Message from the Nebraska EPSCoR Director

Dear Participants,

Welcome to the 2014 Nebraska Neuroscience Symposium. Research in the field of neuroscience continues to make dynamic discoveries, each advance yielding greater understanding of the brain: humanity’s principal resource for addressing the challenges and possibilities we face. Your interactions here are part of what moves this work forward.

Nebraska EPSCoR is proud to host this gathering. EPSCoR—the Experimental Program to Stimulate Competitive Research—was created by the U.S. Congress to improve research infrastructure and capacity of a group of states. We work with research and education partners to enhance their capabilities and benefit Nebraska’s workforce development and economic growth.

At today’s symposium—our 10th annual event and second devoted to neuroscience—we appreciate National Science Foundation funding in support of these important connections. Our speakers bring expertise from standout careers. We greatly value their presence and hope you enjoy the knowledge transfer and networking opportunities.

F. Fred Choobineh, P.E., Ph.D.
Director, Nebraska EPSCoR

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Thomas F. Murray, Committee Chair, Creighton University
Rick Bevins, University of Nebraska-Lincoln
Anna Dunaevsky, University of Nebraska Medical Center
Jeffrey French, University of Nebraska Omaha
Barbara J. Morley, Boys Town National Research Hospital
Wallace B. Thoreson, University of Nebraska Medical Center
Tony W. Wilson, University of Nebraska Medical Center

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Clint Chapman, Symposium graphics
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Structural Basis for Function of Voltage-gated Sodium and Calcium Channels

WILLIAM CATTERALL, Ph.D.
Chair and Professor, Dept. of Pharmacology
University of Washington

8:10 – 8:50 A.M.

ABSTRACT: Voltage-gated sodium and calcium channels initiate action potentials, synaptic transmission, and excitation-contraction coupling that are important targets for drugs. The high-resolution structure of a bacterial ancestor of voltage-gated sodium and calcium channels (NavAb) reveals the structural basis for the ‘sliding-helix’ mechanism of voltage-dependent activation, inhibition by pore-blocking drugs, and slow, voltage-dependent inactivation. The NavAb selectivity filter is short, ~4.6 Å wide, with four glutamate side-chains surrounding the ion-conduction pathway. Addition of two more negative charges increases Ca:Na selectivity >10,000-fold and reveals the mechanism of ion-conduction and selectivity. Binding sites for pore-blocking ions and drugs are being revealed at atomic resolution.

BIO: Dr. Catterall received his B.A. in Chemistry from Brown University (1968), Ph.D. in Physiological Chemistry from Johns Hopkins (1972), and postdoctoral training in neurobiology and molecular pharmacology with Dr. Marshall Nirenberg at the National Institutes of Health (1972-1974). Following three years as a staff-scientist at NIH, he joined the University of Washington in 1977 as associate professor of pharmacology, became professor in 1981, and chair in 1984. Catterall discovered the voltage-gated sodium and calcium channel proteins, which initiate electrical and chemical signaling in excitable cells, and his work has contributed much to understanding their structure, function, regulation, and molecular pharmacology. Catterall is a member of the US National Academy of Science and the Royal Society of London, UK. He has received numerous awards, including the Gairdner International Award of Canada in 2010.

Axon Guidance and Regeneration: Transmembrane Receptors and RNA-based Regulation

JOHN FLANAGAN, Ph.D.
Professor of Cell Biology, Dept. of Cell Biology
Harvard Medical School

8:50 - 9:30 A.M.

ABSTRACT: Axons find their correct targets during development by a process of guided migration. Our lab identified some of the first axon guidance cues, and currently we are interested in mechanisms that produce a spatially appropriate response within the axon, particularly novel RNA-based processes. Mechanisms to be discussed direct RNA networks and mRNA translation with spatial precision to specific subcellular locations, with roles in axon extension. Finally, if connections are lost due to injury or disease, axons in the adult CNS do not regenerate. Our work identified a receptor for a major class of regeneration inhibitors, with implications for strategies toward CNS axon repair.

BIO: Dr. Flanagan received his undergraduate degree in Biochemistry from the University of Oxford, England, and his Ph.D. from the Medical Research Council Laboratory of Molecular Biology at the University of Cambridge, England. He came to the Genetics Department at Harvard Medical School in 1986 as a postdoctoral fellow, and then joined the faculty of the Cell Biology Department in 1991. He is currently a professor in the Cell Biology Department at Harvard Medical School, and a member of the Program in Neuroscience. His research interests are in cell-cell signaling, particularly in the development and regeneration of neuronal connections.
Mouse In Vivo Imaging and Optogenetic Tools for Elucidating Cortical Circuit Structure and Function Following Stroke

TIMOTHY MURPHY, Ph.D.
Professor, Dept. of Psychiatry, Univ. of British Columbia

9:30 – 10:10 A.M.

ABSTRACT: During stroke, neurons can show signs of structural damage after as little as two minutes of ischemia. Using mice and in vivo two-photon imaging of space-filling GFP provides an assessment of fine synaptic structure: before, during, and after the stroke. Methods for local (two-photon) and regional assessment (laser speckle) of blood flow are also introduced. Over time, surviving brain tissue is thought to compensate for regions lost to stroke. It is assumed that recovery is a process that occurs over weeks and involves both the formation of new structural circuits and the alternative use of spared circuits. To assess changes in functional connectivity after stroke, an automated approach was developed to monitor intra- and inter-hemispheric functional relationships by activation of ChR2-expressing cortical neurons at arbitrary cortical points in transgenic mice.

To monitor regional cortical activity, organic voltage sensitive dyes and other genetically encoded sensors are used. In vivo imaging of functional connectivity is extended to GCAMP, iGluSNFR, and VSFP-butterfly. Graph theory and complex network analysis are applied to connection matrices derived from these functional maps, to elucidate reciprocal connections between primary and secondary sensory areas, identify network hubs, and determine asymmetries in intracortical connectivity. Comparisons of functional connectivity map to the cortical structural connectome available from the Allen Institute. Anticipated new optogenetic approaches to both monitor and manipulate neuronal function are important to describe how spared cortical circuits compensate for brain tissue lost to stroke.

BIO: Dr. Murphy earned his Ph.D. from Johns Hopkins in 1989. He is a basic scientist interested in applying high-resolution imaging techniques to questions involving stroke in live animals. Combining high-resolution structural imaging in live animals with somatosensory response mapping, his lab has evaluated relationships between synaptic structure and brain circuit function during and after ischemia. With UBC’s Department of Psychiatry, he constructs and optimizes instrumentation for in vivo structural and functional brain imaging to investigate mouse models of human disease.

Plasticity of the Auditory Cortex on Multiple Time Scales

PATRICK KANOLD, Ph.D.
Associate Professor, Dept. of Biology
University of Maryland

10:30 – 11:10 A.M.

ABSTRACT: One of the hallmarks of the brain is the ability of its circuits to be sculpted by experience. This is especially evident in primary sensory areas during critical periods in development, but also occurs in adults. The mechanisms and circuits underlying these processes are unknown. We use in vivo 2-photon imaging, electrophysiology, and in vitro laser scanning photostimulation to investigate these issues. We find that the adult auditory cortex is plastic on a variety of time scales and conditions. For example, top-down circuits from frontal areas involved in cognitive control are present in primary sensory areas and enable rapid large-scale cortical plasticity. Moreover, short-term visual deprivation after the critical period can lead to altered auditory responses in the auditory cortex. We describe these phenomena and analyze the circuits that give rise to them. Together we find that large-scale plasticity in the cerebral cortex does not stop after development but is the product of a complex and dynamically changing cortical circuit. Collectively, these results provide insight into how sensory information within the auditory cortex is represented and adaptively transformed to enhance auditory function.

