies possible? Impossible? Unavoidable? Is the concept incoherent or does it point to a central question?*
- *What are the environmental factors shaping autonomy? How do autonomous neurodynamics shape the environment? Can autonomous behaviour be counted as a separate factor beyond nature and nurture? Are these divisions faulty?*
- *How do we individuate an autonomous organism? What is the role of embodiment? How do autonomous neurodynamics relate to identity? Will the study of autonomous dynamical systems effect and affect autonomy? How are autonomous neurodynamics conscientiously maintained and increased?*
- *What are our biases?*
- *Which questions are not critical? Which answers are uninformative?*
- *What questions haven't we even imagined?*

INTERMITTENT OSCILLATIONS IN SIMPLE CELLULAR AUTOMATA: COMPUTATIONAL MODELS OF SEIZURES AND PHYSIOLOGIC EPISODIC OSCILLATIONS

Miriam A.R. Madsen

Miriam Madsen & Joseph Madsen
Neurosurgery, Children's Hospital Boston, Massachusetts Institute of Technology

What is the simplest mathematical model capable of going in and out of an oscillatory state? Behavior of large networks of neurons can be correlated with field recordings including those used clinically in electroencephalography (EEG) and electrocorticography (EcoG). Oscillations are a prominent feature of these recordings, which must represent synchronous cellular activity. Many models of complex systems result in stable, persistent oscillations, but oscillations seen with physiological cortical activity (such as memory storage) or pathology (such as seizures) tend to turn on and off. We questioned whether simple dynamic models representing a binary output in each cell depending on the output in the previous time epoch in a small number of cells could achieve such an intermittent oscillatory effect. With the simplest Cellular Automata (CA) with one dimension and k = 2 [two possible positions for each cell] and r=1 [value of each cell determined by corresponding cell in prior generation and one cell on either side] we sought intermittent oscillations by examining computer output of a single cell run over 211 * 100 generations, analyzed as a series of 8-bit numbers in groups of 256 by Fourier analysis in Mathematica. All rules which rapidly entered a uniform or permanently oscillating pattern were systematically excluded from consideration by a screening program. Some of the remaining rules showed the potential for more complexity: for many Wolfram Class IV rules (Wolfram 1983), such as rule 110, starburst-like patterns with gradual build-up and release of particular frequency bands seem reminiscent of EEG activity during seizures. For other rules, a speckled pattern appears. These are the two most complex of five general pattern types observed. We conclude that even very simple systems (CA with k=2, r=1) can show intermittent oscillations.

WHEN ANDROIDS DREAM OF ELECTRIC SHEEP: NEUROMORPHIC ENGINEERING APPLICATIONS IN NEUROSCIENCE

Ping Wang

Ping Wang & Terrence Sejnowski
Salk Institute for Biological Studies

Autonomy infers realtime intelligent systems working in complex natural environments. Artificial neural systems are one way to achieve understanding in that realm. At the crossroads of neuroscience and engineering, while biological inspiration influences robotics and machine learning, on the other hand, scientists apply engineering principles to understand brain circuitry. One developing area that enables both usages is the use of analog VLSI circuitry to mimic neural systems. This allows energy efficient, massively scalable, realtime, embodied computational systems that are useful not only in robotics, but also as a platform for neuroscientific studies. As an example, we demonstrate the use of an artificial retina and an artificial cortical network for the study of spike time synchrony in temporal coding.

PATHOPHYSIOLOGICAL MECHANISMS IN CENTRAL PERTURBATIONS OF BRAIN FUNCTIONS: AN HYPOTHESIS

Paul Hwang

Paul A. Hwang, Homan Cheng, Cecile Alquier, Miles Thompson, Kevin Lam,
Michael Sumner and A.O. Ogunmekan
University of Toronto Epilepsy Research Program, Paediatric Neurology Division, Department of Paediatrics North York General Hospital, Institute of Medical Science University of Toronto

The brain responds to injury in similar stereotypic reactions. Initial cerebral insult is followed immediately by an acute loss of function: “brain shock”. There is a second phase of attempted compensation, with recovery of some functions initially lost in the original injury. Then a third phase of over-compensation for the initial loss, resulting in excessive function, often pathological, resulting in hyperexcitability, synchronization and recruitment of other brain regions.

We hypothesize that recovery from cerebral injury evolves through 3 phases:

1. Initial acute loss of function (“brain shock”)
2. Compensatory recovery of function (recovery phase), and then
3. Overcompensation for functional loss (hyperexcitability phase).

In localisation-related epilepsies, symptomatic (secondary to brain lesions), initial injury results in functional loss, then synaptic reorganization leads to neuronal hyperexcitability and synchronization, producing recurrent seizures. Spasticity due to upper motor neuron lesions as in stroke, produces initial loss of function leads to paralysis, then hyperreflexia ending in spastic hemiplegia . In central pain mechanisms (as in neuropathic pain), loss of large fiber-mediated somatosensory input opens the “gate control” allowing nociceptive afferent input, reorganization of central pain mechanisms, such as in opioid-induced hyperalgesia due the organization of periadequctal gray activity. In these 3 examples, there is initial functional loss, compensatory mechanisms leading to excessive functional capacity of neuronal circuits producing pathophysiological functions: epileptic seizures, spasticity or neuropathic pain. The final common pathway in response to acute injury may reside in axonal sprouting leading to excessive and pathological functions.

