

# Institute for Neuroscience Symposium Mission Statement

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Welcome to the 12<sup>th</sup> annual Institute for Neuroscience Symposium!

For the past twelve years, graduate students of the Institute for Neuroscience have formed a committee to plan and execute this day-long academic event. The symposium planning committee strives to bring the university science community together to hear pioneering and inspiring neuroscience research. We value the opportunity for students from within the Institute to share and discuss their research with individuals from the science community through informative talks and poster presentations. With talks from Institute faculty we intend to acquaint others with current ongoing research at the Institute for Neuroscience. Additionally, every year we aspire to invite a distinguished keynote speaker to share his or her work with the university. Our student body has consistently nominated and voted for prominent scientists from a number of disciplines representing a diverse collection of research interests. Keynote speakers from previous years include Drs. Russell Fernald, Stuart Lipton, Cornelia Bargmann, Bruce McEwen, Daniel Margoliash and William Greenough. This year we continue the tradition by welcoming renowned scientist Dr. Indira Raman. Our symposium provides a shared environment for researchers of many disciplines, and thus, is a highly valued event for both faculty and students at the University of Texas at Austin and surrounding universities.

We hope you enjoy this year's symposium and thank you for your participation in its success!

Brenda Houck  
Symposium Committee Co-chair

# Special Acknowledgments

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Symposium Committee Members:

Brenda Houck, Co-Chair  
Angela Ozburn, Co-Chair  
Sukant Khurana  
Paul Mathews  
Jascha Pohl  
Julio Rojas  
Maureen Scholl  
Deena Walker  
Jessica Zidik

Poster Design:

Jason Bartsch  
Deena Walker

Program Design/Poster Session Chairs:

Julio Rojas  
Maureen Scholl

NGSA and the Events Co Sponsorship Committee

Grant Applications:

Sukant Khurana  
Jessica Zidik

Web Design:

Jason Goltz

Graduate Coordinator:

Krystal Ho

Faculty Supervisor:

Dr. Rick Aldrich

Director of the Institute:

Dr. Dan Johnston

Dr. Theresa Jones and the Society for  
Neuroscience Grass Traveling Award

QuickTime™ and a  
TIFF (Uncompressed) decompressor  
are needed to see this picture.

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And to all speakers, poster presenters and volunteers for their contributions!

# Schedule

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8:30 – 9:00	<b>Breakfast Registration</b> (Poster session set-up)
9:00 – 9:15	<b>Opening Remarks</b> Dr. Dan Johnston, Director of the Institute for Neuroscience Brenda Houck, Co-Chair Symposium Planning Committee
9:15 – 9:45	<b>Dr. Kristen Harris</b> Structural plasticity at hippocampal synapses during long-term potentiation
9:45 – 10:15	<b>Dasa Zeithamova</b> Prototype learning is not a uniform process: What brain and behavior can reveal
10:15 – 10:45	<b>Jennifer Fogel</b> Bone morphogenetic protein (BMP) pathways regulate cellular morphology in the developing midbrain
10:45 – 11:00	<b>Break</b>
11:00 – 11:30	<b>Dr. Rick Aldrich</b> Molecular physiology of calcium activated potassium channels
11:30 – 12:00	<b>Angela Ozburn</b> Chronic self-administration of alcohol results in elevated FosB-IR in nucleus accumbens: comparison of hybrid mice with distinct drinking patterns
12:00 – 1:00	<b>Lunch</b> (Poster session set-up)
1:00 – 1:30	<b>Michelle Dupre</b> Redefining the glycine receptor pore: insights into inter-subunit signal transduction
1:30 – 2:00	<b>Brian Dias</b> Sculpting animal sexuality using molecular parsimony
2:00 – 2:30	<b>Dr. Bas Rokkers</b> Neural circuits underlying the perception of 3D motion
2:30 – 4:00	<b>Break/Poster Session</b>
4:00 – 5:00	<b>Dr. Indira Raman</b> Spontaneous and synaptic signaling in cerebellar circuits
5:00 – 5:10	<b>Closing Remarks</b> Paul Mathews

# Faculty Speaker

## **Kristen Harris**

Center for Learning and Memory  
University of Texas at Austin

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Dr. Kristen M. Harris received her PhD in Neuroscience in 1982 from the Northeastern Ohio Universities College of Medicine in Rootstown Ohio with Dr. Timothy Teyler, when she established postnatal day 15 as the earliest age to express enduring long-term potentiation. In 1984 she completed postdoctoral research in serial section transmission electron microscopy with Dr. Dennis Landis at Harvard Medical School and Dr. John Stevens at the University of Toronto. She then became a member of the faculty in Neurology at the Harvard Medical School and Children's Hospital, Boston where she remained until 1999. In 1999 she moved as tenured full professor to Boston University where she helped to establish an inter-departmental Program in Neuroscience. In 2002 she became a Georgia Research Alliance Eminent Scholar at the Medical College of Georgia where she established the Synapses and Cognitive Neuroscience Center and initiated the Human Brain Laboratory and recruited Dr. Sergei Kirov as its director. In 2006, she was recruited to the University of Texas at Austin, where she is currently Professor in Neurobiology and a Fellow in the Center for Learning and Memory.

### **Structural plasticity at hippocampal synapses during long-term potentiation**

I plan to present findings about changes in synapse structure and composition that occur during long-term potentiation in the developing and mature rat hippocampus especially regarding the redistribution of endosomes and polyribosomes that facilitates synaptogenesis and enlargement.

# Student Speaker

## **Dasa Zeithamova**

PI: Dr. Todd Maddox

Institute for Neuroscience

University of Texas at Austin

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Dasa Zeithamova was born in Prague, Czech Republic. She graduated from Charles University, Prague, in 2003, with master's degree in psychology and a minor in logic and economy. She entered the neuroscience doctoral program here at UT in fall 2003. Her interest focuses on cognitive neuroscience of category learning, aiming to integrate behavioral, neuroimaging and computational modeling research approach.