BIO: Dr. Kanold is an associate professor of Biology at University of Maryland. Dr. Kanold received his M.Sc. (Dipl.-Ing.) in Electrical Engineering at Technical University Berlin (Germany), his Ph.D. in Biomedical Engineering from Johns Hopkins University, and did postdoctoral research at Harvard University Medical School with Dr. Carla Shatz. His research centers on neuroplasticity and neural development, in particular in the visual and auditory cortex. His laboratory uses state of the art electrophysiological, photostimulation and imaging approaches in animals to study neural circuits and mechanisms that enable brain plasticity throughout life.
Imaging Structural Changes: Vesicle Fusion and Endocytosis in Live Cells
LING-GANG WU, M.D., Ph.D.
Senior Investigator, NIH National Institute of Neurological Disorders and Stroke
11:10 A.M. - Noon

ABSTRACT: Vesicle fusion with the plasma membrane generates an Ω-shaped membrane profile. Its pore is thought to dilate until flattening (full-collapse), followed by classical endocytosis to retrieve vesicles. Alternatively, the pore may close (kiss-and-run), but its endocytic roles remain poorly understood. Here, using confocal and STED imaging, we find that fusion-generated Ω-profiles may enlarge or shrink while maintaining vesicular membrane proteins. Closure of fusion-generated Ω-profiles, which produces various sizes of vesicles, is the dominant mechanism mediating rapid and slow endocytosis within ~1-30 s. Strong calcium influx triggers dynamin-mediated closure. Weak calcium influx does not promote closure, but facilitates the merging of Ω-profiles with the plasma membrane via shrinking rather than full-collapse. These results establish a model, termed Ω-exo-endocytosis, in which the fusion-generated Ω-profile may shrink to merge with the plasma membrane, change in size, or change in size then close in response to calcium, which is the main mechanism to retrieve dense-core vesicles.

BIO: Dr. Wu received a Ph.D. degree in 1994 (Baylor College of Medicine, Houston) and from 1994 to 1999 was a postdoc in professor William Betz’s lab (University of Colorado Medical School) and Bert Sakmann’s lab (Max Planck Institute in Heidelberg, Germany). From 1999-2003, he was an assistant professor at Washington University in St. Louis. He joined NINDS as an investigator in 2003 and was promoted to senior investigator in 2007. His laboratory investigates the fundamental mechanisms of synaptic transmission, including how calcium channels control exocytosis; how fusion pores open, close or dilate; how endocytosis is initiated and mediated; and mechanisms of synaptic plasticity.

Please enjoy lunch with colleagues at your tables.

If you use social media, you are encouraged to post about this event, using the hashtag: #NebNeuro.

We look forward to your participation at the poster session in the adjacent room following today’s sessions!
Mechanisms Underlying Nicotinic Cholinergic Control of Cortical Neuron Morphology During Development

MARINA PICCIOTTO, Ph.D.
Charles B.G. Murphy Professor in Psychiatry, Deputy Chair for Basic Science and Professor of Neurobiology at Yale University

1:00 – 1:40 P.M.

ABSTRACT: Nicotinic acetylcholine receptors (nAChRs) are critical mediators of the effects of acetylcholine in the brain. Although the role of nAChRs in circuits underlying reward have been well studied, nAChRs are expressed throughout the brain and are important for many neuronal processes, including those related to appetite and to development of circuits involved in cognitive function. Identification of these diverse central effects of nAChRs provides new avenues for understanding the role of these receptors in normal brain function, and can contribute to the development of novel medications for smoking addiction and obesity.

BIO: Dr. Picciotto is Charles B.G. Murphy Professor in Psychiatry, Deputy Chair for Basic Science and Professor of Neurobiology at Yale University. She is a member of NIDA’s Scientific Council, Treasurer Elect of SFN and was elected to the Institute of Medicine of the National Academies of Sciences. Dr. Picciotto received her B.S. from Stanford and her Ph.D. from The Rockefeller University. She conducted postdoctoral work at the Pasteur Institute before joining the faculty at Yale University. Her laboratory studies the role of nicotinic acetylcholine receptors in mouse models, including research related to addiction, depression, learning and appetite.

How Nicotinic Signaling Shapes Neural Networks

DARWIN BERG, Ph.D.
Distinguished Professor, Section of Neurobiology, Division of Biological Sciences, University of California San Diego

1:40 – 2:20 P.M.

ABSTRACT: Exposure to nicotine early in development is known to have long-lasting effects on subsequent behavior, including increased propensities for addiction and neurological disorders. We find that early exposure to nicotine produces long-lasting increases in the number of glutamatergic synapses and the ratio of excitatory-to-inhibitory input neurons receives. Moreover, the system remains vulnerable to excessive responses to nicotine subsequently, likely to produce behavioural abnormalities. Normally, endogenous nicotinic signalling drives early network development and induces a major transition postnatally. We have identified a microRNA that helps mediate these changes, driven in part by nicotinic input to regulate multiple pathways in parallel.

BIO: Dr. Berg is a Distinguished Professor of Biology at the University of California, San Diego. He received his Ph.D. from the University of California, Berkeley, and carried out postdoctoral studies at Harvard Medical School. He is the recipient of a Guggenheim Fellowship and a Javits Neuroscience Investigator Award. He served as Councillor and Treasurer for the Society for Neuroscience and as Chair of Biology and of Neurobiology at UCSD. He is a Fellow of the AAAS. His research focuses on synapse formation and plasticity, examining the roles of nicotinic cholinergic signaling in shaping neural networks and modulating their functions.
Mechanisms Underlying Motivational Properties of Nicotine

PAUL KENNY, Ph.D.
Professor and System Chair, Pharmacology and Systems Therapeutics; Director, Experimental Therapeutics Institute, Mount Sinai Hospital

2:20 - 3:00 P.M.

ABSTRACT: Tobacco addiction occurs when the motivation to obtain nicotine comes to dominate the behavioral repertoire at the expense of alternative sources of natural reward, but underlying mechanisms are unknown. Hypocretin (orexin) is thought to control nicotine intake by regulating its rewarding effects. I will present evidence that pharmacological or genetic disruption of hypocretin-1 receptor (Hcrt-1R) signaling does not alter nicotine reward but instead reduces the motivational “value” of the drug, reflected in greatly diminished effort to obtain nicotine infusions. Surprisingly, hypocretin controls the value of nicotine not through midbrain dopamine neurons but instead through a novel population of GABAergic neurons in dorsal thalamus that densely express (Hcrt-1R). These Hcrt-1R-regulated cells control the allocation of behavioral resources to obtain nicotine by controlling the activity of local thalamus neurons. Accordingly, pharmacogenetic stimulation of surrounding thalamic neurons decreases effort to obtain nicotine rewards whereas inhibition dramatically increases the value of nicotine, reflected in addiction-like responding for the drug when its delivery is accompanied by noxious footshocks. Hypocretin transmission in dorsal thalamus therefore couples the rewarding effects of nicotine to the allocation of behavioral effort to obtain the drug.

BIO: Dr. Kenny completed his Ph.D. in neuropharmacology at King's College London in 2000, after earning a biochemistry degree from Trinity College Dublin in 1996. His graduate studies focused on understanding the role for nicotinic receptors in regulating anxiety-like behaviors in rodents. He completed post-doctoral training at The Scripps Research Institute in La Jolla, California, in the laboratory of Dr. Athina Markou (2000-2005) where he investigated the role for glutamate transmission in nicotine dependence. After establishing his laboratory at The Scripps Research Institute in Florida in May 2006, he focused on the molecular mechanisms of drug addiction and obesity. This year he moved to the Icahn School of Medicine at Mount Sinai as Chair of the Department of Pharmacology & Experimental Therapeutics.

Nicotine Decreases Ethanol-induced Dopamine Signaling and Increases Self-administration via Steroid Hormones

JOHN DANI, Ph.D.
The David J. Mahoney Professor of Neurological Sciences and Chairman, Department of Neuroscience
University of Pennsylvania

3:15 – 3:55 P.M.

ABSTRACT: Alcohol and nicotine (as obtained from tobacco) are the two most abused and costly drugs to society. Epidemiological studies have found a positive correlation between nicotine and alcohol use, with alcoholism approximately 10 times more prevalent in smokers than in non-smokers. In addition to psychosocial and genetic factors, the interaction between nicotine and alcohol also arises from a complex pharmacological interplay. These drugs activate common neural substrates, including the mesolimbic dopamine (DA) reward system and the hypothalamic-pituitary-adrenal (HPA) axis associated with steroid hormone signaling. Furthermore, both the DA and HPA systems are centrally linked to drug use and addiction. Long-term alterations in the steroid hormone systems are implicated in alcohol use disorders. Steroid hormones, such as the glucocorticoids, have a profound influence on neural function and modulate DA transmission. Neuroactive steroids also modify GABA transmission, which may contribute to the pharmacological action of alcohol.