WAVE GAZING BY EXPANDING THE SCOPE: SEE 'M ALL TO FIND THE ONE
Steven Claus

Steven Claus, Demetrios Velis, Stiliyan Kalitzin
Dutch Epilepsy Foundation Netherlands (SEIN)

Purpose: we have recently demonstrated an association of asymmetry in pharmacologically induced modulation of beta activity and the cerebral hemisphere that contains an epileptogenic lesion in five patients. However, the measurement and analysis results may have been equivocal. Scalp EEG measurements contain confounding signals such as physiological artefacts mainly originating from contracting muscles in addition to fluctuations in the summation of dendritic potentials. We compared measurements of MEG and scalp EEG to see if magnetic field fluctuations caused by neuronal activity result in a cleaner signal as opposed to that recorded by EEG that will enable a wider range of epoch selection before and after the administration of the perturbing pharmacon, and to see if the localization of the epileptogenic lesion will be more reliable.

Methods: we retrospectively analyzed data recorded off five patients with MRI-identified lesions who were evaluated for epilepsy surgery. Half an hour before their co-registered scalp EEG/MEG they had received a single oral dose secobarbital (a short lasting barbiturate) as a sleep-inducer. We use Gabor filters to determine the power of frequencies in the EEG and MEG signal. We compared the first epoch (half an hour after secobarbital administration) to epochs that were recorded 5-30 minutes after the first epoch.

Results: the principal components of cerebral origin in the EEG and MEG measurements seem to be the same. The MEG signal appears to contain a wider spectrum of frequencies of purported cerebral than of extra cerebral origin. Localization and lateralization of the epileptogenic lesion remains an issue, irrespective of whether the MEG or the scalp EEG signal is analyzed, but the analysis here presented is still in a preliminary stage, lacking the statistical power to validate any such pronouncements. Conclusion: MEG seems to show the same cerebral activity as scalp EEG does in a pharmacological modulation of cerebral activity during sleep. The MEG signal contains less confounding extracerebral frequencies than found in the scalp EEG.

DOES PHOTOSENSITIVE EPILEPSY RESTRICT PATIENT'S COGNITIVE AUTONOMY?

Stiliyan Kalitzin

Stiliyan Kalitzin[1] Jaime Parra[1] Fernando Lopes da Silva[2]
[1]Dutch Epilepsy Clinics Foundation (SEIN), [2] Swammerdam Institute of Life Sciences,
University of Amsterdam, Department of Biology

Photosensitive epilepsy (PSE) is the most common form of reflex epilepsy, affecting up to 10% of epileptic children. Despite the high prevalence of this disorder, little is known about the mechanisms of human PSE. We show that two different classes of stimuli can contribute independently to the pathological responses in patients. In addition to the sensitivity to spatial and temporal light intensity modulations, colour modulations with constant luminosity can also cause photo-paroxysmal responses (PPR). We studied features of the EEG evoked potentials measured with both provocative and non-provocative stimuli and we found that the presence of high frequency components, phase-locked to the stimulus may play an essential role in precipitating PPR. In this context we speculate and present some empiric evidence of a link between photosensitivity and performance in tasks of perceptual grouping. The condition of PSE may restrict the cognitive autonomy of a person, making him/her vulnerable to visual input, including contents from mass media products such as television, computer screens and video games. These devices account for up to 60% of the first seizures in photosensitive patients in the Western world. Until now, only the United Kingdom and Japan had specific norms to limit the broadcasting of epileptogenic sequences. The quantitative analysis of the major factors precipitating PSE has allowed us to design algorithms for detection and for subsequent successful removal of the potential provocative content from video sequences, making them safer for carriers of PSE risk factor, even for those who are unaware of their condition.

SENSITIVITY DERIVATIVES FOR FLEXIBLE SENSORIMOTOR LEARNING
Mohamed Abdelghani

Mohamed Abdelghani, Timothy Lillicrap & Douglas Tweed
Department of Physiology, University of Toronto, Toronto, Ontario, Canada

In control theory, variables called sensitivity derivatives quantify how a system's performance depends on the commands from its controller. Knowledge of these derivatives is a prerequisite for adaptive control, including sensorimotor learning in the brain, but no one has explained how the derivatives themselves could be learned by biological neural net-works, and some say they aren't learned at all but are known innately. Here we show that this knowledge can't be solely innate, given the adaptive flexibility of neural systems. And we show how it could be learned using forms of information transport that are available in the brain. The mechanism, which we call implicit supervision, helps explain the flexibility and speed of sensorimotor learning and our ability to cope with high-dimensional work-spaces, tools, and other task complexities.