### **Prototype learning is not a uniform process: What brain and behavior can reveal**

Studies of prototype category learning have a long tradition in cognitive research. Prototype learning studies represent categories as classes of objects that are distortions of a central prototype. The neural underpinnings of prototype learning are not well understood and contradictory findings exist. In the neuropsychological literature, some studies found intact learning in amnesiacs, whereas others found impaired learning. Neuroimaging results are also highly variable. One plausible explanation for the discrepant findings may be that two versions of the prototype task exist: a multiple category/multiple prototype learning task ("A/B task") and a one category/one prototype learning task ("A/nonA task"). In the A/B task, participants are presented with a series of exemplars from two categories and are instructed to learn to classify the exemplars based upon corrective feedback. In the A/nonA task, participants are presented with a series of exemplars from one category only and are later asked to discriminate categorical items from noncategorical items. We hypothesized that these two versions of a prototype learning task are mediated by different cognitive and neural processes. To test this hypothesis, participants performed four prototype learning tasks, two of the A/B type and two of the A/nonA type. Stimuli were cartoon animals varying on 10 binary dimensions. The training phase consisted of feedback training on a mixture of A and B exemplars (A/B task) or passive exposure to A exemplars only (A/nonA task). The testing phase (during which functional MRI scans were obtained) was identical for both tasks and consisted of unsupervised classification of stimuli into the A category or the B (nonA) category. Behavioral data revealed no performance correlation across the A/B and A/nonA tasks despite equivalent difficulty (average performance). Greater activation of a network of regions consistent with episodic memory retrieval was observed for the A/B task, and greater activation of a perceptual learning network was observed for the A/nonA task. The results suggest that learning in these two tasks is mediated by different neural systems and explain why contradictory findings exist in the literature when the type of the prototype task is not taken into account.

# Student Speaker

## Jennifer Fogel

PI: Dr. Seema Agarwala  
Institute for Neuroscience  
University of Texas at Austin

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Jennifer came to the University of Texas for her undergraduate education, in which she received a Bachelors degree in Zoology. Upon graduation she returned to California where she worked as a research technician for US Borax in the wood preservation group. She traveled to many conferences and wrote several papers for the field. While working full time she began her graduate education at the University of California, Northridge. She received a Master's degree in which her research focused on the regulation of *c-myc* in osteoblast proliferation under the supervision of Dr. Reem Medh. She then continued her studies within the Institute of Neuroscience. Currently in her 5<sup>th</sup> year, Jennifer works in Dr. Seema Agarwala's lab studying the role of BMPs in patterning the vertebrate midbrain.

### **Bone morphogenetic protein (BMP) pathways regulate cellular morphology in the developing midbrain**

In the developing chick midbrain several BMPs (BMP2, 4, 5, 6, 7) and their antagonists (CHORDIN, NOGGIN, FOLLISTATIN) are expressed in a spatially and temporally dynamic manner. During development BMPs are expressed ubiquitously through out the midbrain, as well as, strongly in all three signaling centers: the roof plate (RP), the midbrain-hindbrain boundary (MHB), and rostral floor plate (rFP), where they are coexpressed with Sonic Hedgehog (SHH). Therefore, the role of BMP signaling in the development of the midbrain is likely to be more complex than that reported for the spinal cord. In this study, we attenuated BMP signaling by in ova electroporation of *NOGGIN* in the developing chick midbrain. This resulted in the overall reduction of midbrain size, while increasing the thickness of its neuroepithelium. In addition, *NOGGIN* electroporated cells exhibited disrupted cytoskeletal organization such that the normal pseudostratified morphology of the midbrain neuroepithelium was perturbed. Ventral midbrain cell-fates in the *NOGGIN* electroporated brains did not appear to be altered, however, the overall length-width ratio of the midbrain was perturbed in part due to changes in cell-shape and cytoskeletal organization at the ventral midline. Unlike ventral midbrain cell-fates, multiple dorsal cell-fates, including markers of the dorsal midbrain (*PAX7*), neural crest (*ZIC1*, *SOX10*) and RP (*LMX1b*, *WNT1*) were severely reduced. The loss of dorsal fates was preceded by cell-shape changes and a severe delamination of dorsal cells into the lumen of the neural tube followed by their subsequent elimination. We propose that the primary role of BMP blockade in the midbrain is to regulate epithelial morphology via a control of cytoskeletal dynamics. The consequences of altered epithelial morphology include reduced cell survival, altered tissue shape and size, an aberrant delamination of undifferentiated neurons and a positional loss of dorsal cell fates resulting from the detachment, delamination and the ultimate removal of dorsal cell fates from the neural tube.

# Faculty Speaker

## **Richard Aldrich**

Section of Neurobiology and Center for Learning and Memory  
University of Texas at Austin

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Richard Aldrich graduated with high distinction from the University of Arizona in 1975 with a Bachelor of Sciences degree in Biological Sciences. He received his Ph.D. in Neuroscience from Stanford University in 1980, after which he did postdoctoral work at Yale University in Physiology. He joined the faculty at Yale in the Section of Molecular Neurobiology before returning to Stanford in 1985 as a faculty member in the Department of Neurobiology and subsequently the Department of Molecular and Cellular Physiology, where he served as department chair from 2001-2004. Dr. Aldrich was a member of the Howard Hughes Medical Institute from 1990 until moving to The University of Texas in 2006, where he is Professor and Chair of the Section of Neurobiology in the School of biological Sciences and the Karl S. Folkers Chair II in Interdisciplinary Biomedical Research. He has served on the council and as president of the Society of General Physiologists, and on the council and is a Fellow of the Biophysical Society.