BIO: Dr. Dani received his Ph.D. in Physiology from the University of Minnesota. After postdoctoral training, he joined Baylor College of Medicine where he became Professor and Director of the Center on Addiction, Learning, and Memory. He has received a number of awards, including the New Investigator Research Award and the Jacob Javits Neuroscience Award from the National Institutes of Health. During the summer of 2013 he became the Chair of the Department of Neuroscience and Director of the Mahoney Institute for Neurosciences at the Perelman School of Medicine, University of Pennsylvania.
Recent Progress Toward a High-performance Neural Prosthetic Arm and Hand

ANDREW SCHWARTZ, Ph.D.
Professor of Neurobiology, University of Pittsburgh

3:55 – 4:35 P.M.

ABSTRACT: A better understanding of neural population function would be an important advance in systems neuroscience. Neurons encode many parameters simultaneously, but the fidelity of encoding at the level of individual neurons is weak. We have developed a simple extraction algorithm to capture arm movement data and shown that a paralyzed patient who cannot move any part of her body below her neck can use a high-performance “modular prosthetic limb” to control 10 degrees-of-freedom simultaneously. The control of this artificial limb is intuitive and the movements are coordinated and graceful, closely resembling natural arm and hand movement.

BIO: Dr. Schwartz received his Ph.D. in Physiology from the University of Minnesota in 1984. He then went on to a postdoctoral fellowship with Dr. Apostolos Georgopoulos, who was developing the concept of directional tuning and population-based movement representation in the motor cortex. He has been at the University of Pittsburgh since 2002. Through his research, Schwartz developed a paradigm to explore cortical signals generated during volitional arm movements. This effort showed that a high-fidelity representation of movement intention could be decoded from the motor cortex. This has enabled technology now being used by paralyzed subjects to operate a high-performance prosthetic arm and hand.

Rational Design of Therapeutic Neuromodulation Devices: The Devil is in the Dosing

SARAH H. LISANBY, M.D.
Chair of the Department of Psychiatry & Behavioral Sciences, Duke University

4:35 – 5:15 P.M.

ABSTRACT: not available at print time

BIO: Dr. Lisanby, an internationally recognized leader in the field of brain stimulation, is professor and chair of the Department of Psychiatry and Behavioral Sciences at Duke University School of Medicine. She is also a professor of Psychology and Neuroscience at Duke University School of Arts and Sciences. She joined Columbia University’s psychiatry faculty in 1998, and was the founding director of the Brain Stimulation and Therapeutic Modulation Division there from 2005-2010.

An expert in translational research in the field of brain stimulation, Dr. Lisanby has pioneered a novel depression treatment called magnetic seizure therapy (MST), which her team took through the steps from bench to bedside, and is now at the stage of multi-center, international trials. She is the co-author on more than 150 publications in prestigious scientific journals, including The New England Journal of Medicine.

An active researcher supported by a series of NIH, foundation, and industry grants, Lisanby directs the Duke Brain Stimulation and Neurophysiology Center. Her professional awards include the Distinguished Investigator Award from the National Alliance for Research on Schizophrenia and Depression (NARSAD), the Max Hamilton Memorial Prize of the Collegium Internationale Neuro-Psychoharmacologicum (CINP), the Gerald Klerman Award from the National Depression and Manic Depression Association (NDMDA), and the NARSAD Klerman Award.
The Role of CRF-R2 in Alloparental Care in Mongolian Gerbils
Michelle Huffman, Andrew K. Binie, Jeffrey A. French

Both CRF-R1 and CRF-R2 affect parental behaviors, but the relationship between parental care and CRF-R2 remains unclear. We examined the effect of a CRF-R2 agonist and antagonist on alloparental care in Mongolian gerbils. Subjects received either a CRF-R2 agonist (Urocortin) or a CRF-R2 antagonist (Astressin2B) and exposed to a novel pup stimulus. Moderate doses of both hormones affected caregiving behavior. Dose effects depended on previous caregiving experience and appeared independent of CRF-system activation. Given that CRF-R2 is expressed in several social areas of the brain, CRF-R2 may influence parental care by activating other neural systems associated with social behavior.

Determination of roles of different molecular crowding mechanisms using crowding agents on protein secondary versus tertiary structure
Kelsey Christensen, Grant Ozaki, Erin Wilson, Mark Wilson

The natural environment in a human cell contains densely packed macromolecules that crowd the intracellular environment; this crowding affects folding stability and conformation of proteins by providing protection from denaturation. The crowded environment alters the structures and interactions of the proteins through hydrophobic interactions, changes in solvent properties and volume exclusion effects. Our ultimate goal is to develop the best model system of the crowded native environment in order to understand how proteins function in vivo. The model system is chosen because of the difficulty of studying proteins in their natural environments. The goal of this research is to define the nature and size of molecular crowding mechanisms on secondary and tertiary levels of protein structure through crowding with molecular crowding agents and sol-gel encapsulation using circular dichroism spectroscopy to monitor protein folding. The proteins of interest, JAK-1 and osteocalcin, both adopt alpha helical secondary structures in their folded conformational states; however, osteocalcin includes a disulfide bond to stabilize its tertiary structure, while JAK-1 has only secondary structure. Both proteins are disordered or adopt random coil conformation in solution. Changes in the magnitude of the hydrophobic effect, solvent properties and volume exclusion were explored using the crowding agents Ficoll-70, TMAO, and a sol-gel encapsulation technique with JAK-1 and osteocalcin.

Behavioral profile and amygdalar gene expression in a congenic-like fearful DxH recombinant inbred strain with a DBA/2j background
Deniz Yilmazer-Hanke, Bernadette Clement, Rochelle Wickramasekara, Jeff Bussness, Joachim Hanke, Claudia Rose Hanke, Judy Bouma, Kirk Beisel, Herbert Schwegler

Gene expression was compared between a congenic-like DxH recombinant inbred strain showing exaggerated fear and stress responses and the background strain DBA/2j. Non-stressful cognitive learning was studied in the novel object recognition (NOR) paradigm. Quantitative (qPCR) was used to confirm differential gene expression shown in microarrays (n=8-11 per group). In the NOR test, both mouse strains learned the cognitive task equally well, suggesting that differential gene expression did not affect learning per se. In qPCR analyses, Nqo2, GABRB2 and HPCA genes were significantly downregulated and Rgcc was upregulated in DxH mice, compatible with increased anxiety- and fear-related behaviors.

Kappa-opioid receptor activation leads to decreased neurite outgrowth in immature murine cerebrocortical neurons
Matthew Q. Schmidt, Sunnet Mehrotra, Thomas F. Murray

Kappa-opioid receptors (KORs) have gained attention recently as potential therapeutic targets. However, little is known about the effects of KORs on central nervous system development. Our work addressed the role of the KOR system on neurite outgrowth and dendritic arborization in immature cerebrocortical neurons. Primary cultures were prepared from E16 Swiss-Webster mouse. DIV5 cultures were used for immunocytochemistry, which showed the presence of KORs on immature cerebrocortical neurons. Cerebrocortical cultures were treated beginning 3 hours after plating for neurite outgrowth and dendritic arbor complexity. U69593, a KOR-specific agonist, significantly reduced neurite outgrowth at 24 and 48 hours, and also reduced the degree of dendrite branching in DIV5 neurons. These effects were then blocked by norbinaltorphimine, a KOR-specific antagonist. Thus, KOR activation retards neuritogenesis and dendritogenesis in immature cerebrocortical neurons, providing preliminary evidence that opioids could have an inhibitory effect on the developing nervous system.

