December 4 - 8 ■ Philadelphia, PA
69TH ANNUAL MEETING

Merritt-Putnam Symposium
Networks in Epilepsy

Symposium Chair:

Gregory Worrell, M.D., Ph.D.

Monday, December 7, 2015
Convention Center – Grand Ballroom AB

8:45 a.m. - Noon

GENERAL INFORMATION

Accreditation

The American Epilepsy Society is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

Credit Designation

Physicians

The American Epilepsy Society designates this live activity for a maximum of 30.75 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Physician Assistant

AAPA accepts certificates of participation for educational activities certified for *AMA PRA Category 1 Credit*™ from organizations accredited by ACCME or a recognized state medical society. Physician assistants may receive a maximum of 30.75 hours of Category 1 credit for completing this program.

Jointly provided by AKH Inc., Advancing Knowledge in Healthcare and the American Epilepsy Society.

Nursing

AKH Inc., Advancing Knowledge in Healthcare is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

This activity is awarded 30.75 contact hours.

Nurse Practitioners

AKH Inc., Advancing Knowledge in Healthcare is accredited by the American Association of Nurse Practitioners as an approved provider of nurse practitioner continuing education. Provider Number: 030803. This program is accredited for 30.75 contact hours which includes 8 hours of pharmacology. Program ID #21547

This program was planned in accordance with AANP CE Standards and Policies and AANP Commercial Support Standards.

Pharmacy

AKH Inc., Advancing Knowledge in Healthcare is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Select portions of this Annual Meeting are approved for pharmacy CE credit. Specific hours of credit for approved presentations and Universal Activity Numbers assigned to those presentations are found in the educational schedules. Criteria for success: nursing and pharmacy credit is based on program attendance and online completion of a program evaluation/assessment.

If you have any questions about this CE activity, please contact AKH Inc. at service@akhcme.com.

International Credits

The American Medical Association has determined that non-U.S. licensed physicians who participate in this CME activity are eligible for *AMA PRA Category 1 Credits*™.

CME/CE Certificates

For those attendees who wish to claim CME or CE, there is an additional fee. Registrants can pay this fee as part of the registration process. Those who do not pre-purchase the credit will also have the ability to pay this fee at the time they attempt to claim credit. Fees for CME increase after January 16 and are a one-time charge per annual meeting.

The evaluation system will remain open through Friday, February 26, 2016. Evaluations must be completed by this date in order to record and receive your CME/CE certificate.

Member Fees:	$50 through January 15, 2016 $75 January 16 – February 26, 2016
Non-member Fees:	$75 through January 15, 2016 $100 January 16 – February 26, 2016

Attendance Certificate/International Attendees

A meeting attendance certificate will be available at the registration desk for international meeting attendees on Tuesday, December 8.

Policy on Commercial Support and Conflict of Interest

The AES maintains a policy on the use of commercial support, which assures that all educational activities sponsored by the AES provide in-depth presentations that are fair, balanced, independent and scientifically rigorous. All faculty, planning committee members, moderators, panel members, editors, and other individuals who are in a position to control content are required to disclose relevant relationships with commercial interests whose products relate to the content of the educational activity. All educational materials are reviewed for fair balance, scientific objectivity and levels of evidence. Disclosure of these relationships to the learners will be made through syllabus materials and the meeting app.

Disclosure of Unlabeled/Unapproved Uses

This educational program may include references to the use of products for indications not approved by the FDA. Faculty have been instructed to disclose to the learners when discussing the off-label, experimental or investigational use of a product. Opinions expressed with regard to unapproved uses of products are solely those of the faculty and are not endorsed by the AES.

OVERVIEW
Network science is a multidisciplinary field based on fundamental discoveries in mathematics and physics that has had significant impact on a wide range of disciplines spanning engineering, medicine, biology, social and information technology. Advances in the science of networks have led to a deeper understanding of the role of the cellular constituents, assemblies and large-scale brain networks underlying normal and pathological brain activity, and has important implications for epileptogenesis, seizures and epilepsy. In this Merritt-Putman symposium we review the science and technology driving the rapidly evolving, interdisciplinary field of networks, and address some of the key opportunities and challenges. This will include discussion of the role of networks in clinical epilepsy, including evaluation of cognition and planning epilepsy surgery.

LEARNING OBJECTIVES
Following participation in this symposium, learners should be able to:

- Recognize the role of epileptic networks and the emerging evidence for its role in focal epilepsy using EEG or fMRI
- Counsel families regarding prognosis of epilepsy surgery based on understanding of the role of networks
- Participate in counseling families regarding role of networks on memory circuits and association with network phenomena and prognosis

TARGET AUDIENCE
Intermediate: Epilepsy fellows, epileptologists, epilepsy neurosurgeons, and other providers with experience in epilepsy care (e.g., advanced practice nurses, nurses, physician assistants), neuropsychologists, psychiatrists, basic and translational researchers.

Advanced: Address highly technical or complex topics (e.g., neurophysiology, advanced imaging techniques or advanced treatment modalities, including surgery.)

Agenda
Chair: Gregory Worrell, M.D., Ph.D.

Introduction
Gregory Worrell, M.D., Ph.D.

The Concepts of Networks
Olaf Sporns, Ph.D.

Functional Imaging, Networks and Epilepsy
Danielle Bassett, Ph.D.

Electrophysiology: Spanning Units, Local Field Potentials, Large-Scale Networks in Epilepsy
Catherine Schevon, M.D., Ph.D.

Cells/Assemblies/Networks of Physiological Activity and Seizures
Sydney S. Cash, M.D., Ph.D.

Networks in Cognition and Epilepsy Surgery
Hal Blumenfeld, M.D., Ph.D.

Conclusions
Gregory Worrell, M.D., Ph.D.

Education Credit
3.0 CME Credits

Nurses may claim up to 3.0 contact hours for this session.

Pharmacy Credit
AKH Inc., Advancing Knowledge in Healthcare approves this knowledge-based activity for 3.0 contact hours (0.3 CEUs). UAN 0077-9999-15-032-L01-P. Initial Release Date: 12/7/2015.

The American Board of Psychiatry and Neurology has reviewed the Networks in Epilepsy Symposium and has approved this program as part of a comprehensive program, which is mandated by the ABMS as a necessary component of maintenance of certification.

FACULTY/PLANNER DISCLOSURES
It is the policy of the AES to make disclosures of financial relationships of faculty, planners and staff involved in the development of educational content transparent to learners. All faculty participating in continuing medical education activities are expected to disclose to the program audience (1) any real or apparent conflict(s) of interest related to the content of their presentation and (2) discussions of unlabeled or unapproved uses of drugs or medical devices. AES carefully reviews reported conflicts of interest (COI) and resolves those conflicts by having an independent reviewer from the Council on Education validate the content of all presentations for fair balance, scientific objectivity, and the absence of commercial bias. The American Epilepsy Society adheres to the ACCME's Essential Areas and Elements regarding industry support of continuing medical education; disclosure by faculty of commercial relationships, if any, and discussions of unlabeled or unapproved uses will be made.

FACULTY / PLANNER BIO AND DISCLOSURES
Gregory Worrell, M.D., Ph.D. (Chair)
Greg Worrell, MD, PhD is Professor of Neurology and Physiology & Biomedical Engineering at Mayo Clinic in Rochester, Minnesota. He is Vice-chair of Neurology Research, Chair of the Division of Clinical Neurophysiology, and Director of Mayo Systems Electrophysiology Laboratory (MSEL). His clinical practice and research are focused on the evaluation and care of patients with drug resistant epilepsy.

Dr. Worrell discloses receiving support for Receipt of Intellectual Property Rights/Patent Holder from NeuroOne Inc.; for Consulting from Medtronic Inc.; as Contract Research from Medtronic Inc., NeuroPace Inc.; for Ownership (i.e. stocks, stock options or other ownership) from NeuroOne Inc. Stock Options. A start-up company building subdural and depth intracranial electrodes; as Honoraria from Stanford University for Grand Rounds, Harvard Beth Israel Grand Rounds, University of Minnesota Grand Rounds.

Danielle Bassett, Ph.D.
Danielle S. Bassett is the Skirkanich Assistant Professor of Innovation in the Department of Bioengineering at the University of Pennsylvania. She is known for her work blending neural and systems engineering to identify fundamental mechanisms of cognition and disease in human brain networks. She has received multiple prestigious awards, including American Psychological Association's `Rising Star', Alfred P Sloan Research Fellow, MacArthur Fellow Genius Grant, IEEE EMBS Early Academic Achievement Award, and ONR Young Investigator. Her work has been supported by the NSF, NIH, ARO, ARL, the Alfred P Sloan Foundation, the John D and Catherine T MacArthur Foundation, and the Office of Naval Research.

Dr. Bassett has indicated she has no financial relationships with commercial interests to disclose.

Hal Blumenfeld, M.D., Ph.D.
Dr. Hal Blumenfeld is the Loughridge-Williams Professor, Director of the Yale Clinical Neuroscience Imaging Center and Professor of Neurology, Neuroscience and Neurosurgery at the Yale School of Medicine. Dr. Blumenfeld's research focuses on epilepsy and the neural mechanisms of consciousness. His innovative scientific approach combines functional neuroimaging, electrophysiology, behavioral testing, optogenetics and therapeutic deep brain stimulation. He has had numerous peer-reviewed articles, grants from NIH and private foundations, as well as the Dreifuss-Penry Epilepsy Research Award from the American Academy of Neurology, and the Graduate Mentor Award as most outstanding scientific mentor of graduate students at Yale.

Dr. Blumenfeld has indicated he has no financial relationships with commercial interests to disclose.

Sydney Cash, M.D., Ph.D.
Sydney Cash, is a staff physician at Massachusetts General Hospital /Harvard Medical School. Dr. Cash received his MD and PHD from Columbia University in New York City. He then moved to Boston for neurological training in the Partners Program. He stayed on at MGH for further training in epilepsy and neurophysiology during a research fellowship funded by the American Epilepsy Society and a Grass-Morison Fellowship. He remains at MGH where he is an Associate Professor splitting his time between clinical activities and research. Current research in Dr. Cash's lab is, broadly speaking, dedicated to trying to understand normal and abnormal brain activity, particularly oscillations and seizures, using multi-modal and multi-scalar approaches.

Dr. Cash has indicated he has no financial relationships with commercial interests to disclose.