### **Molecular physiology of calcium activated potassium channels**

Work in the Aldrich laboratory is directed towards understanding the mechanisms of ion channel function and the role of ion channels in electrical signaling and physiology. This research relates to transduction, processing, and transmission of information in the nervous and other physiological systems and to basic mechanisms of coupled conformational changes in signaling proteins. We use a combination of molecular biology, electrophysiology, biophysics, cellular and systems physiology, and computational biology. Recently we have focused on the mechanisms of gating and the physiological roles of voltage- and calcium-activated (BK) potassium channels. These ion channels' proteins are important in excitable and non-excitable cells of a very wide range of physiological systems. BK channels are also an outstanding model system for the study of regulated conformational changes in proteins due to their dual activation (by membrane voltage and by calcium binding) and their particular suitability for high-resolution functional manipulation and measurements, including high quality single molecule studies. The broad role of these channels in several tissues provides a rich environment for studying their involvement in cellular and systemic physiological mechanisms. Our work on these channels has been a combination of biophysical studies directed towards understanding the mechanisms of channel gating and transgenic and physiological studies directed towards understanding their role in physiological systems.

# Student Speaker

## Angela Ozburn

PI: Dr. Adron Harris

Institute for Neuroscience

University of Texas at Austin

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Angela Renee Ozburn received a B.S. in Biochemistry from the University of Texas in 2000. She worked in molecular genetics and studied mechanisms of bacterial conjugation under the guidance of Dr. Richard Meyer. During this time, she returned to school and earned a B.S. in Neurobiology in 2002. In 2004, Angela joined the Institute for Neuroscience to study addiction neurobiology in the laboratory of Dr. Adron Harris. The aim of her research is to model moderate and excessive alcohol consumption and identify brain circuitry important for these behaviors. Angela has received several academic and professional honors, including conference travel awards, a merit award from the American Association for the Advancement of Science Program for Excellence, a fellowship from the American Chemical Society, a research supplement from the National Institute on Alcohol Abuse and Alcoholism and the Ruth L. Kirschstein NRSA Individual Fellowship. Outside of research, Angela loves the ocean and is an avid scuba diver.

### **Chronic self-administration of alcohol results in elevated FosB-IR in nucleus accumbens: comparison of hybrid mice with distinct drinking patterns**

Distinct alcohol self-administration behaviors are observed when comparing two F1 hybrid strains of mice: C57BL/6JxNZB/B1NJ(B6xNZB) show reduced alcohol preference (RAP) after experience with high concentrations of alcohol and C57BL/6J x FVB/NJ (B6xFVB) show sustained alcohol preference (SAP). In the present study, we tested the hypothesis that these behavioral differences are represented by differential production of the inducible transcription factor, FosB, in the nucleus accumbens (core and shell) and amygdala (lateral, basolateral, central medial posteroventral, central capsular and central lateral). FosB immunoreactivity (IR) was measured from mice that experienced 72 days of access to either water and alcohol [one group with access from 3-35% alcohol (HiAlc) and another with access from 3-9% alcohol (LoAlc)] or water alone. In B6xFVB mice, experience with HiAlc sustained subsequent 9% alcohol preference (from 0.96 to 0.90). In B6xNZB mice, experience with HiAlc significantly reduced subsequent 9% alcohol preference (from 0.82 to 0.46). For B6xFVB and B6xNZB mice, the LoAlc groups exhibited SAP. Mice (of both genotypes) in HiAlc, but not LoAlc, groups had elevated FosB counts in nucleus accumbens (shell and core) as compared with water groups. For the HiAlc groups, B6xNZB mice (RAP) had elevated FosB counts in nucleus accumbens (shell and core) as compared with B6xFVB mice (SAP). There were no differences between groups or genotypes in FosB counts taken from the amygdala. Given that we found no effect of group or genotype on FosB-IR in amygdala, it appears that neither sustained nor reduced alcohol preference requires elevated production of FosB in these nuclei. Our genetic models provide both stable, high consumption (SAP) and moderate drinking (RAP) in two F1 hybrid strains of mice. Chronic consumption of alcohol resulted in elevated transcription factor levels in the nucleus accumbens, suggesting that these neurons respond to chronic alcohol intake with an experience dependent plasticity. Future work will focus on continued molecular mapping of the SAP and RAP behavioral phenotypes. Supported by grants from NIAAA & INIA consortium (AA06399S, AA16424, AA13520).

# Student Speaker

## Michelle Dupre

PI: Dr. S. John Mihic

Institute for Neuroscience

University of Texas at Austin

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Michelle L Dupre graduated from the University of Texas at Austin in 2002 with a double major in Psychology and History. As an undergraduate, Michelle researched the neurobiology of Parkinson's disorder with Dr. Timothy Schallert. After joining the Institute for Neuroscience, Michelle joined Dr. John Mihic's laboratory in 2004. Her research has been focused on understanding the structure and function of glycine receptors and their modulation by alcohols and volatile anesthetics. Michelle has been the recipient of numerous awards, including the Ruth L. Kirschstein NRSA Individual Fellowship, Institute for Neuroscience and Homer L. Bruce Endowed Graduate Fellowships, UT Professional Development Awards and conference travel awards from the Waggoner Center for Alcohol and Addiction Research and National Institute on Alcohol Abuse and Alcoholism. One of her favorite hobbies is Ashtanga Yoga and she has recently been certified as a Yoga instructor.