Antilatotxin (ATX), a voltage-gated sodium channel (VGSC) activator, stimulates neurite outgrowth through the brain-derived neurotrophic factor (BDNF) - tropomyosin related kinase B (TrkB) signaling pathway
Sunnet Mehrotra, W. H. Gerwick, T. F. Murray

VGSC activators promote neurite outgrowth by elevating intracellular Na+ and upregulating N-methyl D-aspartate receptor (NMDAR) function. The BDNF-TrkB pathway has been implicated in activity-dependent neuronal development. We have previously shown ATX increases NMDA-receptor open probability and Ca2+ influx. Here we address the effect of ATX on the synthesis and release of BDNF, and determine the signaling mechanisms by which ATX influenced neurite outgrowth in immature cerebrocortical neurons. Primary cultures were prepared from E16 Swiss-Webster mice. DIV5 cells were cultured for 24 hours in various compounds, beginning 3 hours after plating. ATX treatment produced a concentration-dependent release and increased synthesis of BDNF. ATX stimulation of neurite outgrowth was prevented by pretreatment with TrkB, PI3K and mTOR inhibitors or transfection with dominant negative Trk-B. Acute treatment with ATX resulted in phosphorylation of Trk-B and its downstream effectors, Akt and mTOR. VGSC activators such as ATX may therefore represent a novel pharmacological strategy to promote neuronal structural plasticity.

Dopaminergic Modulation of Pathological Movement-Related Cortical Beta Responses in Parkinson's Disease
Elizabeth Heinrichs-Graham, Pamela M. Santamaria, Howard E. Gendelman, Tony W. Wilson

In this study, we used magnetoencephalography (MEG) to investigate cortical oscillatory beta responses during movement and rest in patients with Parkinson’s disease, before and after administration of dopaminergic medication, and a group of healthy age-matched controls. Movement-related beta oscillatory responses were examined using beamforming to distinguish the brain areas most affected by PD and modulated by dopaminergic medication. Unmedicated patients with PD exhibited significantly decreased pre-movement beta ERD compared to controls. Administration of dopaminergic medication increased the amplitude of oscillatory responses in both conditions and thus, had a normalizing effect. Resting beta amplitude and coherence were also investigated, and these results showed a similar pattern.
On the high frequency transfer of mechanical stimuli from the surface of the head to the macular neuroepithelium of the mouse

Choongheon Lee, Christopher Gaines, John Grant, Timothy Jones

The transfer of the stimulus to vestibular macular sensors is limited by mechanical properties of the tissues. We measured short time constant and upper cutoff frequency of frequency responses for stimulus transfer from the head to epithelium. Hypothetically, sensitivity of the otoconial apparatus increases according to the decrease in velocity transfer between 0.1 and 2.0ms of step duration. C57BL/6J mice were evaluated by recording VSEP thresholds to measure the sensitivity for neural activation. VSEP thresholds increased exponentially below 1.0ms of step durations. Time constants of 0.5 and 0.79ms for two coupling methods predict high frequency cutoffs near 200 and 300Hz.

Loss of GSK-3 causes abnormal astrogenesis and behavior in mice

Eui-Mang Jung, Minhan Ka, Woo-Yang Kim

Altered activity of glycogen synthase kinase 3 (GSK-3) is associated with psychiatric diseases and neurodegenerative diseases. GSK-3 is a key regulator in multiple aspects of neuronal differentiation in the brain. However, little is known about the role of GSK-3 in astroglial development. To examine the role of GSK-3 in astrocytes, we generated a conditional knockout mouse using a GFAP-cre driver, in which the GFAP-cre allele and beta gene are deleted in astrocytes. We found that GFAP-cre-mediated GSK-3 deletion led to an increase in brain size. The number and size of astrocytes were increased in GSK-3 mutant brains. Furthermore, the levels of GFAP and phospho-STAT3, indicators of astrogliosis, were elevated in GSK-3 mutant brains. We found upregulation of astrocyte proliferation-associated molecules such as phospho-AKT, phospho-S6 and cyclin D in GSK-3 mutant brains as well. Finally, GSK-3 mutant mice exhibited aberrant anxiety and social behavior. Our results suggest that GSK-3 plays a significant role in astrocyte development and behavioral control in mice.

Endogenous calcium dynamics in photoreceptor synaptic terminals of salamander retina

Matthew Van Hook, Wallace B. Thoreson

We used multiple approaches to measure endogenous Ca2+ buffering in the synaptic ribbon-bearing terminals of rod and cone photoreceptors from salamander retinas, finding that it could be mimicked with ~0.05mM EGTA. Using fluorescent Ca2+ indicators, we found that this enhanced the Ca2+ signals in photoreceptor terminals due to promotion of Ca2+-induced Ca2+ release (CICR) in rods, but not cones. Using paired whole-cell recordings to monitor synaptic transmission, we found that mimicking endogenous buffering conditions with 0.05mM EGTA promoted sustained exocytosis in rods, via CICR-dependent non-ribbon release, and in cones, via Ca2+-dependent synaptic vesicle replenishment to the cone ribbon.

Investigating how age-related PRR/Syk/NFkB dysregulation alters synapses and mouse activity

Nicholas DeKorver, Jyothi Arikkath, Stephen Bonasera

Aging presents with CNS mediated alterations in locomotion, metabolism, and cognition. Aged C57BL6 mice mimic locomotor deficits of human aging, have increased CNS expression of immune proteins, and increased excitatory synaptic density in the cerebellum. Mechanisms connecting increased gene expression, synaptic alterations, and functional deficits are not understood. To identify a mechanism, we generated a high purity primary cerebellar granule cell culture (pGCC), pGCCs express pattern recognition receptors and molecules associated with NF-kappa-B signaling. We hypothesize that increased activation of PRRs on cerebellar neurons drives increased NFkB activity resulting in synaptic alterations. Here, we present data demonstrating active NF-kappa-B signaling in pGCCs upon PRR activation. Additionally, we demonstrate that genetic modulation of an immune protein can lead to synaptic alterations. Elucidating molecular signaling pathways underlying synaptic alterations in aging will provide novel therapeutic targets to combat age associated functional declines.

Genetic diversity of AVP/AVPR1a system in New World Monkeys

Dongren Ren, Kelvin R. Chin, Jeffrey A. French

Arginine vasopressin (AVP) and its receptor (AVPR1a) play roles in social monogamy, which is common among New World monkeys (NWM). We herein characterized variation in the AVP and AVPR1a genes throughout NWM. For AVP, only 16 synonymous substitutions were detected. However, 66 predicted amino acids substitutions were identified. The AVPR1a N-terminus, third intracellular, and C-terminus were variable. A phylogenetic tree from AVPR1a revealed a mixed clade. The AVPR1a dN/dS ratio was 0.11, but positive selection was observed in N-terminus. Four substitutions occurred uniquely in marmosets and tamarins. Our findings enhance the appreciation of genetic diversity in the mammalian AVP/AVPR1a system.

Prevention of synaptic and behavioral impairments in a maternal immune activation model of autism


Maternal immune activation (MIA) is a risk factor for both autism spectrum disorder (ASD) and schizophrenia. Here we show that MIA offspring induced by a viral mimic poly(I:C) exhibit impairments in cortical dendritic spine morphogenesis and motility in vivo which persists into adulthood. We also find that the excitatory and inhibitory connectivity on the dendritic spines is altered in the MIA offspring. Postnatal treatment with an anti-inflammatory drug ameliorated the spine impairments observed in adults as well as alteration in an ASD relevant behavior. These data indicate that increased inflammatory state during early postnatal weeks is responsible for altered synaptic connectivity and impaired behavioral impairments.