BIOLOGICAL PLAUSIBILITY OF KERNEL-BASED LEARNING
Kristen Fortney

Kristen Fortney & Douglas Tweed
Depts. of Physiology and Medicine, and Program in Neuroscience, University of Toronto

Modern machine learning algorithms take advantage of the 'kernel trick', a powerful new tool for increasing the fitting power of linear networks. We argue that kernel-based learning algorithms and, more generally, linear-in-the-parameters learning are more biologically plausible than has been supposed, and that they can be combined with neural-network ideas to gain advantages of both approaches. 1. While linear-in-the-parameters learning is fast, it seems to waste neurons because it doesn't permit as high a ratio of adjustable synapses to cells as does nonlinear learning. But we show that the ratios become comparable as the number of output variables increases - i.e. linear learning becomes plausible when one considers that a brain has to learn many different, high-dimensional tasks. 2. Fast linear algorithms like RLS involve computations with large matrices, but we show that the matrices needn't be represented in transmissible form, in cell firing, but can be stored in synapses, which are much more plentiful than cells in the brain - i.e. there is, plausibly, enough storage space for these matrices. 3. Linear algorithms train just one layer of synapses, but with appropriate internal models we show how the process can be repeated at different stations in series, to get supervised learning at many different layers. 4. We show that it is possible to back-propagate through kernels, without needing the weight transport that is the implausible aspect of backprop, and so get more-effective feature-shaping than is normally possible with kernel methods.

OPTIMAL SENSORIMOTOR CONTROL THROUGH GENERALIZED HAMILTON-JACOBI-BELLMAN EQUATIONS
Douglas Tweed

Douglas Tweed, Lakshminarayan Chinta Venkataswararao
Department of Physiology, University of Toronto, Toronto, Ontario, Canada

The aim of optimal control is to steer an effector, for instance an eyeball or limb, so as to minimize some cost that accumulates over time, such as cumulative deviation from some target state. It is a difficult job, because an action that seems like a good idea now may lead to huge, unexpected costs later on. To avoid this sort of surprise, it would help very much to know the optimal cost-to-go, J*. This is a function which takes as input the current state of the system, x, and yields a value J*(x) which is the total cost you will accumulate from now on, until the end of the task, if you choose your motor command u at each instant according to the optimal control law u = γ*(x). In many problems, once J* is known it is a simple matter to build the optimal controller γ*. Unfortunately J* is hard to calculate, but one way to do it is the method of generalized Hamilton-Jacobi-Bellman equations, recently developed for engineering applications by Saridis, Le e, Beard, Lyshevski, Abu-Khalaf, Lewis and others. Here we adapt this method so it can be implemented entirely in biological neural networks and used for online learning. We show initial simulations and discuss the basic network mechanisms that are needed if this algorithm is to provide a viable theory of adaptive optimal control in the brain.

AUTONOMOUS SYSTEMS, PERIPHERAL SELF AWARENESS AND FREE WILL
Uziel Awret

Uziel Awret & Hava Ziegelman
Department of Computer Science, University of Massachusetts

The purpose of this talk is to try and relate some basic questions about quantifying the autonomy in autonomous systems to the problem of free will. We will try and show that attempts to produce a measure of the autonomy of some system are linked to what we mean by free will. To make this connection we will adopt Uriah Kriegel's distinction between peripheral and focused awareness and especially his 'peripheral self awareness'. We will try and argue that Uriah's peripheral self awareness includes a peripheral awareness of the self as related to the autonomy of the system by virtue of its ability to make autonomous choices.

So, if we are in line in the cafeteria and we don't have to choose chicken or pasta until we reach the cook we may still be looking at our shoes and yet have an awareness of ourselves as autonomous systems interacting with an environment. The question of free will is more a question of the peripheral awareness of a representation of our innate sovereignty which is an irreducible part of our self representation which itself must be part and parcel of any mental state that has anything to do with free will.

HYPOXIA-INDUCED SEIZURES IN AGED MICE
Marta E. Wais

Marta Wais, Chiping Wu, Jesse Gillis and Liang Zhang
Division of Fundamental Neurobiology, Toronto Western Research Institute

Stroke is the third leading cause of death and mainly affects the aging population. A variety of complications can occur after a stroke, including seizures. In fact, 60% of epilepsy cases in the elderly are stroke-related. However, the exact pathophysiology of this deadly combination is not known, making treatment very difficult. Currently, there is no reliable model to study epileptic activity in the aged brain.

The purpose of this study was to determine whether episodes of hypoxia can induce seizures in aging mice. This may then lead to a more effective model for global hypoxia/ischemia and a framework for cellular and molecular studies to determine the exact mechanism of stroke-related epileptogenesis.

Eleven C57 black mice up to 19 months of age were used in this pilot study. Electrodes were implanted into the hippocampus and cerebral cortex to evaluate intra-cranial electroencephalographic (EEG) activity. Each mouse underwent two 15 minute episodes of hypoxia (96% nitrogen, 4% oxygen) 10 minutes apart. This was repeated 2-3 times, approximately seven to ten days apart.

Prior to the challenges, animals exhibited behavioural state-dependent EEGs as previously described. Once challenged, all 11 mice showed motor convulsions and had clear episodes of cortical myoclonus and interictal spikes. In all cases, both the hippocampus and the cortex showed epileptic discharges.