### **Redefining the glycine receptor pore: insights into inter-subunit signal transduction**

The glycine receptor (GlyR) is the major inhibitory receptor in the brainstem and spinal cord. As a member of the ligand-gated ion channel family, studies of  $\alpha 1$  GlyR structure and function provide insights into the structures of other ligand-gated ion channels, including GABA<sub>A</sub>, nicotinic acetylcholine (nACh) and serotonin-3 receptors. Glycine receptors are pentameric ion channels, with each subunit containing a large extracellular domain and four transmembrane (TM) domains. Single channel studies have shown that one molecule of glycine binding to a single subunit is sufficient to open the GlyR to maximal conductance. Glycine binds to the extracellular *N*-terminal portion of the GlyR and this binding signal is transduced to the pore at TM 2 via an interaction between extracellular loops 2 and 7 with lysine-276 in the extracellular TM 2-3 linker region. The purpose of the present study was to identify amino acid residues that interact with adjacent subunits to transmit the gating signal among channel subunits, thereby opening the channel. Traditionally, the channel pore is visualized as a funnel, made up of helices starting at residue 253 and ending at residue 270. Recent modeling of the related nACh receptor suggests that the helices may extend to a conserved proline residue (amino acid 275 in the GlyR). This proline may provide flexibility to the extracellular portion of the helix lining the pore, making residues in this region candidates for signal transmission to adjacent subunits. We mutated the adjacent hydrophobic residue leucine-274 (L274) to cysteine to determine its proximity to adjacent subunits. We demonstrate that L274C is close enough to adjacent subunits to form covalent disulfide bonds with L274C residues on neighboring subunits, presumably resulting in receptor possessing a single disulfide bond. This crosslinking disrupts ion flow, greatly reducing the receptor's response to glycine. After restoring function by applying the sulfhydryl reducing agent dithiothreitol, we hypothesize that two disulfide bonds per receptor can be formed by applying mercuric chloride. The formation of two disulfide bonds per receptor disrupts ionic flow to such an extent that the receptor now displays a much greater preference for conducting bicarbonate rather than chloride ions. Our studies suggest that the L274 residue seems to be close enough to interact with equivalent residues on adjacent subunits, and may play a role in transmitting binding signals among receptor subunits.

# Student Speaker

## **Brian G. Dias**

PI: Dr. David Crews

Institute for Neuroscience

University of Texas at Austin

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Brian Dias received his B.S. in Life Sciences and Biochemistry from St. Xavier's College (Mumbai, India) in 2000. He then went on to finish his M.S. in Neuroscience in 2003, in Dr. Vidita Vaidya's laboratory at the Tata Institute of Fundamental Research (Mumbai, India). During this time he investigated the molecular and cellular targets of stress and antidepressant treatments in the rat brain. In keeping with Brian's broad interests in animal behavior and physiology, he joined the laboratory of Dr. David Crews at UT-Austin in spring 2004, and since then, has been examining the neurobiology underlying sexually dimorphic behavioral repertoires.

### **Sculpting animal sexuality using molecular parsimony**

Although the brain is inherently bisexual, it becomes differentiated during development so that in adulthood, males mount receptive females. Yet, vestiges of this bisexuality persist in adults, with heterotypical behaviors (females mounting and males being receptive) observed in some species. Consequently, differences in sexual behavior between the sexes, and between individuals of the same sex, are reflective of the predisposition and degree to which these behaviors are exhibited. Also, sex-typical behaviors are mutually exclusive, suggesting an underlying reciprocal inhibition in the neural mechanisms mediating them. Because male and female vertebrates typically differ in genotype and hormonal histories, the simultaneous study of neural circuits subserving homotypical and heterotypical behaviors in conventional animal models is challenging. In the all-female whiptail lizard *Cnemidophorus uniparens*, individuals naturally display both male-like mounting and female-like receptivity. Data indicate that the serotonergic system gates these homotypical and heterotypical sexual behaviors at the preoptic area. More specifically, serotonin levels, and signaling via distinct serotonergic receptors at behaviorally relevant brain nuclei allows the system to switch between either behavioral repertoire. The use of the same molecule to mediate the reciprocal inhibition of complementary behavioral repertoires is evidence of a phenomenon of molecular parsimony underlying a striking form of behavioral plasticity. Such findings also illustrate that male and female-typical sexual behaviors are sculpted by neurochemical signaling at neural substrates present in both sexes.

# Post Doctoral Speaker

## Dr. Bas Rokers

PI: Dr. Alex Huk

Imaging Research Center, Neurobiology, Center for Perceptual Systems

University of Texas at Austin

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Bas Rokers primarily studies visual motion perception. Although we clearly perceive objects moving through three dimensions, relatively little is known about the visual information and computations underlying such percepts. To address these issues he uses neuro-imaging (fMRI), psychophysics, and computational modeling.

Currently he is a post-doctoral researcher in the lab of Prof. Huk <<http://web.austin.utexas.edu/huk>>, and he closely collaborates with the labs of prof. Ress <<http://web.austin.utexas.edu/ress>> and prof. Cormack. He is funded by a two year Rubicon fellowship

<[http://www.nwo.nl/subsidiewijzer.nsf/pages/NWOP\\_6H2G7R\\_Eng](http://www.nwo.nl/subsidiewijzer.nsf/pages/NWOP_6H2G7R_Eng)>.

## Neural circuits underlying the perception of 3D motion

Although extensive research investigates the encoding of both two-dimensional motion and binocular disparity, relatively little is known about how the human visual system combines these cues to infer three-dimensional motion. 3D-motion stimuli produce two different signals on the two retinas. Percepts of 3D-motion may depend on velocity-based cues (velocity difference of the two retinal motions), or on the corresponding disparity-based cues (change of binocular disparity over time). We performed a series of human fMRI experiments (3T BOLD 2-shot spiral fMRI, 2.2 mm<sup>3</sup> voxels, 3 s TR) to isolate these velocity and disparity signals in the visual system, and to link them to percepts of 3D-motion. Subjects viewed displays via a mirror stereoscope, and performed a task to control attention. We selectively studied the disparity-based cue with random dot dynamic stereograms that did not contain systematic retinal velocity signals, and studied the velocity-based cue by parametrically varying the proportion of anticorrelated dots (which have opposite contrast in the two eyes). We also parametrically varied the orientation of the dot element motions from horizontal (yielding strong 3D-motion percepts) to vertical (no percepts of 3D-motion). We observed strong responses in human MT+ during the presentation of motion through depth. This contrasts with observations of motion opponency in this area, given that 3D-motion displays include oppositely-moving dots in corresponding parts of the visual field. Much like the percepts, MT+ responses were invariant to anticorrelation level for 3D-motion displays, but decreased with anticorrelation for laterally-moving control stimuli. However, MT+ responses were invariant to orientation, suggesting that net activity in this region does not straightforwardly track the strength of 3D-motion percepts. Instead, we noted an area in the posterior parietal lobe that appeared selectively responsive to stimuli that yielded a percept of 3D-motion. These results suggest that the processing of realistic 3D-motion requires more than MT+. Supported by UT Austin Imaging Research Center and NWO Grant 2006/11353/ALW