Inner Ear Hair Cell Loss and Stereocilia Defects in miR-183 Family Knockout Mice

Marsha Pierce, Jennifer Kersigo, Bernd Fritsch, David Nichols, Garrett Soukup

MicroRNA-183 family (miR-183, miR-96, and miR-182) is highly conserved and coordinately expressed in neuronsensory cells. Mutations in miR-96 lead to hair cell (HC) loss and profound deafness in both humans and mice. To investigate miR-183 family member loss of function exclusively, we assessed miR-183/96 and miR-182 knockout (KO) mice. HC-specific MyoVIIa staining demonstrated early HC loss in miR-183/96 KO mice, and scanning electron microscopy (SEM) showed gross stereocilia defects. Accordingly, the mice failed to exhibit a Preyer’s reflex (acoustic startle response) at any age suggesting profound deafness. In miR-182 KO mice, MyoVIIa staining showed later HC loss and mild disorganization, and SEM demonstrated HC stereocilia fusion. These results are consistent with a later loss of Preyer’s reflex suggesting progressive hearing loss. Since microRNAs function to fine-tune gene expression in differentiated cells, analysis of changes in these knockout models is expected to reveal crucial molecular mechanisms of HC maintenance and function.
Developmental neuropeptides alter social behavior and received parental care in Mongolian gerbils
Jack Taylor, Joseph Braddock, Michaela Devitt, Jeffrey French

The neuropeptides oxytocin (OT) and arginine-vasopressin (AVP) have been implicated in developmental social disorders along the autism spectrum. We sought to examine the effects of these neuropeptides on social development and family dynamics in gerbils. Gerbils were treated on the day of birth with OT, AVP, an OT receptor antagonist (OTA), an AVP receptor antagonist (AVPA), or saline, and then observed at various developmental time points. We found that when experimentally displaced from the nest on PND4, mothers retrieved pups that were treated with OTA slower than pups treated with OT. Furthermore, immediately following removal from the parents at weaning, male gerbils treated with AVP engaged in more grooming and play fighting behaviors than males treated with AVPA, but no such difference was found in females. This indicates that neuropeptide levels during the neonatal period affect the behavior of both developing gerbil pups and the responses of the parents toward the pups.

Functional Characterization of the healthy adult human brain and its application to study neurodevelopmental disorders
Simarjeet Negi, Babu Guda

The complexity of the human brain is astounding. Therefore, an integrated view with systems biology approach is necessary to understand human brain transcriptome, and can form the baseline to infer brain disorders. We built a unified gene expression matrix (model) at fine anatomical resolution of brain structures from clinically unremarkable adult human brains. Functionally characterizing this consistent expression blueprint along with defining the key biological processes in the brain will help gain better insights into brains functioning. Also, using the aforementioned model we intend to investigate the genes involved in diseased conditions and explore pathway perturbations and other downstream effects.

Glutamate homeostasis is perturbed in the lysosomal storage disease, Juvenile Neuronal Ceroid Lipofuscinosis
Megan Bosch, Maria Burkovetskaya, Tammy Kielian

Juvenile Neuronal Ceroid Lipofuscinosis (JNCL) is an autosomal recessively inherited lysosomal storage disease caused by a mutation in the CLN3 gene. Previous studies have shown that astrocyte activation precedes and predicts regions of neuronal loss in JNCL patients and CLN3 mutant mouse models. Glutamate levels are elevated in the JNCL brain and neuronal loss is thought to occur, in part, via glutamate excitotoxicity, suggesting the existence of altered glutamate-glutamine cycling required for homeostatic maintenance. Since astrocytes play a major role in regulating extracellular glutamate levels in the CNS, we utilized CLN3Δex7/8 JNCL mouse model to study glutamate regulatory pathways both in vivo and in vitro. Glutamine synthetase was significantly decreased in multiple brain regions of CLN3Δex7/8 mice at 3 months of age compared to wild type animals. Additionally, proinflammatory cytokines altered expression of the glutamate transporter GLAST in CLN3Δex7/8 astrocytes. Our preliminary studies depicted Ca2+ signaling is elevated in CLN3Δex7/8 neurons following glutamate stimulation, bringing the dysregulated glutamate circuit full circle in this context.

Activation of voltage-gated sodium channels with brevetoxin-2 (PbTx-2) increases spine density in murine organotypic hippocampal slice culture
Dina Gomez, Thomas F. Murray

The N-methyl-D-aspartate receptor (NMDAR) is essential for activity-dependent neurite outgrowth, dendritic arborization and spine formation. Previous research has demonstrated that the voltage gated sodium channel activator, PbTx-2, augments NMDAR function in dissociated cultures of cerebrocortical neurons. Here we assessed the effect of PbTx-2 on spine dynamics in an organotypic hippocampal slice culture that better reflects the intact structure. This system also allowed us to ask whether the effects of PbTx-2 on cerebrocortical neurons generalized to hippocampal neurons. The effects PbTx-2 and NMDA on spine dynamics were compared. An organotypic hippocampal slice culture was prepared from postnatal day 2-7 mouse pups. The hippocampus was isolated under a dissecting microscope, and 450 µm thin sections were cut using a tissue chopper. The slices were treated 18 hours after plating with vehicle, PbTx-2 (30 nM and 100 nM) or NMDA (100 nM) for time periods of 24, 48, 72, 120 and 240 hours. Slices were then fixed and diostically labeled. A Leica SP8 microscope was used to generate Z-stack confocal images and Imaris-XT software was used create 3D-reconstructed images of dendrites to analyze dendritic spine dynamics. Our results demonstrated that PbTx-2 at both 30 and 100 nM produced significant increases in spine density after 1 to 5 days of exposure. The PbTx-2 induced fold increment in spine density was similar to that observed with NMDA (100 nM). The use of an organotypic slice culture permits assessment of voltage-gated sodium channel activator influence on spinogenesis, and the effect of PbTx-2 on cerebrocortical neurons generalizes to hippocampal neurons. Sodium channel activators may represent a novel pharmacological strategy to promote neuronal structural plasticity.
Role of language-related FOXP2 and CNTNAP2 in vocal learning

Environmental insults produce long-lasting behavioral alterations in the offspring. Immune challenge and separation exhibited heightened avoidance response, and prenatal immune challenge decreased antipsychotic sensitivity. These results suggest that early tested in conditioned avoidance response, antipsychotic sensitivity, and serotonin 2a/c and dopamine D2 receptor agonist-induced hyperlocomotion. Offspring exposed to both treatments exhibited increased in patients with MDD, following the maintenance phase of rTMS treatment.

Effects of the dual orexin receptor antagonist almorexant on sleep in the Kcnac-null mouse model of epilepsy

This study was designed to test the effects of almorexant, a dual orexin receptor antagonist, on the Kcnac-null mouse. The Kcnac-null mouse is a model for temporal lobe epilepsy that also experience co-morbid sleep disorder. Orexin receptor antagonism has been suggested as an alternative to current pharmacological sleep therapies due to a decreased likelihood of side-effects. Wake, REM, and NREM periods were determined using semi-automatic analysis of subdural EEG and nuchal muscle EMG electrodes, and simultaneous video monitoring. We are the first to demonstrate that a dual orexin receptor antagonist is capable of increasing sleep in the Kcnac-null mouse, a clinically relevant model of epilepsy with co-morbid sleep disorders.

Cytokines secreted by activated microglia enhance neurogenesis through micro-RNA regulation

Activated microglia, the resident immune phagocytic and secretory cells in the CNS, can trigger neurotoxic inflammatory responses or promote neurogenesis and neuronal survival. The underlying mechanisms of neurotrophic microglial secretory cues aren’t fully understood. An in vitro model system, in which microglia are cultured upon transwell membranes suspended above mechanically damaged or undamaged primary neuronal cultures was used to investigate the levels of microglial cytokines in response to neuronal damage. These cytokines enhance neurogenesis by regulating neuronal non-coding microRNA expression. RTPCR analysis demonstrates an enhancement of neurogenesis is associated with time-dependent regulation of mir-9, mir-124, and let-7c in differentiating neurons.

Effects of Environmental Enrichment on d-Amphetamine Self-Administration Following Nicotine Exposure

The purpose of the present study was to determine if enrichment alters nicotine-induced increases in amphetamine self-administration. Enriched and impoverished rats were pretreated with nicotine or saline and tested for levels of amphetamine self-administration. Results indicate that enrichment decreases the ability of nicotine exposure to alter the amphetamine self-administration.