Catherine Schevon, M.D., Ph.D.
Dr. Schevon is Assistant Professor in the Department of Neurology, in the College of Physicians and Surgeons at Columbia University. Prior to her medical training, she studied electrical engineering and computer science, and worked in VLSI design at AT&T Bell Laboratories. She attended medical school at the University of Pennsylvania, and completed an epilepsy fellowship at Columbia in 2004. Beginning with a K08 awarded in 2005, she has focused on the problem of seizure localization using human and animal microelectrode and clinical electrophysiology recordings.

Dr. Schevon discloses receiving support for Consulting from Persyst Development Corp.

Olaf Sporns, Ph.D.
Olaf Sporns earned a PhD at Rockefeller University and conducted postdoctoral work at The Neurosciences Institute in New York and San Diego. Currently he is the Robert H. Shaffer Chair and a Distinguished Professor in the Department of Psychological and Brain Sciences at Indiana University in Bloomington. His main research area is theoretical and computational neuroscience, with a focus on complex brain networks. He has authored over 180 peer-reviewed publications as well as the recent books "Networks of the Brain" and "Discovering the Human Connectome", published by MIT Press. Sporns was awarded a John Simon Guggenheim Memorial Fellowship in 2011 and elected Fellow of the American Association for the Advancement of Science in 2013.

Dr. Sporns has indicated he has no financial relationships with commercial interests to disclose.

CME Reviewer
Leonardo Bonilha, M.D., Ph.D.
I am a neurologist, epileptologist and clinical neurophysiologist. I am an Associate Professor of Neurology at the Medical University of South Carolina, where I work as a clinician scientist. My research involves the mechanistic aspects of brain structure and function (through neuroimaging and EEG) in relationship with language recovery after brain injury, as well as seizures and epilepsy.

Dr. Bonilha discloses receiving support as Consulting from Health Advances, LLC I have provided paid advice regarding best uses of PACS imaging software.

Lara Jehi, M.D.
Dr Lara Jehi is an adult epileptologist, the head of the Outcomes Research Program, and the Director of Research at the Cleveland Clinic Epilepsy Center. Her interests have focused on understanding and improving outcomes of epilepsy treatment. She serves as the Associate Program Director of the Clinical Research Unit at Cleveland Clinic within the auspices of the NIH-funded Clinical and Translational Science Collaborative, is serving in leadership roles on many educational committees within the American Epilepsy Society and American Academy of Neurology, and is a reviewer for the Epilepsy Study Section at NIH. She has authored several original manuscripts, editorials and book chapters and spoke at multiple national and international meeting.

Dr. Jehi has indicated he has no financial relationships with commercial interests to disclose.

Suchitra Joshi,Ph.D.
I am a research assistant professor at the Department of Neurology, University of Virginia. My research is focused on understanding the molecular mechanisms regulating the plasticity of GABA-A receptors in temporal lobe epilepsy, particularly that of the delta subunit-containing GABA-A receptors. I am also studying the mechanisms that regulate distinct rates of trafficking of the delta and gamma2 subunit-containing GABA-A receptors.

Dr. Joshi has indicated he has no financial relationships with commercial interests to disclose.

Paul Levisohn, M.D. (Medical Content Specialist, AES)
Dr. Levisohn is a member of the faculty of the section of Pediatric Neurology at The University of Colorado School of Medicine and Children's Hospital Colorado Neuroscience Institute, having joined the faculty over 15 years ago following a similar period of time in the private practice of pediatric neurology. His academic career has focused on clinical care for children with epilepsy with particular interest in clinical trials and on the psychosocial impact of epilepsy. Dr. Levisohn is currently a consultant on medical content for CME activities to staff of AES. He is a member of the national Advisory Board of EF and has been chair of the advisory committee for the National Center of Project Access through EF.

Dr. Levisohn has indicated he has no financial relationships with commercial interests to disclose.

AKH STAFF / REVIEWERS
Dorothy Caputo, MA, BSN, RN (Lead Nurse Planner) has indicated she has no financial relationships with commercial interests to disclose.

Bernadette Marie Makar, MSN, NP-C, APRN-C (Nurse Planner) has indicated she has no financial relationships with commercial interests to disclose.

John P. Duffy, RPh, B.S. Pharmacy (Pharmacy Reviewer) has indicated he has no financial relationships with commercial interests to disclose.

AKH staff and planners have nothing to disclose.

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Physicians can claim CME credit online at **https://cme.experientevent.com/AES151/**

This Link is NOT Mobile-friendly! You must access it from a laptop, desktop or tablet.

How to Claim CME Credit
To claim CME credits online, please follow the on-screen instructions at the above url. Log in using your last name and zip code, OR your last name and country if you're not from the United States. All CME credits must be claimed **by February 26, 2106**.

Questions?
Contact Experient Customer Service at: 800-974-9769 or **AES@experient-inc.com**

NURSING & PHARMACY

PLEASE NOTE: Providing your NABP e-profile # is required.
The National Association of Boards of Pharmacy (NABP) requires that all pharmacists and pharmacy technicians seeking CE credit have an ID number issued by NABP. Pharmacy CE providers, such as AKH Inc., Advancing Knowledge in Healthcare, are required to submit participant completion information directly to NABP with your ID number and birth information to include month and date (not year) as a validation to this ID number. If you do not have an ID number (this is not your license #), go to: www.MyCPEmonitor.net

Nursing and Pharmacy credit (per session) is based on attendance as well as completion of an online evaluation form available at:

WWW.AKHCME.COM/2015AES

THIS MUST BE DONE BY JANUARY 15, 2016 TO RECEIVE YOUR CE CREDIT.
We cannot submit credit to NABP after this date.
If you have any questions, please contact AKH at service@akhcme.com.

DISCLAIMER
Opinions expressed with regard to unapproved uses of products are solely those of the faculty and are not endorsed by the American Epilepsy Society or any manufacturers of pharmaceuticals.

Merritt-Putnam Symposium:
Epilepsy Networks

Greg Worrell MD, PhD
Mayo Clinic

December 7, 2015

American Epilepsy Society 69th Annual Meeting December 4 - 8, 2015 Philadelphia, PA

Disclosure

Industry Disclosures

- NeuroOne Inc.
- Medtronic Inc.
- BlackFynn Inc.
- NeuroPace Inc.

Research Funding

National Institute of Neurological Disorders and Stroke

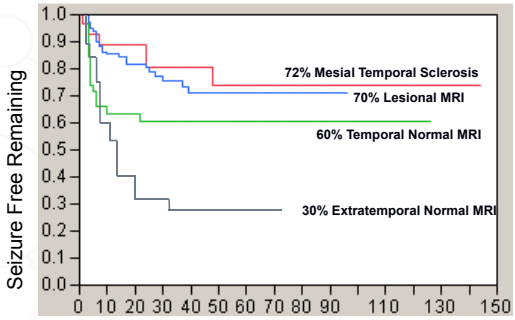
DARPA

FNUSA ICRC

Learning Objectives

- Learn basic network concepts
- Recognize the role of networks in normal brain function and epilepsy
- Counsel families regarding the prognosis of surgery and brain stimulation based on understanding the role of networks

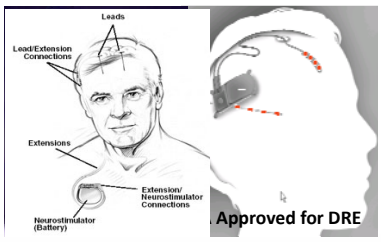
Surgery Outcomes



Devices for Epilepsy

SANTE
Medtronic Inc

RNS
NeuroPace Inc



5 years SANTE
- 69% Sz Reduction
- 68% Resp. Rate
- 16% w/ 6 mon. of Sz freedom
- Improved QOL

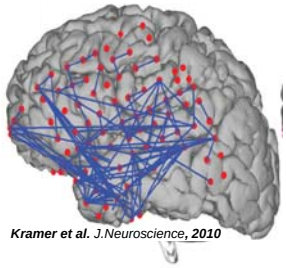
7 years RNS
- 66% Sz Reduction
- 56% Resp. Rate
- 13% had >1 yr Sz freedom
- Improved QOL

Epileptic Brain & Networks

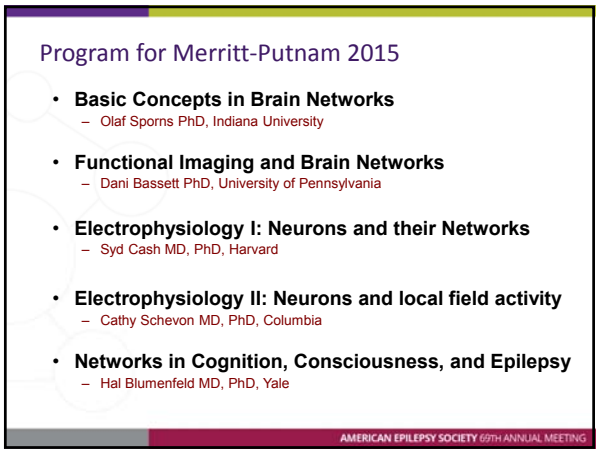
Focal pathological tissue
Seizure onset zone
Irritative zone

EZ: Surgery & Sz-free

Network Physiology
Structural
Functional:
Imaging/Electrophysiology/Molecular/…



Kramer et al. J.Neuroscience, 2010


Program for Merritt-Putnam 2015
• Basic Concepts in Brain Networks
– Olaf Sporns PhD, Indiana University
• Functional Imaging and Brain Networks
– Dani Bassett PhD, University of Pennsylvania
• Electrophysiology I: Neurons and their Networks
– Syd Cash MD, PhD, Harvard
• Electrophysiology II: Neurons and local field activity
– Cathy Schevon MD, PhD, Columbia
• Networks in Cognition, Consciousness, and Epilepsy
– Hal Blumenfeld MD, PhD, Yale
AMERICAN EPILEPSY SOCIETY 69TH ANNUAL MEETING

The Concepts of Networks

Olaf Sporns, PhD
Department of Psychological and Brain Sciences
Network Science Institute
Indiana University, Bloomington, IN 47405
http://www.indiana.edu/~cortex ,
osporns@indiana.edu

spornslab

December 7, 2015

AMERICAN EPILEPSY SOCIETY 69TH ANNUAL MEETING DECEMBER 4 - 8, 2015 PHILADELPHIA, PA

Disclosure

The speaker has no conflicts of interest or commercial interests to disclose

Learning Objectives

Basic understanding of the major components of networks

Basic understanding of how network measures can capture
- Centrality
- Segregation
- Integration

Basic definition of network modules and hubs

Basic definition of a connective core or rich club

Fundamental properties of structural and functional networks

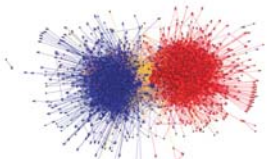
Basic understanding of computational tools for simulating brain networks

What are Networks?