With repeated hypoxia challenges, aged mice appeared susceptible to rhythmic epileptiform discharges. Our data shows for the first time that global hypoxia/ischemia can produce epileptic activity in older animals. We are currently examining the pharmaceutical features and the dynamics of these seizures as well as the prevalence of recurrent spontaneous seizures.

THE IMPACT OF 4-AMINOPYRIDINE ON AGING-DEPENDENT HIPPOCAMPAL SHARP WAVES

Shun-ting Chang

Shun-ting Chang, Chiping Wu, Liang Zhang
Toronto Western Research Institute

The rodent hippocampus exhibits large amplitude potentials called sharp waves (SPWs). The SPWs are thought to participate in hippocampal-neocortical communication and memory process. Previous experiments in our lab have shown that hippocampal slices prepared from adult mice (ages of 3-4 months) were able to generate spontaneous in vitro SPWs, but slices prepared from aging mice (ages of 14-15 months) failed to do so although SPW-like events could be induced by treatments of slices with 4-aminopyridine (4-AP), a clinically used drug known to facilitate the central synaptic activities. We hypothesize that 4-AP may promote the SPW generation in aging hippocampus when applied chronically in vitro. We tested this hypothesis using 4 aged mice (25-26 months), treated by 4-AP at the age of 14 months for 3 weeks, to see whether we can still find SPWs. After dissecting the hippocampus into slices, we did extracellular recordings to detect the SPWs. As a result, a majority of slices showed spontaneous or stimulation-induced SPWs, and these SPWs were similar to those observed from adult mouse hippocampal slices in terms of waveform, regional initiation and pharmacological properties. We speculate that the effects of 4-AP attribute to the functional improvement of aging hippocampal circuit as a result of chronic and moderate stimulation of brain activities.

HIPPOCAMPAL CA3 INTERNEURONAL RESPONSES TO ELEVATED [K+]E

Wilson Yu

Yu W, Fawcett A, Derchansky M, Shin DS & Carlen PL
Toronto Western Research Institute, Toronto Western Hospital, University Health Network

It is well established that seizure-like events (SLE), in vitro and in vivo, are concomitantly observed with increases in extracellular potassium concentrations [K+]e. Although many papers have examined the effects of elevated K+ on neuronal and synaptic plasticity in the hippocampal formation using extra- and intracellular recordings, no one has investigated the effect of various concentrations of K+e, per se, on hippocampal CA3 interneurons. In this study, we used whole-cell patch-clamp recordings in CA3 interneurons to determine the excitability of these cells from 2.5 to 5, 7.5, 8.5, 10 and 12.5 mM K+ bath application. Our data demonstrate that CA3 interneurons are hyper-excited from 5 to 10 mM K+ bath perfusion. At 12.5 mM K+, the interneurons depolarized by 21.4 ± 9.3 mV and exhibited a depression in spontaneous activity, eventually leading to a depolarization block (DB). Interestingly, DB of interneurons with +ve current, to values seen with 12.5 mM K+ bath application, did not mimic the raised K+-mediated attenuation of activity. In fact, a depolarization of 37.9 ± 4.6 mV from the resting membrane potential was required to DB interneurons with +ve current. This K+-mediated DB is possibly mediated by an enhanced ionic conductance since interneurons in this state had lower input resistance (48 ± 14% of pre-treated values) than interneurons depolarized to DP with +ve current (67 ± 8% of pre-clamped values). Taken together, we conclude that elevated bath application of K+e, consistent with concentrations observed during SLE, mostly enhanced the excitability of CA3 interneurons. Only at 12.5 mM [K+]e was interneuronal activity depressed, in part by a yet to be identified increase in ionic conductance. The significance of these findings to neuronal dynamics during SLE has yet to be investigated.

SPATIOTEMPORAL INVESTIGATION OF HIPPOCAMPAL ELECTRICAL ACTIVITY USING ADAPTIVE FILTERS
Marija Cotic

Marija Cotic[1], Miron Derchansky[2], Peter L. Carlen[2,3], Berj L. Bardakjian[1,4]
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A large area of research is currently focused on the development of signal processing tools able to quantify the level of association, synchrony and/or correlation within and between different regions of the brain, as the initiation, maintenance and spread of electrical activity in the brain is still poorly understood. Such tools have provided effective analysis options, but are constrained by limitations, such as stationarity conditions, time-frequency resolution and the inability to identify non-concurrent commonalities arising from shifts or delays in signal conduction. METHODS: We are proposing the application of adaptive linear filters for an organised investigation of electrical activity in the brain. Adaptive filters are advantageous in system identification, as they are able to self-adjust their frequency response with time, as a function of the input signal. We use an adaptive filter model with the least mean square (LMS) algorithm, to track the changes of the frequency response of the system. Here we have implemented our adaptive filter model to characterize and track the short term changes from four simultaneous extracellular field recordings in the CA1 region of the intact mouse hippocampus in a low-Mg2+ epilepsy model. The adaptive filter system provided the input-output response of our model temporally, across individual channels, and spatiotemporally, between neighbouring recording sites. DISCUSSION: The development of effective signal processing tools-which aid in characterizing the spatiotemporal spread of electrical activity in the brain-would lead to a deeper understanding of cellular and network function during normal and pathological neuronal processes.