Septohippocampal GABAergic transmission is optimized for short bursts of gamma frequency activity

Hippocampal (HC) interneurons receive GABAergic inhibition from parvalbumin-positive septohippocampal (SH) neurons. We used optogenetics and variance-mean (VM) analysis to investigate quantal parameters and short-term plasticity of inhibitory postsynaptic currents (IPSCs) from SH or local (HC) synapse types in PV-CRE mice. During trains of 20 IPSCs at gamma (20-50 Hz) frequencies, reduced paired-pulse depression (PPD) and accelerated recovery from PPD was observed at SH than HC synapses. Kinetic modeling suggested that the presynaptic calcium transient is longer at SH than HC synapses. These findings suggest that information transfer at SH synapses is optimal during short bursts of gamma frequency activity.

Maternal immune activation and early psychosocial stress alters offspring learning and antipsychotic response

The current project determines the behavioral characteristics of rat offspring exposed to maternal immune activation and maternal separation. Pregnant dams were injected with polyinosinic:polycytidic acid on gestation days 13 and 15, and offspring were separated from mothers for three hours every other day from postnatal days 2-14. Offspring were then tested in conditioned avoidance response, antipsychotic sensitivity, and serotonin 2a/c and dopamine D2 receptor agonist-induced hyperlocomotion. Offspring exposed to both immune challenge and separation exhibited heightened avoidance response, and prenatal immune challenge decreased antipsychotic sensitivity. These results suggest that early environmental insults produce long-lasting behavioral alterations in the offspring.

Role of language-related FOXP2 and CNTNAP2 in vocal learning

FOXP2, the gene affected in a severe speech disorder, and its target, CNTNAP2, an autism-susceptibility gene, are important candidates to study the genetic basis of language disorders. Both genes are differentially expressed in brain areas essential for vocal learning in human and songbird. Their precise role in neural development and function is not completely understood. We show that both molecules are detected early in developing avian neurons, consistent with a role in neural circuit formation. Additional work will clarify the functional relationship between FOXP2 and CNTNAP2 in songbird, and assess the functional consequences of manipulating CNTNAP2 levels in developing neurons.
The NMDA receptor GluN2C subunit regulates behavioral and cellular phenotypes relevant to schizophrenia
Aparna Ravikrishnan, Brandon C. Hillman, Subhash C. Gupta, Ratna Pavuluri, Dustin J. Stairs, Shashank M. David

The NMDA receptor (NMDAR) hypofunction hypothesis in schizophrenia posits that reduced NMDAR function leads to behavioral abnormalities observed in schizophrenia. Lower expression of GluN2C subunit of NMDAR has been reported in the cortex and thalamus in postmortem brains from schizophrenic patients, however its functional implications remain unknown. We found cellular and synaptic deficits in GluN2C knockout mice including lower parvalbumin labeling and lower dendritic spine density, features similar to those observed in human condition. GluN2C heterozygous and knockout mice also exhibit behavioral and cognitive deficits relevant to schizophrenia. Moreover, a GluN2C/GluN2D potentiator, CIQ, attenuated NMDAR channel blocker-induced hyperlocomotion, working memory deficit as well as prepulse inhibition deficit in wildtype and heterozygous mice but not in GluN2C knockout mice. These results demonstrate that deficit in GluN2C-containing NMDARs leads to schizophrenia-like phenotypes, and establish that pharmacologic enhancement of GluN2C-containing NMDARs may lead to beneficial effects for behavioral and cognitive deficits in schizophrenia.

Abnormal MEG Theta Activity in Veterans with PTSD during Working Memory Processing
Timothy McDermott, Amy Badura Brack, Elizabeth Heinrichs Graham, Katherine Becker, Tara Ryan, Tony W. Wilson

Posttraumatic stress disorder (PTSD) is a psychiatric condition that may develop following the experience of an emotionally overwhelming and/or traumatic event. Previous studies have demonstrated that these patients suffer from a number of executive functioning deficits, including impairments in working memory. In order to further examine this, we examined how PTSD affects the dynamics of working memory processing by recording the brain activity of 27 male combat veterans with PTSD, and 24 psychologically healthy, demographically-matched control participants using magnetoencephalography (MEG). During the MEG recording, participants performed a Sternberg-type working memory task. Our results showed that, despite comparable performance, veterans with PTSD showed abnormal theta (4-8 Hz) activity in the right dorsolateral prefrontal cortex (DLPFC) and the right supramarginal gyrus during the encoding phase. Abrupt activity in the right DLPFC was strongest in the 400-800 ms range, whereas that in the supramarginal gyrus peaked at 1200-1600 ms post-stimulus onset.

The Role of Host Factors in Prion Strain Interference
Jason Bartz

The alpha 9/10 nicotinic acetylcholine receptor (nAChR) mediates cholinergic eff erent activity in vestibular sensory hair cells. We studied the structure of eff erent axon terminals and measured vestibular sensory evoked potentials in alpha9 knockout mice, alpha 9/10 double knockouts, and wild type controls. Eff erent boutons on vestibular cells appeared normal, but VsEP thresholds were signifi cantly reduced in knockout animals. Some knockout animals had normal or near normal thresholds, while others were greatly affected. Despite variability in threshold, latencies were consistently shortened. Genetic characterization was used to evaluate the genetic background of the animals with the best and worst thresholds.

Vestibular physiological defi cit in alpha9 and alpha9/10 nicotinic acetylcholine receptor knockout mice
Barbara Morley, A. Lysakowski, S. Vijayakumar, S.D. Price, D.Menapace, T. Jones

The alpha 9/10 nicotinic acetylcholine receptor (nAChR) mediates cholinergic eff erent activity in vestibular sensory hair cells. We studied the structure of eff erent axon terminals and measured vestibular sensory evoked potentials in alpha9 knockout mice, alpha 9/10 double knockouts, and wild type controls. Eff erent boutons on vestibular cells appeared normal, but VsEP thresholds were signifi cantly reduced in knockout animals. Some knockout animals had normal or near normal thresholds, while others were greatly affected. Despite variability in threshold, latencies were consistently shortened. Genetic characterization was used to evaluate the genetic background of the animals with the best and worst thresholds.

Transcranial Doppler Assessment of Cerebral Blood Flow Velocity During Visuospatial Tasks
Benjamin Hage, Erin Barney, Mohammed Alwatban, Mark Mills, Michael Dodd, Gregory Bashford

Transcranial Doppler (TCD) sonography is a neuroimaging technique that uses ultrasound refl ections from the cranium to measure fl ow velocities in blood vessels. Cerebral blood flow velocity increases with increasing oxygen demand, allowing TCD measurements to serve as a proxy for cognitive function. Previous studies using TCD have evaluated visuospatial function by comparing a wide variety of visuospatial tasks to one another, but have not used the same set of images for all tasks. This study investigated cerebral hemodynamics and lateralization during two visuospatial tasks (scene memorization and visual search) using the same set of images, allowing systematic comparison between tasks.

Blunted Baroreflex Function Associated with Impaired BDNF-TrkB Signaling in the NTS During Heart Failure
Bryan Becker, Hanjun Wang, Irving H. Zucker

The nucleus tractus solitarius (NTS) is the primary central target of baroreceptor afferents and plays a critical role in regulating baroreflex sensitivity. BDNF and its receptor, TrkB, are highly expressed in the NTS, but their function there is unknown. We hypothesized that in the NTS, BDNF enhances baroreflex sensitivity, and impaired BDNF-TrkB signaling desensitizes baroreflex function in chronic heart failure (CHF). Injections of 50 nL of BDNF or the TrkB antagonist ANA-12 in the NTS evoked a signifi cantly greater sympathoinhibitory or sympathoexcitatory response respectively in sham vs. CHF rats. ANA-12 blunted baroreflex sensitivity in sham rats (1.7±.0.3 vs. 1.9±.0.1 bpm/mmHg, p<.05 before vs. after, n=4). ANA-12 had little eff ect on baroreflex sensitivity in CHF (2.3±0.1 vs. 2.0±0.1 bpm/mmHg, n=4). These data suggest that endogenous BDNF has a critical role in maintaining baroreflex sensitivity in the NTS. Furthermore, BDNF-TrkB signaling is impaired in CHF, which may contribute to autonomic imbalance.
Synaptic mechanisms of motor skill learning in the fmr1 KO mouse

Anand Suresh

Fragile X syndrome is the most common inherited form of an intellectual disability and is caused by silencing of the FMR1 gene. We previously reported that fmr1 KO mice have deficits in motor skill learning as well as in the structural and functional synaptic plasticity in the primary motor cortex. To investigate the synaptic mechanisms that underlie motor skill learning, we follow GFP-tagged AMPA receptor sub-units by in-vivo transcranial two-photon imaging of dendritic spines. Our preliminary data suggest that motor skill learning-induced AMPA receptor dynamics in spines are impaired in the fmr1 KO mice.