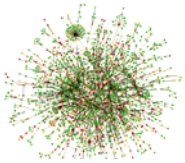
Networks are representations of complex systems – such as the brain.

Networks reveal how a complex system is organized, by providing a map of how its elements (nodes) are interconnected (network topology).

Networks are encountered in many social, technological and biological systems.



social network (political blogs)



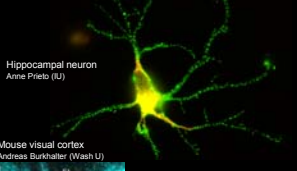
biological network (protein interactions)

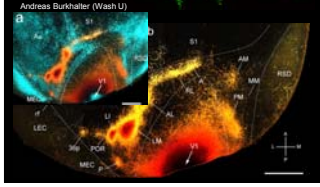
The nature of the system defines the nature of the nodes and edges – this is important when considering brain networks.

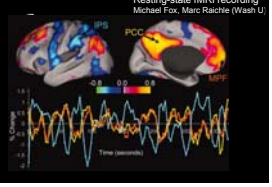
What are Brain Networks?

Networks across scales:
- micro (neurons, synapses)
- macro (regions, projections)

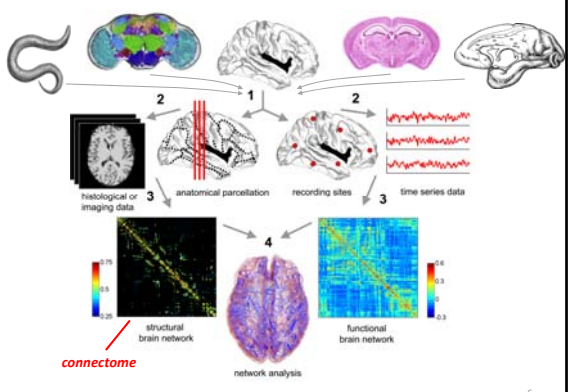
Networks across modes:
- structural (anatomical couplings)
- functional (dynamic interactions)





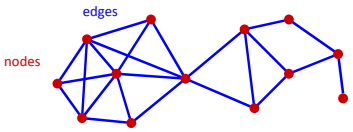


Extraction of Brain Networks from Empirical Data



Bullmore & Sporns (2009) *Nature Rev Neurosci* 10, 186.

Basic Concepts



The basic ingredients of networks are the elements (nodes) and their connections (edges).

Network science offers a plethora of tools and methods for analyzing and quantifying many aspects of network structure and topology.

Numerous software packages enable network analysis and visualization across many applications.

Brain Connectivity Toolbox
www.brain-connectivity-toolbox.net

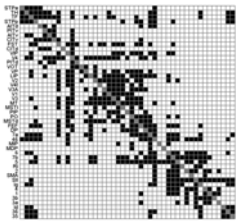
Rubinov & Sporns (2010)
NeuroImage 52, 1059

Basic Concepts

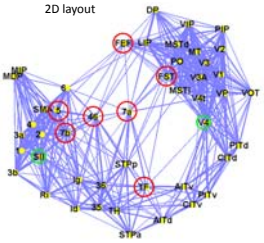
Networks can be displayed as an adjacency matrix or with special visualization tools.

Both plots below show the same data – a network of projections among macaque cortical regions.

adjacency matrix

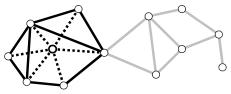


2D layout

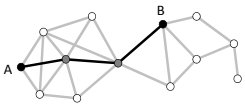


Basic Concepts

node degree – a measure of centrality or influence (e.g. importance of nodes in network structure and function)

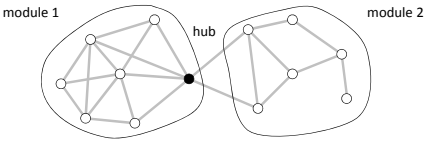


clustering coefficient – a measure of local specialization and segregation (e.g. density of connections surrounding a central node)



path length and distance – a measure of global communication and integration (e.g. propensity for transmitting information)

Network Modules and Hubs



community structure – modules and hubs

Modules can be defined as collections (clusters, communities) of nodes or edges.

Modules highlight functional organization and hub nodes in brain networks.

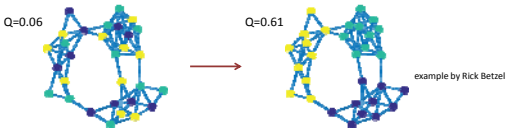
Hubs have several key attributes: high degree and centrality, pivotal role for communication, inter-module links, high vulnerability

There are many methods for detecting modules in networks…

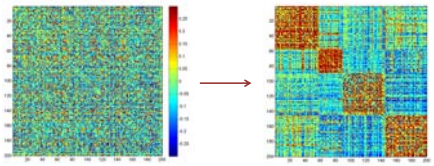
Network Modules and Hubs

Commonly used in brain network analyses: modularity maximization ("Q")

Newman & Girvan (2004) *Phys Rev E* 69, 026113

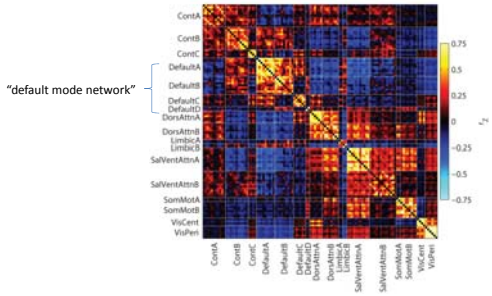


fMRI cross-correlations, whole-brain, 200 ROIs, 21 subjects, Oxford University FMRIB



Network Modules and Hubs

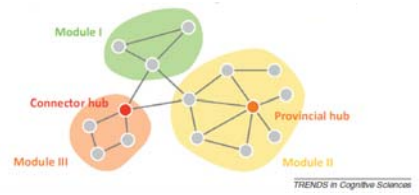
Modules in functional networks estimated from resting brain fMRI correspond to so-called "intrinsic connectivity networks" (or "resting-state networks")



Betzel et al. (2014) Neuroimage 102, 345

Network Modules and Hubs

Once an optimal set of modules has been identified, different classes of hub regions may be distinguished – for example by the way connections are distributed among modules.

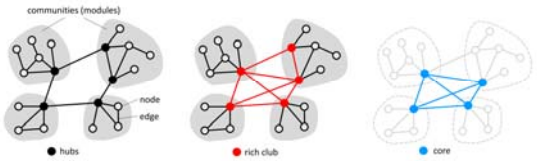


A provincial hub is highly connected but mainly or exclusively within one module.

A connector hub is highly connected, and these connections are distributed among different modules (high participation coefficient)

Network Modules and Hubs

In some networks (including the brain) hub nodes are very densely linked to form a "connective core" or "rich club"



Connections between hubs potentially allow for integration of information across different specialized subsystems.

Core/rich club organization has been demonstrated across several species – suggesting a common theme in the way nervous systems are connected.

Structural and Functional Networks

Structural and functional networks capture two different modes of brain connectivity

Structural connectivity:

- Physical/material in nature
- Large but finite set of elements and connections
- Sparse adjacency matrix – edges can be directed or undirected
- Complex attributes (including density, strength, conduction speed, biophysics)
- Relatively slow changes across time (development, plasticity)
- Multiscale organization (micro, meso, macro-scale)

Functional connectivity:

- Statistical/dynamic in nature
- Large and virtually infinite set of network configurations
- Full matrix of dynamic relationships – edges can be directed or undirected
- Complex attributes (including strength, flexibility, temporal persistence)
- Rapid changes across time (moment-to-moment, input- and task-dependent)
- Modular organization reveals functional communities

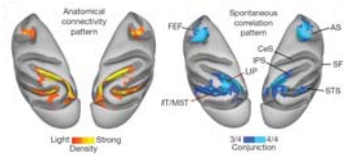
15

Structural and Functional Networks

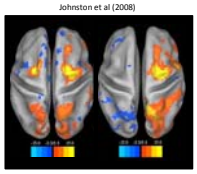
The topology of functional networks is partly shaped by structural networks:

- Robust (but complex) relationship between structural and functional connections (Vincent et al., 2007; Hagmann et al., 2008; Honey et al., 2009)
- Modules in functional networks are internally linked via structural projections (e.g. Greicius et al., 2009; van den Heuvel et al., 2009)
- Cutting anatomical connections (callosotomy) causes immediate changes in functional connections (Johnston et al. 2008; O'Reilly et al. 2013)

Vincent et al (2007)

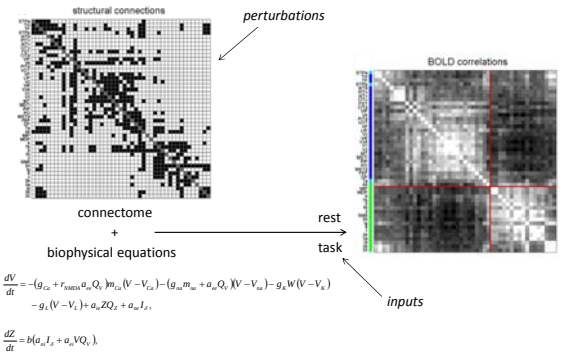


Johnston et al (2008)



Vincent et al. (2007) Nature 447, 83. -- Hagmann et al. (2008) PLoS Biol. 6, e159. -- Honey et al. (2009) PNAS 106, 2035.
Greicius et al. (2009) *Cerebr Cortex* 19, 72. -- van den Heuvel et al. (2009) *Hum Brain Mapp* 30, 3127.
Johnston et al. (2008) J Neurosci 28, 6453. – O'Reilly et al. (2013) PNAS 110, 13982.

Computational Modeling of Functional Connectivity



$$\frac{dV}{dt} = -(g_{Ca} + r_{NMDA} a_m Q_V) m_{Ca} (V - V_{Ca}) - (g_{Na} m_{\infty} + a_m Q_V)(V - V_{Na}) - g_K W (V - V_K) - g_L (V - V_L) + a_m Z Q_Z + a_m I_d,$$

$$\frac{dZ}{dt} = b(a_m I_d + a_m V Q_V).$$

Honey et al. (2007) *PNAS* 104, 10240.