# Keynote speaker

## **Indira M. Raman**

Department of Neurobiology and Physiology  
Northwestern University

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Indira Raman received her Ph.D. in Neuroscience in 1994 from the University of Wisconsin-Madison, where she worked with Dr. Laurence Trussell. She did a first postdoctoral fellowship at the Vollum Institute for Advanced Biomedical Research in Portland, Oregon with Dr. Craig Jahr and a second postdoctoral fellowship at Harvard Medical School with Dr. Bruce Bean. Dr. Raman joined Northwestern in 1999, and became an Associate Professor in 2005. She was a recipient of an Alfred P. Sloan Foundation Award, a Klingenstein Fellowship Award in the Neurosciences, and a Searle Scholar Award. She is currently a Reviewing Editor for the Journal of Neuroscience as well as a study section member, and she has received recognition for both undergraduate and graduate teaching while at Northwestern. Dr. Raman's research is directed toward identifying, explaining, and interpreting the electrical and chemical signals produced by neurons to encode and transmit information. By using electrophysiological and imaging studies of ion channels and synaptic transmission, she and her lab members are studying cerebellar signaling under physiological conditions, in healthy mice, as well as under pathological conditions, in mice with genetically inherited movement disorders.

### **Synaptic signaling in cerebellar circuits**

Many neurons that regulate motor coordination, including cerebellar Purkinje cells and their targets in the cerebellar nuclei, spontaneously fire tens of action potentials per second. Such high intrinsic activity raises specific questions regarding how spikes are generated, how synaptic strength is maintained, and how synaptic plasticity occurs. We have addressed these questions with in vitro electrophysiology, computer simulations, and immuno-electron microscopy. First, we find that rapid firing in Purkinje neurons requires a voltage-gated, tetrodotoxin-sensitive "resurgent" Na current, which results as an endogenous protein blocks and unblocks the open Na channel. Endogenous open-channel block can be mimicked by the cytoplasmic tail of the Na channel beta4 subunit. Thus, beta4 may permit switching between slow and rapid signaling. Transgenic mice lacking resurgent current exclusively in Purkinje neurons are ataxic, implicating the current in motor coordination. Second, our experiments indicate that Purkinje neurons signal via an unusually effective spillover-mediated transmission. Each bouton has many release sites, without intervening neurotransmitter transporters, permitting a single release event to activate many postsynaptic sites. By converting low presynaptic release probabilities into high postsynaptic response probabilities, Purkinje terminals support high-frequency inhibitory transmission with little synaptic depression. Third, we find that cerebellar nuclear neurons lack spike-timing-dependent-plasticity, consistent with the idea that this rule would generate noisy signals in spontaneously firing neurons. Instead, excitatory postsynaptic currents in nuclear cells potentiate only when NMDA-receptor mediated synaptic excitation precedes a post-inhibitory rebound Ca influx. These neurons thus appear optimized to detect coincident synaptic excitation and inhibition, which can induce adaptive plasticity during cerebellar associative learning.

**12<sup>th</sup> Annual INS Symposium**  
The University of Texas at Austin  
**Poster Session**

- 1. Single channel analysis of alcohol actions on the glycine receptor reveals its complex pharmacology**  
BT Welsh<sup>1</sup> & SJ Mihic<sup>1</sup>  
<sup>1</sup>Section of Neurobiology, Institutes for Neuroscience and Cell & Molecular Biology, and Waggener Center for Alcohol & Addiction Research, University of Texas at Austin
- 2. Dynamic control of intrinsic excitability by hyperpolarization-activated mixed cationic currents (I<sub>h</sub>) in principal neurons of the medial superior olive**  
S Khurana<sup>1</sup> & NL Golding<sup>1</sup>  
<sup>1</sup>Institute for Neuroscience, University of Texas at Austin
- 3. Social modulation of startle behavior: slow modulation of a fast response**  
KW Whitek<sup>1</sup> & HA Hofmann<sup>1,2,3</sup>  
<sup>1</sup>Institute for Neuroscience, <sup>2</sup>Section for Integrative Biology, & <sup>3</sup>Institute for Cellular & Molecular Biology, The University of Texas at Austin
- 4. The *in vivo* function of Id2 in retinal proliferation and differentiation in the vertebrate eye**  
RA Uribe<sup>1,2</sup> & JM Gross<sup>1,2,3</sup>  
<sup>1</sup>Section of Molecular Cell and Developmental Biology, <sup>2</sup>Institute for Cell and Molecular Biology, & <sup>3</sup>Institute for Neuroscience, The University of Texas at Austin
- 5. Neuroprotection against ethanol mediated oxidative stress and apoptosis is via Nrf2/ARE**  
JL Stewart<sup>1</sup> & GI Hendriksen<sup>1</sup>  
<sup>1</sup>Department of Pharmacology, UTHCSA, San Antonio, TX 78229
- 6. Neuroprotective effects of photobiontation with near-infrared light in an *in vivo* rat model of retinal degeneration induced by rotenone**  
JC Rojas<sup>1</sup>, J Lee<sup>1</sup>, M Webb<sup>1</sup>, JM John<sup>1</sup> & F Gonzalez-Lima<sup>1</sup>  
<sup>1</sup>Institute for Neuroscience, University of Texas at Austin
- 7. Chronic unpredictable stress induces a cognitive deficit and anxiety-like behavior in rats that is prevented by chronic antidepressant drug treatment**  
J Doyen<sup>1</sup>, CO Bondi<sup>1</sup>, G Rodriguez<sup>1</sup>, D Lapiz-Bluhm<sup>1</sup>, T Bedard<sup>1</sup> & DA Morikak<sup>1</sup>  
<sup>1</sup>Dept. Pharmacology, UT Health Sci. Center, San Antonio and Ctr for Biomed. Neuroscience
- 8. Noradrenergic facilitation of shock-probe defensive burying in lateral septum**  
GA Rodriguez<sup>1</sup>, CO Bondi<sup>1</sup>, J Doyen<sup>1</sup>, D Lapiz-Bluhm<sup>1</sup>, T Bedard<sup>1</sup> & DA Morikak<sup>1</sup>  
<sup>1</sup>Dept. Pharmacology, UT Health Sci. Center, San Antonio and Ctr for Biomed. Neuroscience