Gating effects of a novel positive allosteric modulator at GluN1/GluN2A receptors

Diyvan Chopra, Daniel T. Monaghan, Shashank M. Dravid

Excitatory neurotransmission mediated by NMDA receptors (NMDARs) is known to play an important role in synaptic plasticity that underlies processes of learning and memory. NMDAR dysfunction is implicated in a variety of neuropyschiatric and neurological disorders including schizophrenia, epilepsy, stroke and depression. We have previously described a series of allosteric modulators for NMDARs with varying degree of subtype selectivity. We evaluated the effect of a novel molecule (UBP684) on GluN1/GluN2A NMDARs using whole cell and cell attached patch voltage-clamp recordings from HEK293 cells in the absence or presence of 0.5 mM extracellular Ca2+. Whole-cell recordings demonstrated that UBP684 potentiates GluN1/GluN2A currents in the absence of extracellular Ca2+ but inhibits currents in the presence of 0.5mM Ca2+. Single channel analysis revealed that UBP684 increases the efficiency with which the receptor opens by primarily affecting a single gating step.

Evaluating mitochondrial superoxide formation in cochlear cells during antibiotic exposure

Danielle Desa, Heather Jensen Smith

Aminoglycoside antibiotics treat gram-negative bacterial infections but also damage cochlear sensory cells, resulting in permanent hearing loss. These studies evaluate mitochondrial dysfunction and reactive oxygen species (ROS) formation during antibiotic exposure. Low levels of ROS, primarily superoxide, are produced at electron transport chain complexes I and III during normal metabolism, yet increase when metabolism is altered. Using the complex I-specific inhibitor rotenone, we studied relative changes in superoxide formation at complex I in cochlear cells during acute exposure to gentamicin, a representative aminoglycoside antibiotic. ROS formation at complex I was unaltered, suggesting gentamicin did not directly alter complex I activity.

Responses to inequity following oxytocin manipulation in marmoset monkeys

Benjamin Hochfelder, Aaryn C. Mustoe, April Harinsch, Jeffrey A. French

We investigated inequity aversion in marmosets by testing how oxytocin influences food sharing and social behavior in opposite-sex dyads. Marmosets performed a prosocial-choice task where donors provision food in equitable and unequitable outcomes to themselves and to their pairmates or to strangers. We also administered two oxytocin agonists, an oxytocin antagonist, and saline. Overall, marmosets did not show sensitivity to inequity aversion, did not differentially provision food, and this was not influenced by oxytocin. However, marmosets tested with strangers spent increased time in proximity with their homocage pairmate following testing compared to marmoset donors tested with their pairmate or tested alone.

Regulation of brain PPARgamma mediates ketogenic diet anti-seizure efficacy

Timothy Simeone, Stephanie Matthews, Kaeli Samson, Kristina Simeone

The high fat, low carbohydrate/protein ketogenic diet (KD) is an effective anti-seizure therapy primarily used in pediatric patients refractory to current anti-seizure medications. The mechanism of KD anti-seizure efficacy is unclear, but it is known that the KD engages anti-inflammatory and anti-oxidant pathways and promotes mitochondrial health. Many of these effects mirror the downstream effects of the nutritionally-regulated transcription factor peroxisome proliferator activated receptor gamma, PPARgamma. Here, we provide pharmacologic and genetic evidence that brain PPARgamma is involved in the anti-seizure efficacy of KD in chronic epilepsy and acute seizure models.

A novel mitochondria-targeted antioxidant treatment

Kristina Simeone, Stephanie A. Matthews, Kaeli K. Samson, Timothy A. Simeone

Mitochondria actively participate in neurotransmission by providing energy (ATP) and maintaining normative concentrations of reactive oxygen species (ROS) in both presynaptic and postsynaptic elements. In human and animal epilepsies, ATP-producing respiratory rates driven by mitochondrial respiratory complex (MRC) I are reduced, antioxidant systems are attenuated and oxidative damage is increased. We report that MRCI-driven respiration and functional uncoupling (an inducible antioxidant mechanism) are reduced and levels of H2O2 are elevated in mitochondria isolated from KO mice. Experimental impairment of MRCI in WT hippocampal slices via rotenone reduces paired-pulse ratios (PPRs) at mossy fiber-CA3 synapses (resembling KO PPRs), and exacerbates seizure-like events in vitro. Daily treatment with AATP [a combination therapy composed of ascorbic acid (AA), alpha-tocopherol (T), sodium pyruvate (P) designed to synergistically target mitochondrial impairments] improved mitochondrial functions, mossy fiber PPRs, and reduced seizure burden index (SBI) scores and seizure incidence in KO mice. AATP pretreatment reduced severity of KA-induced seizures resulting in 100% protection from the severe tonic clonic seizures in WT mice. These data suggest that restoration of bioenergetic homeostasis in the brain may represent a viable anti-seizure target for temporal lobe epilepsy.
Neuroscience Poster Presenters

RESEARCH AREA: BIOLOGICAL NEUROSCIENCE, continued

Removal of the Renal Nerves Increases Renal Blood Flow Variability in Conscious Rabbits
Alicia Schiller, Peter R. Pellegrino, Irving H. Zucker

Activation of the renal nerves, as observed in multiple disease states, is known to have a profound impact on renal blood flow (RBF) and hemodynamics. However, less is known about their role in maintaining renal hemodynamics under normal conditions. Renal nerves were surgically removed and flow probes implanted in New Zealand White rabbits. Denervated rabbits had increased RBF and greater beat-to-beat RBF variability quantified by the standard deviation of the beat-to-beat RBF and analysis of the beat-to-beat RBF probability distribution compared to innervated rabbits. These data indicate that the renal nerves serve to limit fluctuations in renal blood flow.

Inflammation-associated microRNAs increase in hippocampal neurons in a controlled cortical impact mouse model of traumatic brain injury
Emily Harrison, Sowmya V. Yelamachili, Matthew L. Kelso, Howard S. Fox

Inflammation contributes to neuronal death and dysfunction following traumatic brain injury (TBI). The magnitude and duration of inflammation is regulated by miRNAs through post-transcriptional regulation. We examined the levels of inflammation-associated miRNAs in a controlled cortical impact (CCI) model of TBI and found that the expression of all of the inflammation-associated miRNAs examined (miR-223, miR-155, and miR-21) increased in the injured hippocampus following moderate CCI in mice. In situ hybridization revealed that increases in inflammation-associated miRNAs were primarily localized to hippocampal neurons. These findings suggest that inflammation-associated miRNAs may play a role in the neuronal response to TBI.

RESEARCH AREA: COGNITIVE NEUROSCIENCE

Cerebral hemodynamics reflects temporal structure of auditory input and motor output variability
Michael Hough, Steven Harrison, Nicholas Stergiou

The variability present in human movements is not random, but deterministic, with a characteristic fractal structure that can be driven by synchronizing actions with a fractal-structured auditory stimulus. Similar fractal structure has been detected in more slowly-changing hemodynamic signals in resting states and during simple movements. This study demonstrates that during a simple finger-tapping task, the link between the fractal structure of auditory input and motor output variability is captured by cerebral hemodynamics. Despite the differing timescales of the various subsystems, important information about the dynamics of the system as a whole is carried through the temporal structure of variability.

Neural correlates of auditory stream segregation
Nicholas Smith, Suyash Joshi

The temporal order discrimination of target tone pairs is hindered by the presence of flanker tones, but is improved when the flanker tones are captured by a separate stream of tones that match the flankers in frequency (Bregman & Rudnicky, 1975). In an event-related potential (ERP) study with these stimuli, listeners’ mismatch negativity (MMN) responses were temporally linked to the position of the changing target tones, irrespective of streaming. In contrast, N1 response latency varied as a function of the perceived grouping of flanker tones established by previous behavioral studies, providing a novel neurophysiological index of auditory stream segregation.