Deco et al. (2011) *Nature Rev Neurosci* 12, 43.

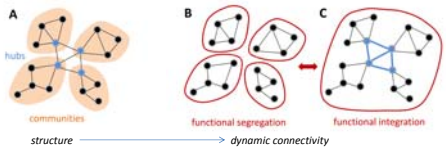
Dynamic Functional Networks

Recent work has shown that functional networks can **fluctuate** on short time scales.

The dynamic functional networks may represent an exploration of possible functional networks across time ("dynamic functional connectivity")

These dynamic changes may be associated with different cognitive operations.

Dynamic brain networks show different degrees of functional segregation and integration and transitions between states may be mediated by network hubs



Deco et al (2011) *Nature Rev Neurosci* 12, 43
Deco et al (2015) *Nature Rev Neurosci* 16, 430

Sporns (2013) *Curr Opin Neurobiol* 23, 162

Brief Summary

Networks = nodes + edges

Brain networks – micro/macro – structural/functional

Brain network measures probe centrality, segregation, integration

Network modules/communities – reveal functional organization, components, hubs

Structural networks – often sparse, synaptic links and projections, physical architecture

Functional networks – often dense, dynamic relations, statistical patterns

Functional networks are shaped by neuronal signaling and communication taking place in structural networks

Computational network models are important tools for understanding the relation between brain connectivity and dynamics

The emerging science of brain networks: connectomics

Further Reading

Further Reading:

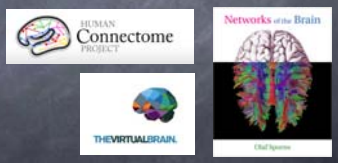
• Sporns O, Betzel RF (2016) Modular brain networks. *Annu Rev Psychol* 67, 19.1-19.28
• Petersen SE, Sporns O (2015) Brain networks and cognitive architectures. *Neuron*
• Sporns O (2014) Contributions and challenges for network models in cognitive neuroscience. *Nature Neuroscience* 17, 652-660.
• van den Heuvel MP, Sporns O (2013) Network hubs in the human brain. *Trends Cogn Sci* 17, 683.
• Bullmore ET, Sporns O (2012) The economy of brain network organization. *Nature Rev Neurosci* 13, 336-349.
• Rubinov M, Sporns O (2010) Complex network measures of brain connectivity: Uses and interpretations. *Neuroimage* 52, 1059-1069.
• Bullmore, ET, Sporns, O (2009) Complex brain networks: Graph-theoretical analysis of structural and functional systems. *Nature Rev Neurosci* 10, 186-198.

Lab: www.indiana.edu/~cortex

NIH Human Connectome Project: www.humanconnectome.org

The Virtual Brain Project: http://thevirtualbrain.org

Network Analysis Toolbox (Matlab): www.brain-connectivity-toolbox.net



Funded by the James S. McDonnell Foundation, NSF, NIH

Functional Imaging & Brain Networks

Danielle S. Bassett
University of Pennsylvania
Department of Bioengineering

December 7, 2015

AMERICAN EPILEPSY SOCIETY
69TH ANNUAL MEETING DECEMBER 4 - 8, 2015 PHILADELPHIA, PA

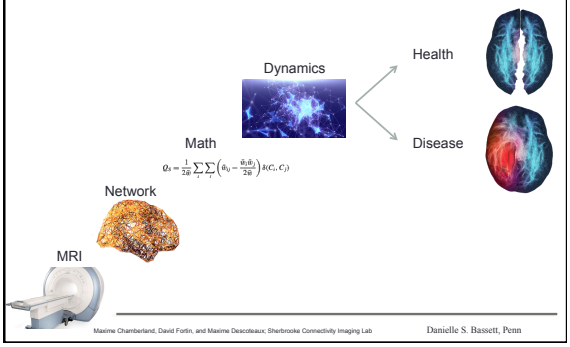
Disclosure

None.

Learning Objectives

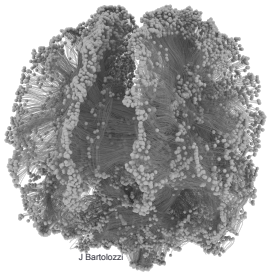
- Define a functional brain network
- Describe structure and dynamics of functional brain networks
- Illustrate the utility of these approaches in understanding cognition in health and disease

From MRI to Brain Networks in Health and Disease



Maxime Chamberland, David Fortin, and Maxime Descoteaux, Sherbrooke Connectivity Imaging Lab

Where do we begin our story?



J Bartolozzi

The brain's structural connections …

Bassett et al. 2011 Neuroimage; Bassett et al. 2010 PLoS CB

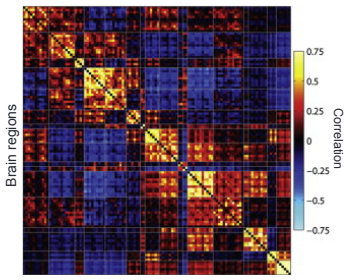
Measuring Shared Information

A **functional brain network** is a representation of shared information between areas spanning the whole brain.

- **Network nodes:** Anatomically distinct brain areas
- **Network edges:** Statistical similarities in area activity
  - *NOT* White Matter Tracts

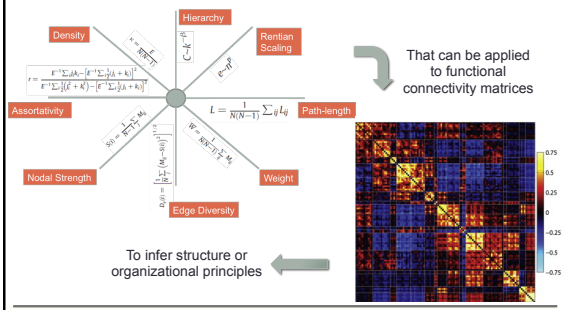
Hermundstad et al. 2013 PNAS; Hermundstad et al. 2014 PLoS CB

The Architecture of a Functional Brain Network



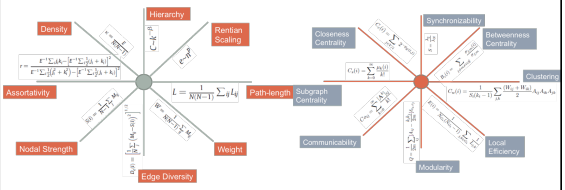
Betzel et al. 2014 Neuroimage

And then there is the math …



Bassett & Lynall. In Cognitive Neurosciences (Gazzaniga, Ivry, Mangun)

What Statistics Matter for Cognition?

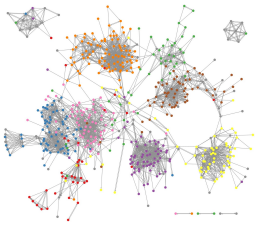


There are many graph statistics that have been defined mathematically.

Medaglia et al. 2015 J Cogn Neurosci

Network Statistics to Quantify Community Structure

Community Structure in Social Networks



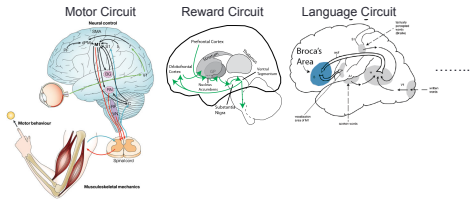
CalTech Facebook Friends

$$Q_S = \frac{1}{2\tilde{w}} \sum_i \sum_j \left(\tilde{w}_{ij} - \frac{\tilde{w}_i \tilde{w}_j}{2\tilde{w}} \right) \delta(C_i, C_j)$$

Maximization of Modularity Quality Function Provides a Partition into Communities.

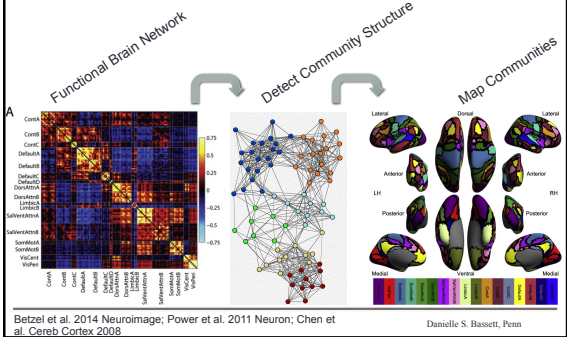
Modularity in the Brain

Functional circuits are defined by brain areas linked by functional interactions.



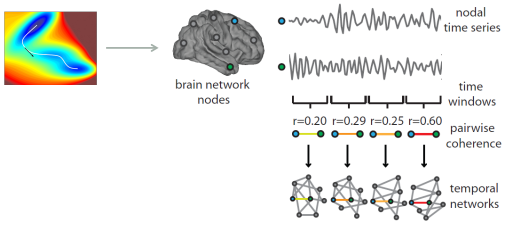
Each functional circuit can therefore be conceptualized as a network module.
Do functional connectomes display modular structure?

Modular Structure Maps to Cognitive Functions



Betzel et al. 2014 Neuroimage; Power et al. 2011 Neuron; Chen et al. Cereb Cortex 2008

Dynamic Functional Brain Networks

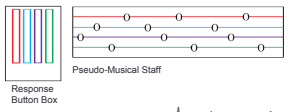


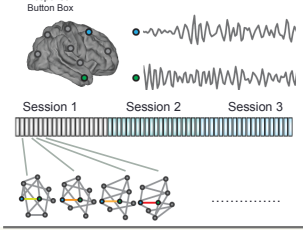
How do brain communication patterns change over time?

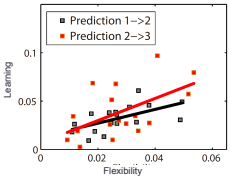
Bassett et al. PNAS 2011 — Danielle S. Bassett, Penn

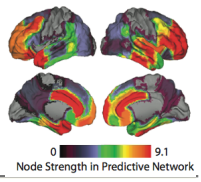
During Learning

Sequential Movement Task Over 3 Days to 6 weeks



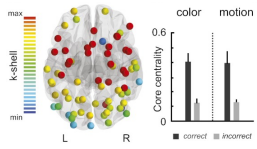






Bassett et al. PNAS 2011, PLoS CB 2013, Nat Neurosci 2015 — Danielle S. Bassett, Penn

Predicting Errors; Coding Cognitive Load



Task-relevant visual areas moved to network core.