- 9. Behavioral characterization of rats before and after learned helplessness training and testing**  
E Padilla<sup>1</sup>, D Barrett<sup>1</sup>, JC Rojas<sup>1</sup>, F Gonzalez-Lima<sup>1</sup>  
<sup>1</sup>Institute for Neuroscience, University of Texas at Austin.

- 10. Possible role for 5-HT in rat orbitofrontal cortex in the impairment of reversal learning induced by chronic intermittent cold stress**  
MD Lapiz-Bluhm<sup>1</sup>, A Soto-Pina<sup>1</sup>, J Doyen<sup>1</sup>, D Rossi<sup>1</sup>, TF Burke<sup>1</sup>, J Hensler<sup>1</sup> & D Morikak<sup>1</sup>  
<sup>1</sup>Pharmacology, University of Texas Health Science Center, San Antonio, TX

- 11. Changes in brain metabolism associated with fear extinction learning and retrieval**  
AK Bruchey<sup>1</sup> and F Gonzalez-Lima<sup>1</sup>  
<sup>1</sup>Department of Psychology and Institute for Neuroscience, University of Texas at Austin

- 12. Search for rough endoplasmic reticulum (RER) in dendrites and spines**  
L Dickey<sup>1</sup>, J Bowden<sup>2</sup>, W Abraham<sup>2</sup> & KM Harris<sup>1</sup>  
<sup>1</sup>Institute for Neuroscience, University of Texas, <sup>2</sup>Department of Psychology, University of Otago

- 13. Circadian genes are necessary for the acquisition of rapid tolerance to ethanol in *Drosophila***  
JB Pohl<sup>1</sup>, A Ghezzi<sup>1</sup>, K Bieri<sup>1</sup>, T Yustaf<sup>1</sup>, & NS Atkinson<sup>1</sup>  
<sup>1</sup>Section of Neurobiology and Waggener Center for Alcohol and Addiction Research, The University of Texas at Austin

- 14. The development of a semi-automated phototaxis assay to identify genes responsible for ethanol tolerance**  
KV Ramachandran<sup>1</sup>, RB Ramirez<sup>1</sup> & NS Atkinson<sup>1</sup>  
<sup>1</sup>Section of Neurobiology, University of Texas at Austin

- 15. Dynamic reproductive decision-making in túngara frogs**  
AT Baugh<sup>1</sup> & MJ Ryan<sup>1,2</sup>  
<sup>1</sup>Institute for Neuroscience, <sup>2</sup>Section of Integrative Biology, University of Texas at Austin

- 16. Noradrenergic modulation of the hypothalamic-pituitary-adrenal axis in the bed nucleus of the stria terminalis**  
T Bedard-Arana<sup>1</sup>, E Rubino<sup>1</sup>, G Rodriguez<sup>1</sup>, J Doyen<sup>1</sup>, CO Bondi<sup>1</sup>, D Lapiz-Bluhm<sup>1</sup> & D Morikak<sup>1</sup>  
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- 17. Vasopressin associated with play fighting in golden hamsters**  
S Cheng<sup>1</sup> & Y Delville<sup>1</sup>  
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- 18. Serotonin 1A receptors in an animal model of impulsive aggression**  
MC Cervantes<sup>1</sup> & Y Delville<sup>1</sup>  
<sup>1</sup>Psychology Department and Institute for Neuroscience, University of Texas at Austin

- 19. Semantic processing in Hindi-English bilinguals using functional neuroimaging**  
R Sebastian & S Kiran  
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- 20. Mechanisms underlying ethanol enhancement of GABAergic transmission on VTA-Dopamine neurons**  
JW Theil<sup>1</sup>, H Morikawa<sup>1</sup>, RA<sup>1</sup> Gonzalez, RA<sup>1</sup> Morisset Col Pharm, Waggener Ctr, ICMB, INS, Section Neurobiology, University of Texas at Austin

- 21. Conversion of synaptic depression to potentiation after intermittent ethanol exposure in the nucleus accumbens**  
ZM Jeanes<sup>1</sup> & RA Morisset  
<sup>1</sup>University of Texas at Austin, College of Pharmacy, Waggener Center for Alcohol and Addiction Research

- 22. Burst-dependent plasticity of NMDA receptor-mediated transmission in midbrain dopamine neurons**  
MT Harrett & H Morikawa  
<sup>1</sup>Waggener Center for Alcohol & Addiction Research, Institute for Neuroscience, and Section of Neurobiology, University of Texas at Austin

- 23. Mechanisms of receptor and channel-specific modulation of neuronal ion channels by phosphoinositides**  
O Zaika, C.C Hernandez, GP Tolstikhin and MS Shapiro  
<sup>1</sup>Department of Physiology, UT Health Science Center, San Antonio, TX

- 24. Repetition priming in a response learning task using novel objects**  
M Sagar, M Sathishkumar, R Mikkulainen and DM Schryer  
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- 25. Activity-dependent expression of Kv1 channels in the hippocampus and the visual cortex**  
K Raab-Grain<sup>1</sup>, P Haddick<sup>1</sup>, K Kasik<sup>1</sup>, Y Fu<sup>1</sup>, Y Jan<sup>1</sup> and LY Jan<sup>1</sup>  
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- 26. Regionally-specific enhancement by ethanol of cocaine- and amphetamine-regulated transcript and peptide expression in mesolimbic structures**  
A Salinas, RE Malave, RA Morisset  
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## **1. Single channel analysis of alcohol actions on the glycine receptor reveals its complex pharmacology**