'OBSERVABLE FLUCTUATIONS' IN THE HEALTHY MOUSE BRAIN: A 'NOISY' ANALYSIS
Demitre Serletis

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To most scientists, noise is disruptive, detrimental, and uninformative. Great efforts are made to eliminate noise from experimental recordings, at the potential expense of losing relevant, and often times, critical information pertaining to the dynamical activity inherent to the brain. However, it has become evident that a more rigorous approach to subthreshold fluctuations in brain activity, which we refer to as 'observable fluctuations' (to differentiate from the all-encompassing term, 'noise'), is necessary and fruitful. In particular, recent studies confirm that certain 'noisy' elements reveal underlying details regarding transitions of neural network states – these elements include, amongst others, synaptic channels and gap junctions.

This study will therefore focus on the 'observable fluctuations' inherent to the healthy mouse brain. Specifically, we propose to analyze the baseline characteristics of subthreshold brain activity in C57/Bl mice in the context of either synaptic blockers (APV, gabazine, and CNQX) or a gap junction blocker (carbenoxolone). Using certain analytical tools, including the continuous wavelet transform analysis, we are hopeful that the contributions of synaptic channels and gap junctions to these 'observable fluctuations' will be determined and quantified, thereby better characterizing the 'noise' in the system. More importantly, however, we propose that this simple attempt at 'noise' analysis will open up a field of investigation that has, until recently, been much ignored in most experimental contexts.

SEIZURE PREDICTION - DO WE HAVE TO STIMULATE?
Piotr Suffczynski

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The majority of existing methods of seizure prediction is based on analysis of ongoing neuronal activity. This approach can face certain limitations. It is likely that such passive methods based on analysis of spontaneous EEG activity will not bring the necessary information about the state of the underlying network. As an alternative, active paradigms that are based on stimulation of the brain and on analyzing its response can improve prediction methods. It has been shown that so called relative Phase Clustering Index (rPCI) measured from evoked EEG signals can reliably anticipate transition to seizure in both photosensitive and temporal lobe epilepsy patients. Here we investigate a realistic computational model of a hippocampal network in order to provide a functional link between physiological parameters controlling excitability of the hippocampal tissue and the rPCI measured during stimulation. Using the model we also demonstrate that transition to seizure can not always be predicted based on purely passive measures.

LEADING ROLE OF THE DEEP INTRINSICALLY-BURSTING CELLS IN THE GENERATION OF ACTIVE STATE DURING SLOW-WAVE SLEEP
Sylvain Chauvette

Sylvain Chauvette & Igor Timofeev
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Slow-wave sleep is characterized by spontaneous alternations of active and silent states in corticothalamic networks, but the causes of transition from silence to activity remain hypothetical. We investigated the mechanisms underlying initiation of active state in naturally sleeping or anesthetized cats, using either multiple simultaneous local field potential recordings or multiple intracellular recordings from either closely located cells or from cells separated by few millimeters. Local field potential recordings were performed with a Michigan probe inserted perpendicularly to the cortical surface. Simultaneous intracellular recordings were performed from 2-4 cortical neurons. The experiments were conducted on cats either anesthetized with Ketamine-Xylazine, or on non-anesthetized and non-paralyzed during natural sleep. We found that activity may start in a neuron of any type and at any cortical depth in some cycles. However, typically active state started in deep layers, but intrinsically-bursting neurons from any layer had tendency to lead the onset of active states. Delays between the onset of active state in the leading neuron (or field recordings) and active state onset in other neurons (or other field recordings) were up to tens of milliseconds, and varied from cycle to cycle. This range of variability was present in all type of experiments namely, local intracellular recordings, distant intracellular recordings, local field potential recordings, and both under anesthesia or during natural sleep. We suggest that activity is caused by spontaneous spike-independent mediator releases and may originate in any neuron. Layer V pyramidal neurons, having an apical dendrite that reaches the cortical surface, have the largest dendritic surface of cortical cells and thus receive a larger number of synapses. Thus they are more subject to summation of spontaneous potentials. Neurons having a larger postsynaptic impact are better situated to generate the onset of active states.