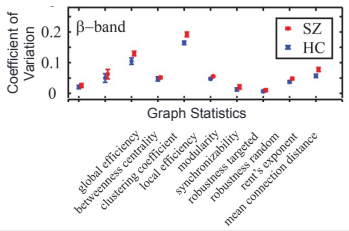
Failure to reconfigure was predictive of errors.

Networks reconfigure to meet increasing task demands.

Ekman et al. PNAS 2012; Kitzbichler et al. 2011 — Danielle S. Bassett, Penn

How do networks reconfigure in disease?

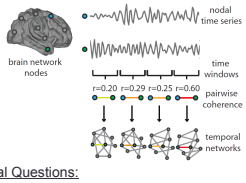
People with schizophrenia show higher network reconfiguration than controls.



2-back WM

Siebenhuhner et al. 2013; Braun et al. In Prep — Danielle S. Bassett, Penn

How does this translate to Epilepsy?



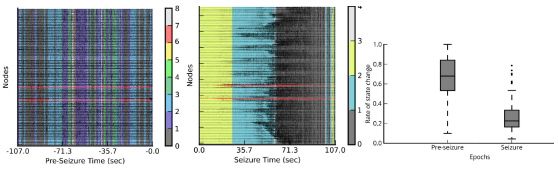
Dynamic network approaches are directly applicable to other imaging modalities and cohorts.

Critical Questions:

- Is reconfiguration during **cognitive tasks** altered in the disease and how?
- Is **baseline** reconfiguration altered?
- Can we understand **seizure** propagation and termination?

Siebenhuhner et al. 2013; Braun et al. In Prep — Danielle S. Bassett, Penn

Mapping Seizure Propagation and Termination



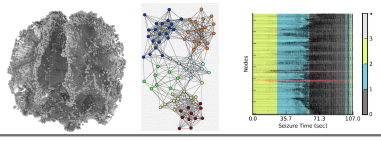
Healthy flexibility -> low dimensional dynamics.

Network connectivity tightens near foci, which may aid seizure termination.

Khambhati et al. PLoS CB 2015; Burns et al. PNAS 2014; Kramer et al. 2011 — Danielle S. Bassett, Penn

Functional Brain Networks

- Represent statistical dependencies between regional activity patterns
- Display modular architecture that changes with behavior and cognitive process
- Offer insight into dynamic and distributed mechanisms of disease and neurological disorders



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Peter Mucha (University North Carolina) & **Mason Porter** (Oxford)

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NIH, NSF, Office of Naval Research

#AESmtg15

American Epilepsy Society

69TH ANNUAL MEETING DECEMBER 4 - 8, 2015 PHILADELPHIA, PA

Merritt-Putnam Symposium

Electrophysiology:

Spanning Units, Local Field Potentials, and Large-Scale Networks in Epilepsy

Catherine Schevon, MD, PhD
Columbia University

December 7, 2015

AMERICAN EPILEPSY SOCIETY 69TH ANNUAL MEETING DECEMBER 4 - 8, 2015 PHILADELPHIA, PA

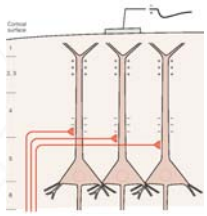
Disclosures

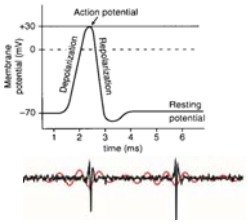
Persyst Development Corp.

Grant Support:
NIH/NINDS
CURE
DARPA

Learning Objectives

- Understand the neural firing patterns that define seizures, and how they relate to EEG recordings



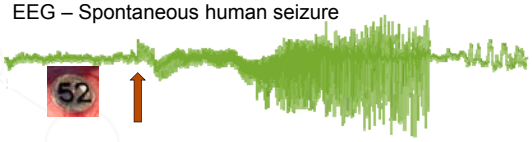


Kandel & Schwartz, Principles of Neural Science

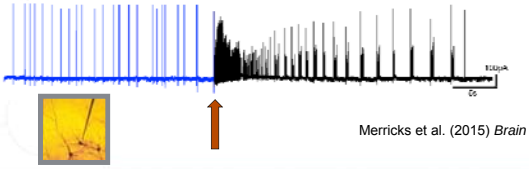
Learning Objectives

- Learn the distinction between activity that *drives* seizures and activity that *responds* to seizures
- Understand the role of inhibition in shaping the EEG appearance of seizures, and their dynamic spatial patterns

EEG – Spontaneous human seizure

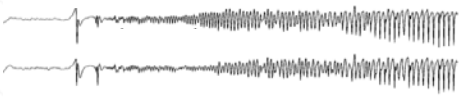


Cell-attached – *in vitro* mouse 0 Mg^{++} model



Merricks et al. (2015) *Brain*

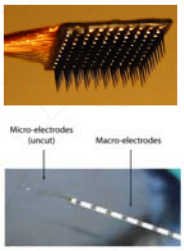
?



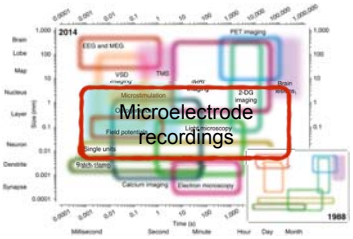
Assumption: EEG is a reliable index of summated neuronal activity in the tissue underneath the electrode

Bishop (1932) *Am J Physiology*

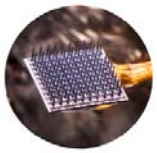
Seizure electrophysiology: Discrepancies of scale



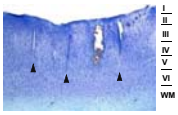
Misra et al. (2014) *JNeurEng*



Sejnowski et al. (2014) *NatNeuro*



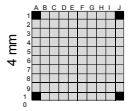
Depth 1 mm (Layer IV/V)
96 microelectrodes in a 10x10 grid
400 micron orthogonal spacing
Active tips 35-75 µm long x 3-5 µm radius



Sampling at 30 Khz/channel:
Action Potentials
- 0.3-6 Khz band
- Biased toward pyramidal cells
- Single Neuron Aps
- **Multiunit Activity (MUA)**

Local Field Potentials (LFPs)
- 2-200 Hz
- **Summated synaptic potentials near electrode**

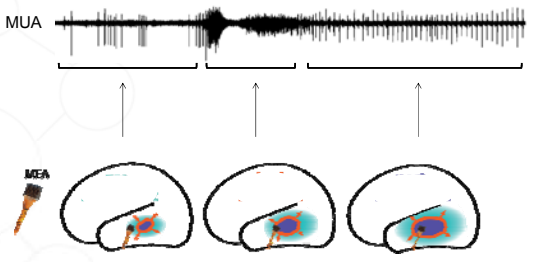
4 mm



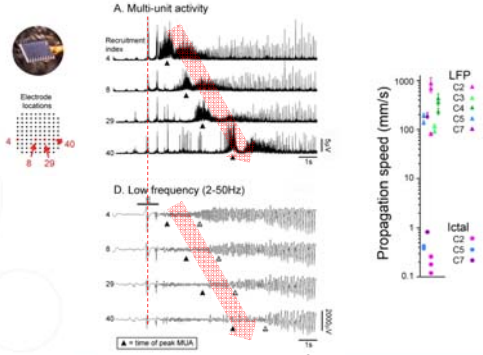
2D Structure
Propagation Speeds

Maynard, Electroencephalogr Clin Neurophysiol, 1998

Human focal seizure



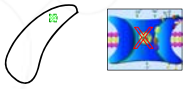
Penumbra ? Ictal wavefront Ictal core



Schevon et al. (2012) *NatComm*

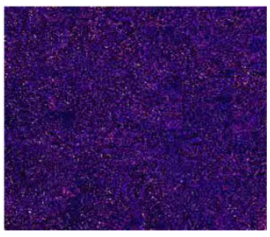
Ca^{++} imaging of a mouse seizure model

Zero Mg^{2+} model in mouse neocortex



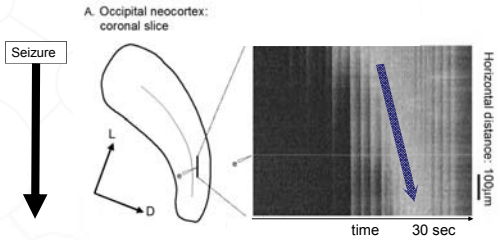
- Facilitates NMDA Receptors
- Preserves inhibition

Propagating seizure



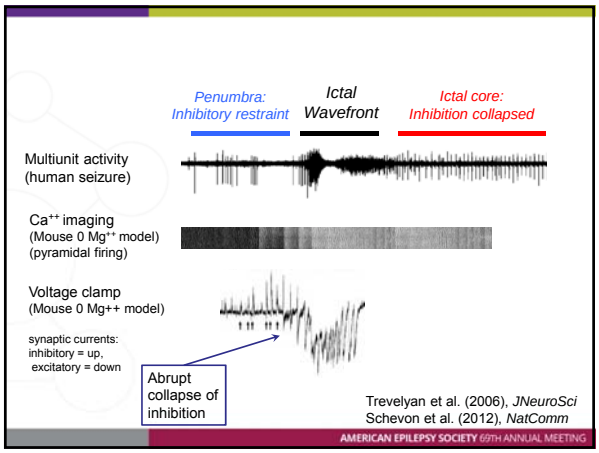
Courtesy of Andrew Trevelyan, Univ Newcastle, UK

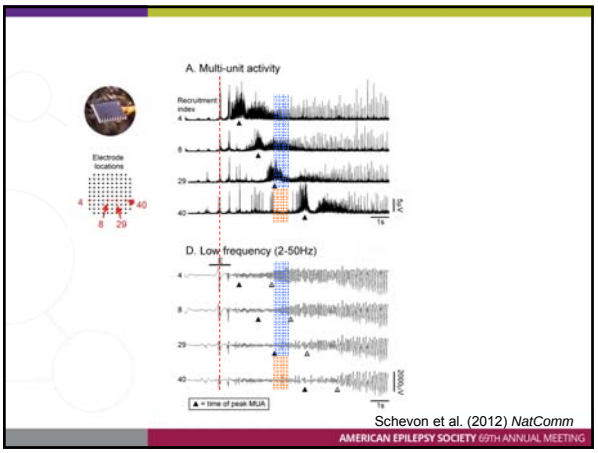
Line scan image of Ca^{++} fluorescence during a seizure