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The glycine receptor (GlyR) is a ligand gated ion channel and member of the nicotinic acetylcholine receptor superfamily. Acting as allosteric modulators of receptor function, drugs such as alcohol and volatile anesthetics enhance the function of wild-type GlyRs. The actions of these drugs at inhibitory receptors in the brain and spinal cord are thought to produce many of the physiological effects associated with their use. As an anesthetic however alcohol seems to be less efficacious than traditional anesthetics such as isoflurane. The action of ethanol on the GlyR has been well studied on the macroscopic, whole cell level. Ethanol is thought to bind specifically to the GlyR, in a putative water-filled pocket that is formed by residues within transmembrane (TM) domains two and three and the TM2-TM3 linker region. Previous research has shown that alcohol may have both inhibitory and potentiating effects on the GlyR. We examined the effects of 3 $\mu$ M glycine  $\pm$  50mM ethanol on outside-out patches pulled from *Xenopus* oocytes expressing wildtype  $\alpha$ 1 GlyR to determine the effects of alcohol at the single channel level. Alcohol appeared to have two opposing effects on GlyR single channel properties. The first was to increase mean burst duration, which is similar to anesthetic actions on the GlyR. The second property of 50mM ethanol was to decrease the mean open time of the receptor, which is opposite to the effects of volatile anesthetics at the GlyR. It is the net effect of these two opposing actions that we believe leads to a decreased ability of ethanol to enhance GlyR function, in comparison to volatile anesthetics.

## **2. Dynamic control of intrinsic excitability by hyperpolarization-activated mixed cationic currents (I<sub>h</sub>) in principal neurons of the medial superior olive**

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Hyperpolarization and cyclic nucleotide-gated cationic currents, also known as I<sub>h</sub> contributes to neuronal pacemaking, synaptic integration and plasticity in many central and peripheral neurons. The role of I<sub>h</sub> in auditory neurons involved in temporal coding is particularly intriguing, as these neurons integrate synaptic inputs (1 to 2ms long EPSPs) that are individually far briefer than I<sub>h</sub> gating kinetics, but are received at frequencies that may well exceed 1 kHz. To address the role of I<sub>h</sub> dynamics in MSO neurons, we used current and voltage clamp recordings in brainstem slices taken from Mongolian gerbils (16 to 22 days old, 35°C). In current-clamp recordings, we found that I<sub>h</sub> contributes substantially to the resting potential (avg. -58mV) and input resistance (avg. 8.2 MW) as evident by 12.5 mV hyperpolarization and a three-fold increase in input resistance in the presence of 50  $\mu$ M ZD7288, a specific blocker of I<sub>h</sub>. (n=6) Correspondingly, whole-cell voltage clamp measurements demonstrated a large average I<sub>h</sub> conductance (47.1  $\pm$  5.9 nS, n=5) with 35% of the channels activated at the average resting potential (18.7  $\pm$  1.6 nS at -58 mV). The V<sub>1/2</sub> of activation was -64.5  $\pm$  0.5 mV (k=7.1  $\pm$  0.4 mV, n=5), and reversal potentials averaged -38.6  $\pm$  3 mV (n=8). In current-clamp recordings, trains of simulated subthreshold EPSPs at the soma triggered increases in input resistance by an average of 34.7% (1s train at 500 Hz, 8-10 mV amplitude, n=12). Changes in input resistance were mediated by the cumulative deactivation of I<sub>h</sub>, as they were sensitive to duration, amplitude and frequency of EPSP trains, and blocked by 75% in 50  $\mu$ M ZD7288 (n=8). In addition, changes in input resistance occurred over a time scale of tens to hundreds of milliseconds, consistent with time constants of activation and deactivation of I<sub>h</sub> measured in voltage-clamp experiments. Finally, using irregular trains of brief suprathreshold depolarizations (1s duration) we demonstrated that changes in I<sub>h</sub> gating are insensitive to short term variations in the frequency of input pattern, instead serving to integrate the overall level of membrane depolarization during high-frequency. In the depolarizing voltage range, dynamic changes in I<sub>h</sub> gating may play a role in short-term sensory adaptation, counteracting the effects of frequency-dependent synaptic depression and shunting from synaptic conductances.

### 3. Social Modulation of Startle Behavior: Slow Modulation of a Fast Response

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Social experience regulates behavior by altering brain function. The African cichlid fish *A. burtoni* has become an important model system to study the molecular and neural underpinnings of socially controlled behavior. In this species, males alternate between two phenotypic states: Either they are conspicuously colored, reproductively active and territorial (T) or camouflaged, reproductively suppressed and non-territorial (NT). Possibly due to the increased predation pressure on conspicuous males, when presented with an unexpected auditory pulse, Ts respond with a startle/escape behavior with higher probability compared with NTs. This startle escape behavior (known as a C-start) is mediated by two large, paired command neurons, the M-cells, located in the medulla. Each M-cell receives sensory input through two large dendrites (lateral: auditory, lateral line; ventral: visual). Activation of one M-cell inhibits the other and causes a characteristic “C” shape by contraction of the muscles along the contralateral side of the fish.

This simple circuit lends itself to a detailed analysis of the molecular and physiological mechanisms by which the social environment can alter neural function. Prior research has shown that differences in C-start performance between Ts and NTs correspond to changes in the biophysical properties of the M-cell and are modulated by serotonin (5-HT<sub>2</sub>). We now propose a series of experiments aimed at understanding the mechanisms of this reversible plasticity: 1) Analysis of auditory-evoked C-starts after administering 5HT subtype-specific agonists and antagonists will show which subtype of receptors are functionally involved in the M-cell circuit. 2) We will determine the localization of 5-HT<sub>2A</sub> receptors by immunocytochemistry and in-situ hybridization to assess the mechanism underlying the hypothesized dendrite-specific functional expression of these receptors. 3) We will compare the differences of auditory-evoked startle responses to the serotonergic drugs found to be interesting in Aim 1 between closely related cichlid species that differ in life history (e.g., predation pressure, social organization). By correlating these results with receptor subtype expression in M-cells of individuals of different species, we will have an understanding of how serotonin receptor expression varies in nature and the impact this has on behavior.