BEYOND THE ISOELECTRIC LINE: NOVEL ACTIVITY PATTERNS IN THE ANESTHESIA-INDUCED COMATOSE BRAIN

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Several anesthetics induce, in a dose-dependent manner, EEG patterns ranging from slow-wave sleep and burst-suppression, to a continuous isoelectric line. Here we present evidence that an even further increase of the administered dose of anesthesia results in a novel kind of activity characterized by high amplitude (~0.5 mV) quasi-rhythmic EEG spikes, henceforth termed v-complexes (NCs). Experiments were carried out in cats under isoflurane and consisted of intracellular recordings of cortical, thalamocortical, and hippocampal neurons and glia, together with local field potentials and EEG recordings. NCs were recorded intracellularly in the cortex, thalamus and hippocampus as spontaneous excitatory events triggering action potentials. In paired intracellular recordings hippocampal NCs preceded the cortical and thalamical ones by about 50 ms. The frequency of NCs was 0.65 Hz and their duration at the EEG level (measured at half amplitude) ranged between 100 a nd 200 ms. A second novel activity pattern, henceforth termed δ-ripples (DRs), occurred in the intervals between NCs with a frequency of ~2 Hz. DRs were recorded intracellularly as full-sized excitatory events with action potentials in hippocampal neurons whilst the EEG showed only minor deflections (~0.05 mV) with a duration at half amplitude ranging from 80 to 120 ms. In cortical neurons this activity was absent altogether. Interestingly, electrolytic lesions of the hippocampal CA1 region abolished DRs, strongly implying a hippocampal involvement in the generation of this phenomenon. Overall, the results show that very high levels of anesthesia (beyond the achievement of a continuous isoelectric line) sustain rhythmic subcortical (hippocampal) activities.

ISSUES OF EEG ANALYSIS AND ANESTHESIA

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Monitoring the depth of anesthesia based on EEG signals has gained a great interest in the recent years. Although several monitoring systems are already available in the market, demands for better reliability and accuracy are still high. The objective of our study is to determine the characteristic features of EEG at different level of anesthesia which can be utilized in the monitoring systems to effectively identify the levels of anesthesia. Electrical brain activities were recorded subcutaneously from rat brain under different anesthetic levels. Different levels of anesthesia were achieved by administering the animals with different concentrations of isoflurane (1%, 1.5%, 2% and 2.5%). EEG signals were decomposed using wavelet transform and time-series signals are constructed from wavelet coefficients for certain frequency bands. Various linear and non-linear dynamic analysis tools can be applied to this sub-frequency band signals to identify the key features of different anesthetic states.

ADENOSINE A LOCAL MODULATOR OF HIPPOCAMPAL SHARP WAVES

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Adenosine is a neuro-modulator involved in a wide range of physiological activities including sleep regulation and synaptic plasticity. However, it is unclear as to whether adenosine serves as a local mechanism to control sleep-related network activities in the forebrain structures. The primary goal of this study is to explore the adenosine control of hippocampal sharp waves (SPWs), which represent electroencephalographic events that originate from the hippocampal CA3 circuit and occur during slow wave sleep and wake immobility as the result of cooperative network activities of hippocampal CA3 neurons. We have recently developed a thick mouse hippocampal slice preparation that is capable of exhibiting spontaneous sharp waves in vitro. We report here that in vitro sharp waves are highly sensitive to modulation by endogenous adenosine via A1 receptors. Endogenously activated adenosine A1 receptors control the induction of sharp waves via a NMDA receptor-dependent manner. The spontaneous sharp waves, once appeared, do not necessarily require NMDA receptors for their maintenance but their incidence rates are controlled by A1 receptor activities via a pre-synaptic inhibitory action on glutamatergic synapses. We hypothesize that physiological variations of adenosine play an important role in generation of SPWs in the hippocampus.

POSTSYNAPTIC IMPACT OF EPSPS AND MINIS ON NEOCORTICAL NEURONS IN VIVO

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Intracellular studies have shown that the hyperpolarizing phase of the slow oscillation and paroxysmal discharges are associated with disfacilitation, a temporal absence of synaptic activity. This study tests hypothesis that spike independent synaptic potentials (MINIs) could have a role comparable to EPSPs in the generation of active network states. Here the amplitude and time course of spontaneous MINIs was compared to single-axon excitatory postsynaptic potentials (EPSPs) during silent network states and to spontaneous EPSPs recorded during active network states in neocortical slabs in vivo. During silent network states, the presynaptic spikes elicited in postsynaptic neurons EPSPs variable in amplitude (from failure to 1.4 mV), which lasted tens of milliseconds. They were similar to minis or larger in amplitude. During active network states the spontaneous EPSPs were of the same amplitude as minis during silent states, but were dramatically shorter in the duration. These data demonstrate that network activity significantly decreases the amplitude and duration of postsynaptic potentials suggesting that during active state mostly single vesicle mediates generation of unitary EPSPs in neocortex. Thus, both MINIs and EPSPs have comparable efficiency in triggering active network states during sleep and paroxysmal discharges.

SMALL WINDOW OF T-CHANNEL NUMBERS INFLUENCES THE RESPONSE OF THE THALAMOCORTICAL CELL

Reza Zomorrodi

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We developed a multi-compartment model of thalamocortical cell to consider effects of dendritic currents on response of the cell. We tuned active parameters of dendrites by considering different Gaussian distribution of T-channel for our 1270 compartments model. First, we attribute uniform T-channel distribution for all compartments in model, then we find a threshold value, (cm/sec), for Low Threshold Calcium Spike (LTS). By multiplication area of each section to its permeability we found threshold number of channels that was necessary to reproduce an LTS. We normalized our Gaussian distribution to this threshold value, then for different means and variances we examined LTS response and IV- curve of T-current. Our simulations show that independent of the Ca2+ channel distribution, for a total channel number below or above the threshold value, cell always gives a passive or active LTS response. However, in a window in the total channel number, which is located below the threshold, the shape of channel distribution makes a difference on the cell response. In such window, for uniform T-channel distribution cell always reproduces passive response, while for a non-uniform distribution with total T-channel number 5-20% below threshold value, cell reproduces LTS response depending on the mean and variance of channel distribution,. We conclude that firing patterns and IV curve of T-current with a non-uniform distribution and higher channel density in sections near to soma generate responses that closer mimic the experimental data.