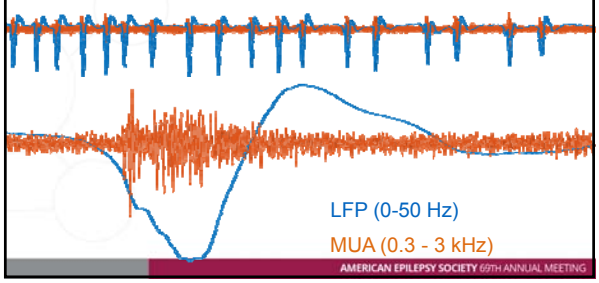
Ictal wavefront

Trevelyan et al, J Neuroscience 2006

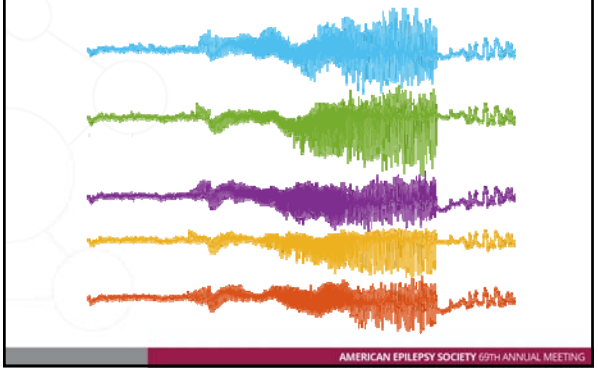




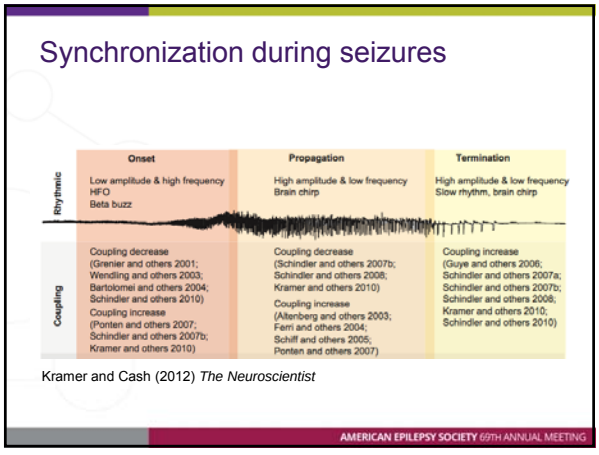
- Why do seizures appear to spread so quickly on clinical EEG recordings?
- What is the basis of apparent wide-area synchronization of the EEG signal?



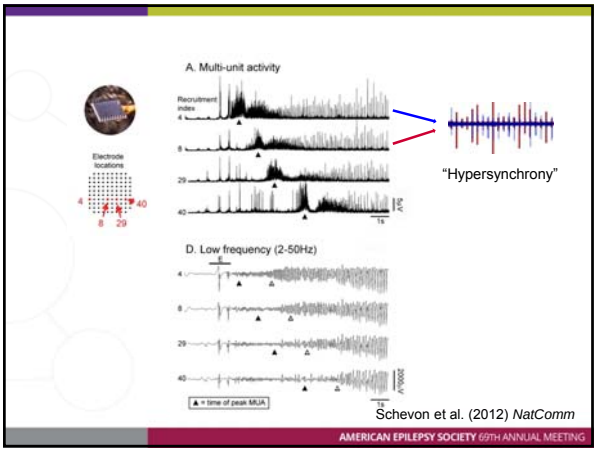
Synchronization: a hallmark of seizures



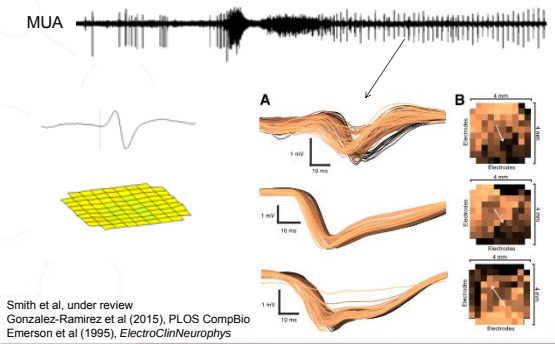
Synchronization during seizures



Kramer and Cash (2012) *The Neuroscientist*

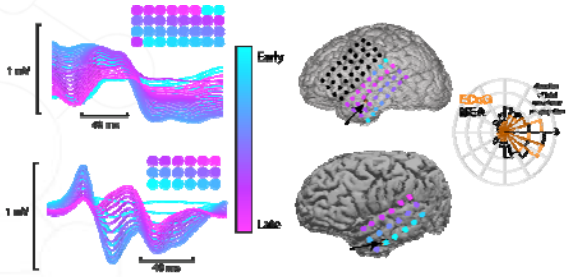


Ictal discharges as traveling waves



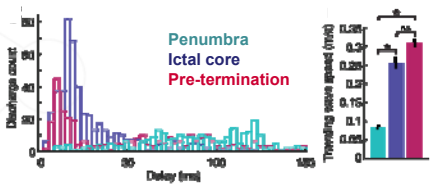
Smith et al, under review
Gonzalez-Ramirez et al (2015), PLOS CompBio
Emerson et al (1995), *ElectroClinNeurophys*

Traveling waves extend across subdural grid



Smith et al, under review

Wave speed depends on location

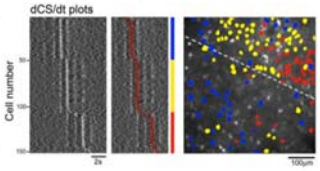


- Traveling wave speed is slower in the penumbra
- Speeds are much faster than ictal wavefront propagation (mean 0.2 m/s vs. < 1 mm/sec)

Smith et al, under review

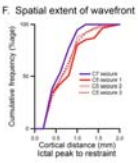
Ictal Wavefront – Spatial Dynamics

The seizing region enlarges by stepwise recruitment of small groups of cells (~50)

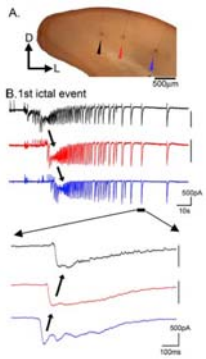


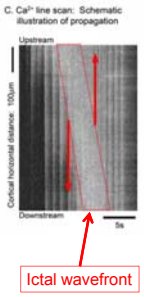
Trevelyan et al. (2006), *JNeuroSci*

The ictal wavefront is ~1 mm wide



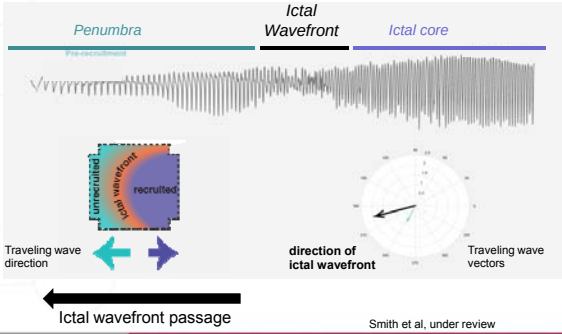
Schevon et al. (2012) *NatComm*





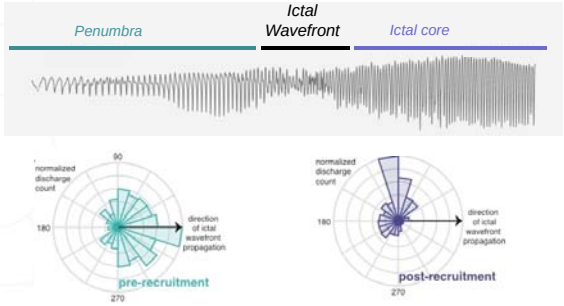
Trevelyan et al (2007) *JNeuroSci*

Traveling wave direction depends on location of the ictal wavefront



Smith et al, under review

Traveling wave direction depends on location of the ictal wavefront



N = 3 patients, 6 seizures

Summary

- The ictal wavefront is the source of seizures:
  - Functionally divides cortical territory into two regions (core = strong inhibition, penumbra = collapsed inhibition)
  - Advances slowly (< 1 mm/sec)
- Epileptiform discharges during a seizure
  - Originate from the ictal wavefront
  - Can travel fast and far
  - Give the appearance of long range EEG synchrony

Merritt-Putnam Symposium: Electrophysiology I: Neurons and their Networks

Sydney S. Cash MD, PhD
Massachusetts General Hospital
Harvard Medical School

December 7, 2015

AMERICAN EPILEPSY SOCIETY 69TH ANNUAL MEETING DECEMBER 4 - 8, 2015 PHILADELPHIA, PA

Disclosure

Industry Disclosures

- None

Research Funding

Learning Objectives

- Understand some of questions and early findings in examining networks dynamics during seizure initiation and propagation
- Learn some of the complexities underlying networks during seizures across multiple scales
- Appreciate the relationship and roles specific cortical circuit and inhibitory neurons may play in sculpting ictal network dynamics

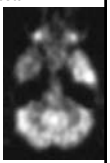
Outline

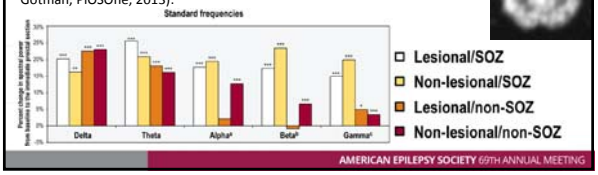
1. Evidence for seizures as network phenomenon from physiology.
2. Macroscopic network dynamics during seizure initiation / propagation
3. Changing circuit involvement and networks at the microscale as seizures spread.
4. Networks before termination
5. Conclusions and a network based model of seizure activity.

Seizures as network phenomenon - how focal is a focal seizure?