Psychophysiological Effects of Nature Images
Garrett Schwindt, Frank Ferraro III

The Stress Reduction Theory (SRT) states nature can reduce psychophysiological components of stress. Nature images improve behavioral, autonomic, and electro-cortical parameters in humans. However, previous studies use scenic vistas of mountains, lakes, and forests that are not typical of Midwestern landscapes. The current research will recruit undergraduate students. Psychophysiological and behavioral measurements will be recorded before and after exposure to nature, urban, or geometric images. It is hypothesized that participants randomly assigned to the nature condition will have lower stress indices compared to the urban and geometric conditions. This study may indicate local outdoor outlets for stress-management in college-aged students.

Age-related differences in alpha/beta oscillatory dynamics during a visual working memory task
Amy Pruskovec, Elizabeth Heinrichs-Graham, Tony W. Wilson

Working memory is central to the execution of a variety of daily functions and is typically broken down into three phases: encoding, maintenance, and retrieval. While working memory performance has been shown to decline with age, little is known regarding the underlying neural processes. In this study, we examined age-related differences in the neural dynamics that serve working memory by recording high-density magnetoencephalography (MEG) in young and old adults while they performed a modified, high-load Sternberg working memory task. MEG data were evaluated in the time-frequency domain and significant oscillatory responses were imaged using a beamformer. In concordance with previous literature, we observed left fronto-temporal activation in both groups. There were also age-related differences in right inferior frontal and temporal areas. Older participants exhibited strong event-related desynchronization in right inferior frontal cortices that was not observed in younger participants. This bilateral desynchronization within the older group may reflect compensatory processing.
Abnormal Cortical Oscillations in Children with Cerebral Palsy during a Target Matching Knee Extension Task

Dave Arpin, Max J. Kurz, James E. Gehring, Tony W. Wilson

Prior magnetoencephalographic (MEG) and electroencephalographic (EEG) brain imaging experiments have established that beta (15-30 Hz) oscillatory activity in the sensorimotor cortices serves the motor planning and control of movement. Prior investigations have also shown that individuals with cerebral palsy (CP) have motor control problems, including a greater amount of error in their performance of goal-directed movements. In this study, we used MEG to evaluate the neural oscillatory activity in the sensorimotor cortices of children with CP and typically-developing children (TD) during a goal-directed knee force task. Our primary findings were that children with CP exhibited a stronger beta desynchronization in the supplementary motor area, left premotor cortices, paracentral lobule, and the left prefrontal cortex relative to TD children. These results are consistent with a previous study of basic leg movements, and suggest that aberrant beta oscillations may partially contribute to the motor control deficits in children with CP.

Glutamate delta-1 receptor regulates dendritic spine morphology and density in cortico-limbic circuit

Subhash Gupta, Max Kurz, Roopali Yadav, Barbara Morley, Dustin S. Stairs, Shashank M. Dravid

The delta family of ionotropic glutamate receptors consists of glutamate δ1 (GluD1) and glutamate δ2 (GluD2) receptors. GluD1 receptors are expressed throughout the forebrain during development with high levels in the hippocampus during adulthood. We have recently shown that deletion of GluD1 receptor results in aberrant emotional and social behaviors such as hyperaggressiveness, depression-like behaviors and social interaction deficits. Our previous studies suggest that GluD1 KO mimics some of the behavioral phenotype of autism spectrum disorder (ASD). In this study we demonstrated that deletion of GluD1 results into higher spine density in mPFC and CA1 region of hippocampus. However, in mPFC a significant increase in the spine density of mature spines was observed. In electrophysiological recording we observed significant increase in the frequency of mEPSCs in mPFC of GluD1 KO mice. In addition, we observed significantly lower expression of phospho cofillin both in CA1 and mPFC of GluD1 KO mice.

Oscillatory Activity in the Somatosensory Cortices Predicts the Motor Performance of Children with Cerebral Palsy

Max Kurz, Elizabeth Heinrichs-Graham, Katherine M. Becker, Tony W. Wilson

Our recent magnetoencephalography experimental work on neural oscillatory activity has shown that children with cerebral palsy (CP) have aberrant 4-14 Hz event-related desynchronization within the sensorimotor cortices following tactile stimulation to the bottom of the foot. In this investigation, we explored the relationship between the neural synchronization within the somatosensory cortices, the strength of the ankle plantarflexors and gait spatiotemporal kinematics of a group of children with CP and a typically developing cohort. Our results revealed that amount of synchronization within the somatosensory cortices of the children with CP had a strong positive relationship with the ankle strength, step length and walking speed. These results indicate that stronger synchronization within the somatosensory cortices in response to foot somatosensations was related to enhanced ankle plantarflexor strength and improved mobility in the children with CP.

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Circadian Modulation of Beta Oscillatory Dynamics in the Motor Network

Tony W. Wilson, Elizabeth Heinrichs-Graham, Katherine M. Becker

Previous electrophysiological studies of motor control have shown that a variety of movement parameters modulate the amplitude of beta oscillatory activity across the motor network. In this study, we evaluated whether the amplitude of beta responses follow a biological temporal rhythm (e.g., circadian), as it is known that motor performance varies with the circadian cycle. We used magnetoencephalography (MEG) to evaluate oscillatory activity during a motor task at three different times (09:00, 12:00, 16:00) on three consecutive days. MEG data was imaged in the time-frequency domain using beamforming. We found a significant linear increase in beta event-related desynchronization (ERD) from 09:00 to 16:00 across cortical motor network regions. Beta activity during the baseline also increased from 09:00 to 16:00. These data show that beta levels strongly increase from morning to afternoon, which may indicate that oscillatory beta has to be suppressed to a specific threshold before movements can be executed.
Implantable artificial and biological nanoscale sensors and actuators are envisioned to be among the next revolutionary achievements of bionanotechnology, enabling low cost and noninvasive health monitoring and control. However, their coordination and control relies on in-vivo communication networks able to propagate messages within the body and to/from the outside environment. The techniques proposed so far for in-vivo networking rely on classical conduction of electromagnetic waves through body tissues, and suffer from high noise, low biocompatibility, and security risks. We propose a new research direction, called Biological Neuron Communication Network (BNCN), where the peripheral nervous system is exploited for in-vivo networking.

Large scale production of dopaminergic neurons from human pluripotent stem cells for Parkinson's disease
Yuguo Lei

Implanting dopaminergic (DA) neuron progenitors into the Parkinson’s (PD) patients had been proved to be effective to relief the motor symptoms. However, this treatment hasn’t been widely used partially due to the ethic problem and limited source of fetal tissue. Human pluripotent stem cells (hPSCs) are promising to overcome these problems. However, a GMP compliant and cost effective culture system is required to produce these cells at various scales before they can be used in clinic. In this presentation, we will introduce a simple, defined, scalable and GMP compliant 3D culture system for producing DA progenitors.

Shining a light on cellular metabolism of skin cancer with time- and wavelength-resolved multiphoton microscopy
Christina Miller, Michael G. Nichols

Like most cancers, the key to effective treatment of skin cancer is early detection. To help develop better, noninvasive and sensitive techniques, we began by using intensity-, time-, and wavelength-resolved multiphoton, fluorescence microscopy. By using these techniques, high- and low-HER2 expressing, cultured squamous cell carcinoma cell lines can be clearly distinguished by measuring fluorescence intensity and lifetimes of reduced nicotinamide adenine dehydrogenase (NADH) and flavin cofactors. To begin bridging the gap between in vitro and in vivo imaging, we then applied similar techniques to excised mouse skin. A spectral analysis of the skin distinguished fluorescent signals (e.g. NADH, flavins, keratin, and extracellular structures) helping us to identify and characterize keratinocytes. Multiphoton, fluorescence microscopy shows promise as a non-invasive technique to identify metabolic changes that occur with the early development of cancer.