A ROLE FOR THE THALAMUS IN HIPPOCAMPO-PREFRONTAL INTERACTIONS

Éliane Proulx

Éliane Proulx & Igor Timofeev
Centre de Recherche Université Laval Robert-Giffard

The involvement of the hippocampus and prefrontal cortex in mnemonic function has become widely accepted. How these two structures interact, however, remains unclear. Interestingly, the prefrontal cortex does not project to the hippocampus. The reuniens nucleus of the midline thalamus, however, is reciprocally connected to both the hippocampus and prefrontal cortex and for this reason has been proposed to serve as an interface between these two structures. With the aim of elucidating the nature of hippocampo-prefronto-thalamic network interactions, we have performed intracellular, single unit and local field potential recordings in the medial prefrontal cortex of ketamine/xylazine anesthetized cats. This presentation will provide a physiological description of synaptic responses of medial prefrontal neurons to reuniens nucleus stimulation along with evidence that a spatially restricted area of medial prefrontal cortex mediates the hippocampo-cortico-thalamic relay. Electrical stimuli delivered to the reuniens nucleus elicited EPSPs, often followed by periods of disfacilitation and rebound excitation, in a large proportion of medial prefrontal cortex neurons. Antidromic responses were observed in a confined cortical region and hippocampal stimuli were found to elicit evoked potentials and synaptic responses in this same area. Thus, we present evidence that the reuniens nucleus of the midline thalamus exerts a synaptic influence on medial prefrontal cortex neurons and that a restricted locus of the medial prefrontal cortex both forms a reciprocal loop with the reuniens nucleus and receives input from the hippocampal formation.

NEURONAL DYNAMICS LINKING FOOD ANTICIPATION AND FEEDING STATES

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The states of food anticipation (FA) and feeding represent disparate motivational and rewarding conditions that depend on different sensory inputs. Detection of patterns of neuronal activation during FA and feeding will help to understand how the brain processes signals related to feeding states and regulates the activity of neuroendocrine and autonomic systems. To characterize the neuronal circuitries activated during FA and feeding we used the detection of c-fos mRNA expression in the brain of rats subjected to tree weeks of restricted scheduled feeding. On fourth week food-restricted rats were sacrificed at 3, 2, 1 and 0 hour before scheduled feeding or after 1 hour of feeding. Results: Plasma corticosterone was significantly increased during FA and deceased by feeding. The FA and feeding were associated with a particular pattern of c-fos mRNA expression. The parvocellular part of the paraventricular hypothalamic nucleus (PVH) was activated during FA, whereas feeding activated magnocellular PVH. Activation of the parvocellular PVH together with significant increase of plasma corticosterone suggests that FA affects the hypothalamic pituitary adrenal axis. In the dorsomedial hypothalamic nucleus c-fos mRNA was highly expressed in the dorsal part during FA and in the ventral part after feeding. In the brainstem the sympathetic (ventrolateral medulla) and parasympathetic (nucleus ambiguus) preganglionic regions were activated respectively during FA and feeding. The present results suggest that FA and feeding involve in activation the particular brain circuitries that allow the state-dependant regulation of neuroendocrine and autonomic systems.

EVIDENCE FOR THE ANTICONVULSANT EFFECTS OF OMEGA-3 POLYUNSATURATED FATTY ACIDS IN RATS AND MICE

Ameer Taha

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Epilepsy is a serious neurological disorder which is characterized by spontaneous, recurrent seizures. Current anticonvulsant medications have side effects including weight gain, fatigue and sedation. Omega-3 (n-3) polyunsaturated fatty acids (PUFA), derived from marine fish oils, have been considered as an alternative treatment for patients with epilepsy. Accordingly, we hypothesized that enrichment of brain lipids with n-3 PUFA would inhibit the epileptic-like seizures induced by pentylenetetrazol (PTZ). Three experiments were conducted in order to test the hypothesis. In experiment 1, we showed that intra-peritoneal injections of the n-3 PUFA alpha-linolenic acid to male rats, increased docosahexaenoic acid composition in brain free fatty acid lipid pool, and increased latency to seizure onset ($P<0.05$). In experiment 2, dietary supplementation of fish oil containing high levels of n-3 PUFA, increased afterdischarge seizure thresholds in the amygdala and cortex of rats. In experiment 3, we demonstrated that increased levels of n-3 PUFA in brain total lipids of transgenic fat-1 mice, which are capable of de novo synthesis of n-3 PUFA from n-6 PUFA, is associated with increased latency to seizure onset ($P<0.05$). These findings indicate that n-3 PUFA have anticonvulsant properties, and would be potentially useful in the treatment of epilepsy.