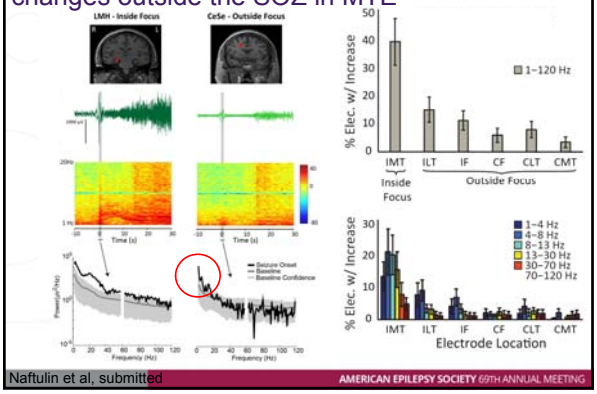
Variety of different evidence suggesting that even "very focal" seizures involve widespread brain structures and networks:

- Substantial evidence of extra focal changes in structure and function:
  e.g. in patients with clear-cut mesial temporal sclerosis with "proven" onsets in hippocampal structures:
  -- widespread changes in white and grey matter (Staba et al)
  -- Common finding of hypometabolism throughout temporal lobe
- Physiological changes at/before seizure onset onside the SOZ:
  -- Embedded in multiple prediction attempts
  -- Changes in various frequencies before seizure onset (Perruca, Dubeau, Gotman, PlOSOne, 2013):





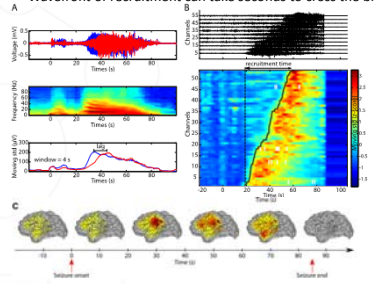
Seizures as network phenomenon – activity changes outside the SOZ in MTE



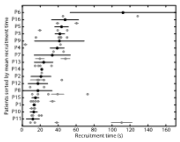
Naftulin et al, submitted

Network recruitment is relatively slow

Wavefront of recruitment can take seconds to cross the brain …



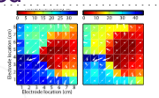
… showing slow seizure spread with significant variability in and between patients …

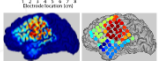


Martinet et al, and Kramer, 2015

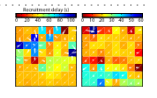
Network recruitment may be organized or disorganized

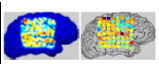
… well organized spread in some patients …



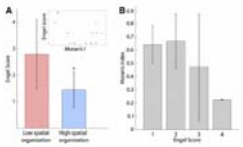


… and poorly organized in others.



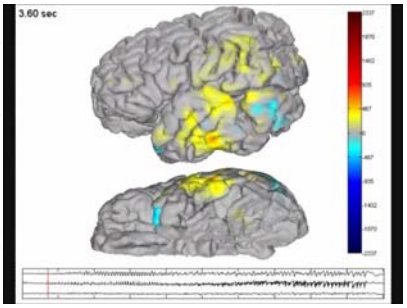


Organization corresponds to Engel outcome



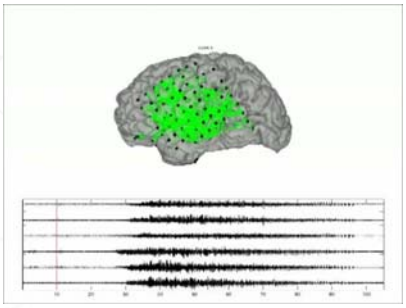
Martinet et al, and Kramer, 2015

Wave propagation during the seizure shows variable pattern across the cortical surface



Rodrigo Zepeda, Alex Chan, Andrew Dykstra

Evolution of the network during the seizure shows multi-stages

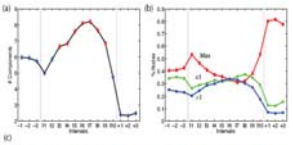


Kramer et al, J. Neurosci. 2010

sec

Evolution of the network during the seizure shows multiple stages

components in the network increases in mid-seizure



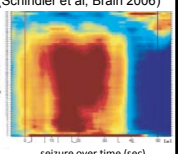
Size of largest component decreases in mid-seizure

Early Ictal

Late Ictal

(red = members of largest subgroup)

Eigenvalue decomposition method shows similar results (Schindler et al, Brain 2006)

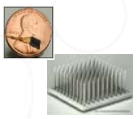


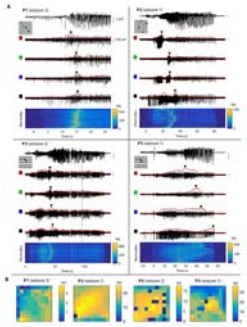
seizure over time (sec)

Kramer et al, J. Neurosci. 2010

Multiple stages of network dynamics during propagation reflected at microscale as well

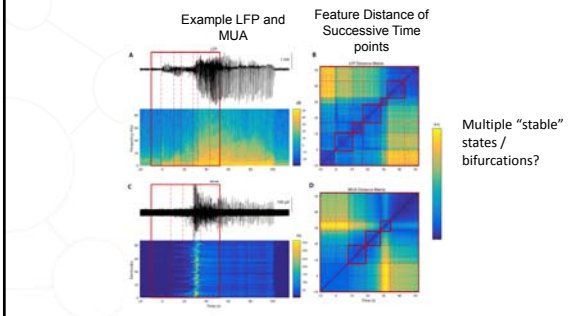
Examples of MUA / LFP changes in 3 patients, 4 seizures as seizure spreads to microelectrode array





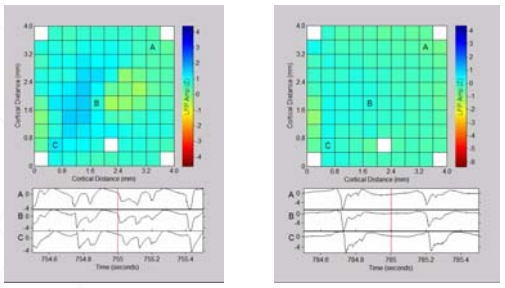
Wagner, et al., Truccolo, Neuroimage 2015

Multiple stages of network dynamics during propagation reflected at microscale as well



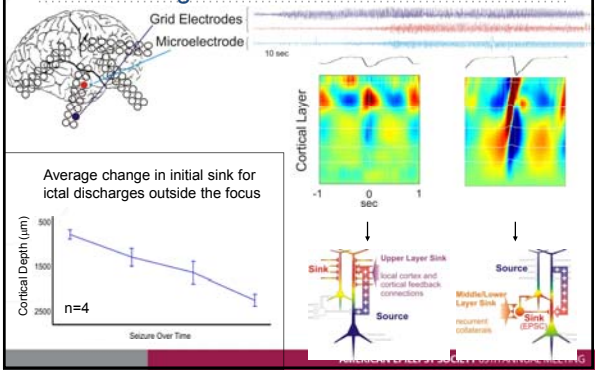
Wagner, et al., Truccolo, Neuroimage 2015

Change in dynamics from complex to simple wave propagation at microscale



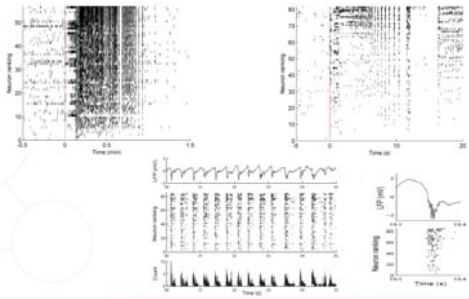
Mid-Seizure End of Seizure

Dynamics of microcircuitry correlates with network changes -



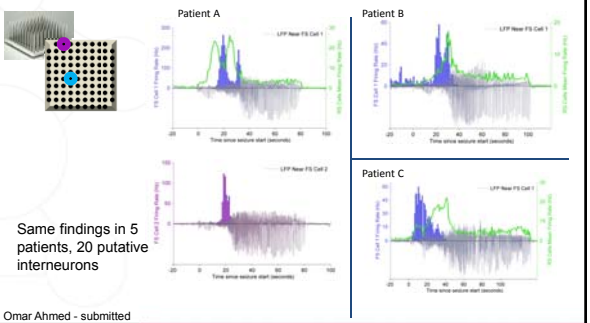
… and at the level of individual neurons

Heterogeneous firing early in seizure changes to more synchronized firing by the end of the seizure (especially in spike-wave seizures)



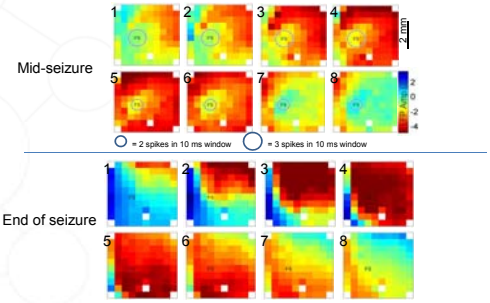
Truccolo et al, 2011, 2014

Change from fragmented to coalescent networks may reflect loss of inhibition



Omar Ahmed - submitted

Change from fragmented to coalescent networks may reflect loss of inhibition

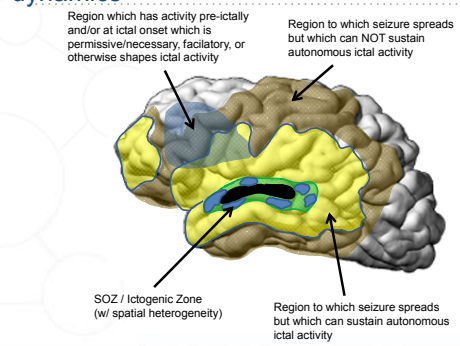


Omar Ahmed - submitted

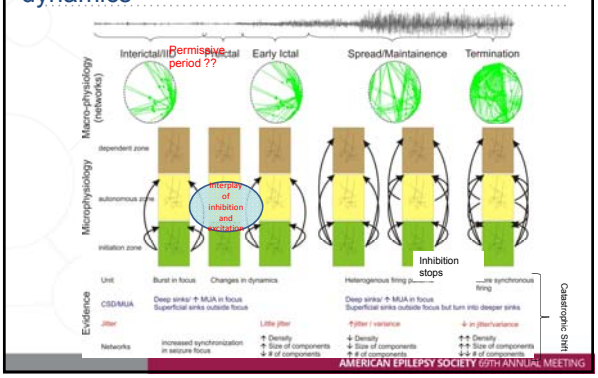
Conclusions

1. Focal epilepsy is a network phenomenon
2. Networks at multiple scales show rich dynamics during seizure initiation, propagation, maintence and termination
3. Those dynamics are characterized by multiple stages:
   a. an initiation period where the focus dominates (but is probably not the only player)
   b. an early period when other areas are being recruited
   c. a middle period where different areas with seizure activity may be acting semi-idependently.
   d. a termination period during which there is greater coalescence (perhaps due to loss of inhibition)

A spatiotemporal model of seizure network dynamics



A spatiotemporal model of seizure network dynamics



Acknowledgements

PATIENTS!

Lab Members

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Massachusetts General Hospital
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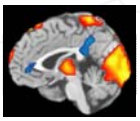
Emad Eskandar
Leigh Hochberg

NYU Epilepsy Center
Orrin Devinsky
Ruben Kuzneicky
Werner Doyle
Thomas Thesen
Daniel Friedman

Networks in Cognition, Consciousness, and Epilepsy

Hal Blumenfeld, MD, PhD
Yale School of Medicine



December 7, 2015

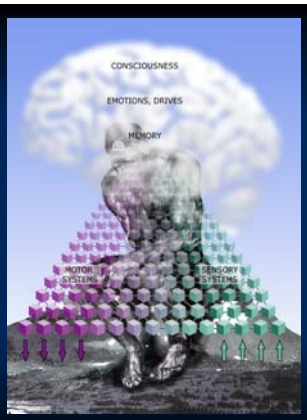
AMERICAN EPILEPSY SOCIETY 69TH ANNUAL MEETING DECEMBER 4 - 8, 2015 PHILADELPHIA, PA

Disclosure

None

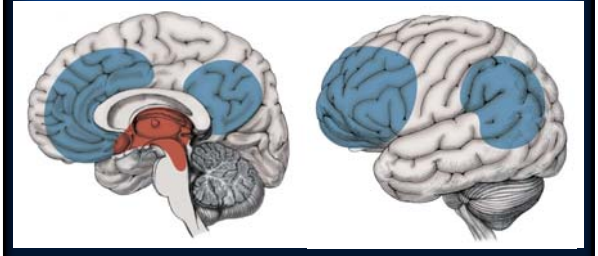
Learning Objectives

- Understand why some absence seizures impair consciousness while others do not
- Interpret subcortical network changes to explain impaired consciousness in generalized tonic-clonic seizures
- Identify decreased subcortical network function in focal seizures as a therapeutic target for neurostimulation to restore consciousness



Blumenfeld, 2002

The "Consciousness System"



Blumenfeld, 2010

EFA, 1991

Childhood Absence Epilepsy

- **Transient unconsciousness; Onset age 6-7 yrs**
- **Generalized ~3Hz spike-wave on EEG**

Question

Why is consciousness impaired in absence seizures?

Focal brain dysfunction

OR

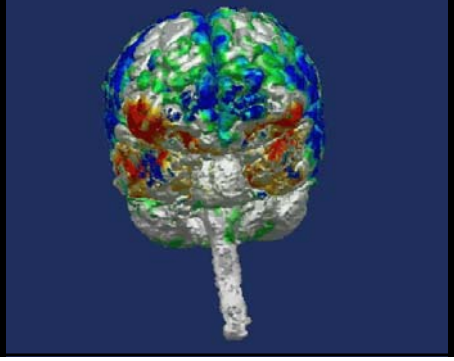
Widespread bilateral network dysfunction

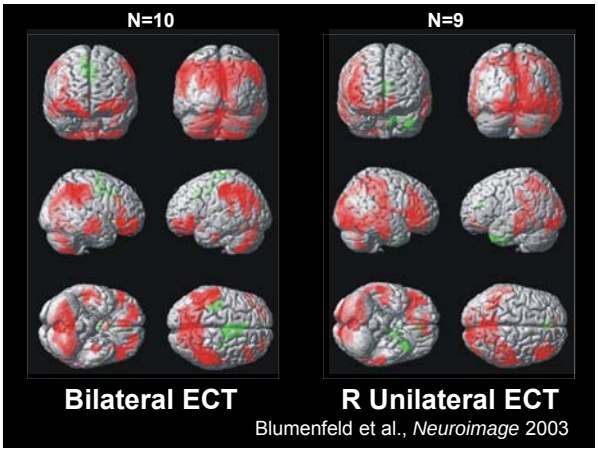
Unpublished fMRI results will be shown here

Guo et al., *In preparation* 2016

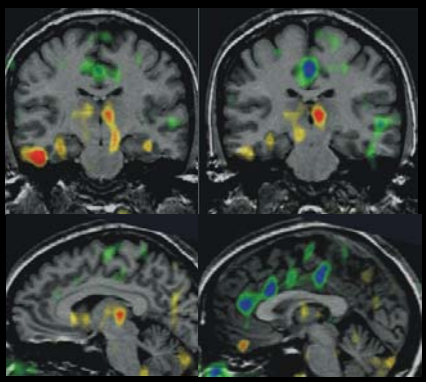
Unpublished fMRI results will be shown here

Guo et al., *In preparation* 2016

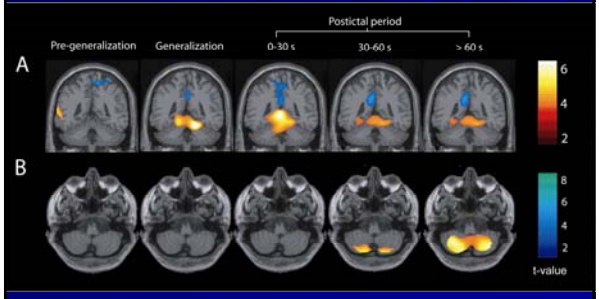




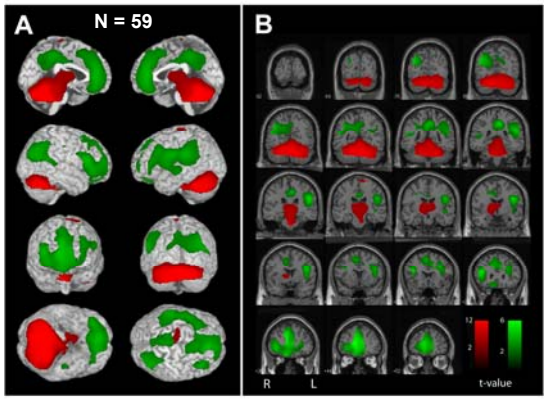
Blumenfeld et al., *Neuroimage* 2003



Cerebellar Network Effects



Blumenfeld et al, 2009 *Brain*

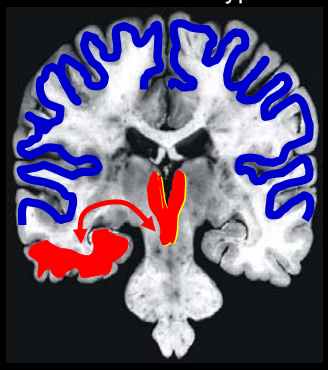


Blumenfeld et al, 2009 *Brain*

Temporal Lobe Seizure

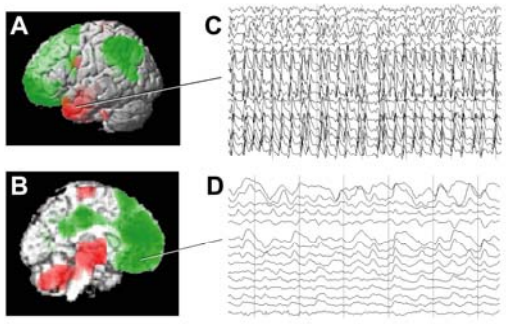
Impaired Consciousness

Network Inhibition Hypothesis



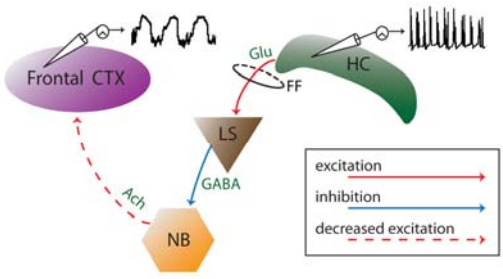
Norden and Blumenfeld, 2002

Digital Anatomist Project, University of Washington



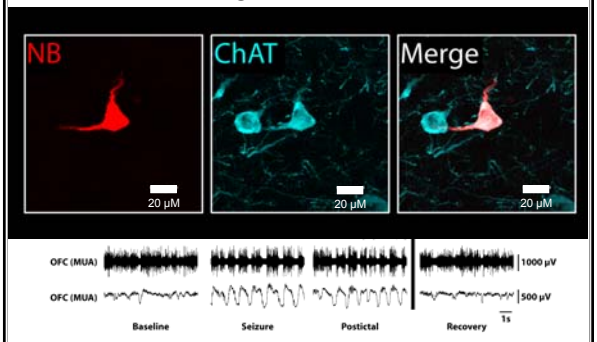
Blumenfeld et al, 2004 *Cerebral Cortex* (left) *Neurology* (right)

Network Inhibition Hypothesis Revisited: Cortical Deactivation in Limbic Seizures



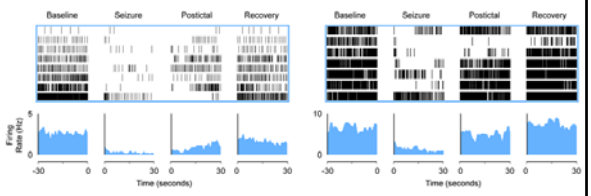
Englot and Blumenfeld 2009

Brainstem cholinergic firing decreases during limbic seizures



Motelow et al 2015 *Neuron*

PPT Ach neurons NB Ach neurons



Unpublished Raphe magnus 5-HT neuron data will be shown here

Motelow et al, 2015 *Neuron*

Zhan et al, 2015 in prep

Unpublished video will be shown here

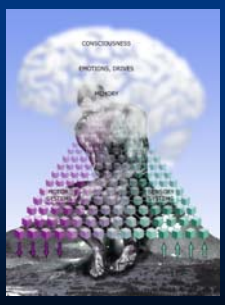
Kundishora et al, 2015 unpublished

Networks and Consciousness in Seizures

Temporal Temporal

TC ictal TC post-ict TC ictal

Absence Absence Absence



Merritt-Putnam Symposium: Epilepsy Networks

Greg Worrell MD, PhD
Mayo Clinic

December 7, 2015

Conclusions

- Networks are representations of complex systems
- Brain networks span multiple scales: Synapses, Neurons, projections…
- Brain networks & the role in epilepsy can be explored with multiple modalities of data: MRI, fMRI, EEG, MEG ….

Panel Discussion

#AESmtg15