THE EFFECTS OF RIGHT AND LEFT SEIZURES ON REPRODUCTION AND FEEDING
Kathryn M. Hum

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Introduction: Women with epilepsy often suffer comorbid reproductive dysfunction and weight gain. Previous studies suggest that individuals with partial onset seizures are at a greater risk, and that seizures that originate in right and left hemispheres are associated with different dysfunctions. The impact of these co-morbidities on quality of life is considerable. The present study examined the effects of seizures of limbic origin on the reproductive and feeding systems using the amygdala kindling model.

Methods: Female Wistar rats were kindled from the left or right basolateral amygdala. Subjects were weighed weekly and vaginal cytology was assessed daily for the duration of the study. Kindled subjects received a minimum of forty generalized seizures. Sham-kindled subjects were handled similarly but not stimulated. Twenty-four hours following the last seizure, kindled subjects and their yoked controls were sacrificed with brain and serum extracted.
Results: Kindled subjects had significantly more abnormal estrous cycle days and significantly elevated levels of estradiol as compared to controls. Kindled subjects also weighed significantly more than controls and had significantly higher levels of leptin. No differences were seen between right and left groups. Correlational analyses reveal that measures of reproductive dysfunction and obesity were significantly related.

Conclusion: Seizures of limbic origin cause changes in both estrous cycling and weight gain, and they are sufficient to disrupt function in multiple hormone systems. Correlational analyses suggest that the reproductive and feeding pathways are inter-related. The present study emphasizes the need for the comprehensive medical management of the reproductive health and weight of patients with epilepsy.

THE JOURNEY SO FAR: MY FIRST TEN YEAR WITH EPILEPSY

Melanie Jeffrey
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This is a multi-media, arts-inspired look at my journey with epilepsy. I was diagnosed with idiopathic adult onset tonic-clonic epilepsy in 1996.

There have been struggles and triumphs over the last ten years. I have moved through denial and resistance to a slow acceptance of my identity with epilepsy in my life. Expressing this through art and activism has been important to my journey, and a more intuitive way to communicate the experience of living with epilepsy. As I pursue a second undergrad in sciences and come to understand my mysterious “pathology” in academic terms, I still turn to art for solace.

The journey has taken me through many drug regimes with all the attendant side effects, including depression, which has been more damaging than epilepsy in many respects. My current meds have given me a slight learning disability; more challenges to dreams and realities. It was this change that angered me the most. I had to learn to learn again, mid-degree. Although the seizures have been controlled the last year, epilepsy continues to confront me in other ways. Laughter, art, love, and determination get me through it all.

Outreach to others sharing this journey has been healing and humbling. The outreach others have made to me has changed me forever, and I am thankful for it.

FEATURED SPEAKER

Peter L. Carlen
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Introduction by Marija Cotic

PERCEPTION IS NOT REALITY: THE MANY REASONS FOR OUR MISUNDERSTANDINGS OF BRAIN DYNAMICS AND EPILEPSY

Peter L. Carlen
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Our perception of brain dynamics and mechanisms of epilepsy is a figure of our overactive imaginations and our measuring technologies. Because of the above, the reality is most elusive. Herein I will present several examples leading to misunderstandings, starting with technological deficiencies and ending with conceptual misapprehensions.

Technology:

1. EEG. The gold standard of epilepsy is the EEG. Since the EEG was discovered by Hans Berger in 1924, even to the present day, the EEGer reads and interprets data almost always based on frequencies below 30 Hz, and using scalp electrodes which are remote from the brain surface and limited in the amplitude of the signals measured. Intracranial electrodes greatly improve the signal to noise ratio but still the usual amplifiers cut off at 200 Hz. Contrary to popular belief, high frequencies (100's of Hz) can be measured on the scalp. Now with the discovery of ripples, it is becoming obvious that there is a wealth of important data in the higher frequency ranges that has to be looked at re brain dynamics and epilepsy.
2. Field recordings will pick up local activity be it low or high frequency, depending on the filters used. There are many drawbacks to understanding brain activity via electrical fields. In epilepsy, metabolic dysfunction has been measured minutes prior to any electrographic abnormalities. If the electrode is not in the right place, epileptic activity can be missed. Voltage sensitive dyes, which are often neurotoxic, also measure field activities, but what is exactly being measured is also open to much interpretation.
3. Intracellular recordings measure the averaged electrical activity for a cell and not the local transmembrane potentials. Also field effects can be superimposed and the intracellular milieu is often disturbed. Space clamp issues are significant in large multibranched cells.
4. fMRI measures the neurovascular responses to neural activity, a secondary or tertiary response to this activity.

Conceptions:

1. Underlying generators of electrographic activity are unclear and controversies will be discussed. What is the key foundation of brain activity; is it electrical, metabolic, or both?
2. Coupled oscillators. Our concept of brain activity is confused at best. A new way of thinking is to consider brain activity as a manifestation of coupled oscillators at many different anatomic levels. These oscillators will change dynamically over time and space.
3. States and state transitions are frequently used concepts whose bases are controversial.
4. Autonomy and environmental impact on brain activity are other concepts to be discussed.