### 4. The *in vivo* function of Id2 in retinal proliferation and differentiation in the vertebrate eye

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The Inhibitor of Differentiation (Id) family of proteins is comprised of four distinct helix-loop-helix factors that resemble basic-helix-loop-helix (bHLH) transcription factors, but lack the basic DNA binding domain. bHLH factors dimerize in order to regulate transcriptional activity, and Id proteins serve as negative regulators of this process by binding and sequestering bHLH factors. Id proteins have also been shown *in vitro* to interact with non-bHLH proteins—such as Retinoblastoma and Pax family transcription factors. Importantly, many different types of cancers, such as prostate and breast cancer, demonstrate distinctly misregulated Id expression. Although many previous studies have focused on Id protein dynamics *in vitro*, studies focusing on the endogenous cell and molecular role of the Ids is lacking *in vivo*. Interestingly, Id1, Id2 and Id3 are highly expressed in the developing zebrafish retina and brain suggesting that they function therein. When Id2 protein expression is knocked-down using a translation-blocking morpholino oligonucleotide, brain and eye size is smaller in these “morphant” embryos. Most neuron retinal subtypes in Id2 morphant retinas are absent, and overall eye development is delayed when compared to control-injected embryos. Id2 morphant retinas contain ganglion cells—other differentiated cell types such as amacrine, bipolar and cone photoreceptors are absent at 3 days post fertilization. We hypothesize that 1) Id2 expression is required for certain populations of retinal progenitor cells to exit the cell cycle, and thus, 2) that Id2 expression is spatially and temporally required for the differentiation of later born cell types in the developing retina. We will utilize a combination of BrdU incorporation assays and phosphohistone H3 immunoreactivity to assess cell cycle progression, and we will assay the expression of cell cycle markers such as Cyclin D1, Cyclin E2 and p57Kip2, and markers of cell fate specification within the retina to determine the molecular mechanism underlying this phenotype. Taken together, these studies will begin to shed light on the molecular and cellular roles of Id proteins *in vivo* in the retina.

## 5. Neuroprotection against ethanol mediated oxidative stress and apoptosis via Nrf2/ARE

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This study characterizes a neuroprotective pathway responsible for coordinated enhancement of astrocyte glutathione (GSH)-homeostatic machinery. Injuries in fetal rat cortical neurons associated with Fetal Alcohol Syndrome are correlated to ethanol (E) exposure leading to increased oxidative stress, GSH depletion, and ultimately neuroapoptosis. We hypothesize that neuroprotection is regulated by activation of the anti-oxidant response elements (ARE) of cytoprotective genes, via the master transcription factor Nrf2. Primary cultured rat neonatal astrocytes were treated with 4mg/ml E at various time points. There was increased nuclear Nrf2 expression within 15 minutes after E treatment, and lasted up to 4 hours. Immunohistochemical studies corroborate cytoplasmic to nuclear translocation. Enhanced nuclear Nrf2 expression was further augmented by BSO pre-treatment. In addition, the transcription factor Maf, which obligatorily dimerizes with Nrf2 to activate gene transcription, was increased by E or BSO. Known ARE inducers and oxidative stress mimicked the cytoplasmic to nuclear translocation seen in E treatment. Next, cells were pre-incubated with Actinomycin D and subsequently treated with E. Nrf2 expression induced by E was abolished suggesting that E increases Nrf2 by stimulating gene transcription. Transfection of Nrf2 siRNA completely ablated Nrf2 expression, and furthermore blocks the tbHQ induced Nrf2, GGT, and Mrp1 expression. Taken together, this suggests that Nrf2 is required for activation of ARE. The role of E in Nrf2-ARE control of astrocyte neuroprotection need to be further investigated. These points of regulation may allow for pharmacological augmentation of this crucial neuroprotective mechanism.

## 6. Neuroprotective effects of photobiomodulation with near-infrared light in an *in vivo* rat model of retinal degeneration induced by rotenone

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Tissue radiation with near-infrared light (NIL) promotes a wide range of biological effects including enhancement of energy production, gene expression and prevention of cell death. In this study, we test for the first time the *in vivo* neuroprotective effects of NIL using a novel model of retinal degeneration induced by rotenone, a mitochondrial complex I inhibitor. Pre- and post-treatment measurements of visual function were obtained for 36 male Long-Evans rats (40 days old) using a behavioral apparatus designed to detect changes in illuminance sensitivity. Subjects received single bilateral intravitreal injections of 1) 200 mg/kg rotenone alone or rotenone plus 2) 4 J/cm<sup>2</sup> NIL post-injection, 3) 8 J/cm<sup>2</sup> NIL post-injection or 4) 4 J/cm<sup>2</sup> pre-injection + 4 J/cm<sup>2</sup> post-injection. The photobiomodulator source consisted of two R30-123 narrow-angle light-emitting diode arrays (LEDtronics, Inc., Torrance, CA) with  $\lambda=633$  nm and energy density of 2 mW/cm<sup>2</sup>, placed at 1.5 in from the subject's head. The total NIL doses were fractionated in three or six sessions of 30 min given at 24 hr intervals. The effects of treatments were also analyzed through histopathologic analysis of retinal sections stained with the NADH dehydrogenase histochemical technique. The *in vitro* effect of NIL on oxygen consumption was measured using dynamic fluorescence quenching in brain homogenates treated with 10 mM rotenone. Rotenone induced a decrease in visual function, as determined by changes in the mean dark-adapted illuminance threshold, escape latency and rate of successful trials, compared to vehicle-treated controls. NIL treatments were equally effective at preventing the increase in mean illuminance threshold and escape latencies induced by rotenone, but only the 8 J/cm<sup>2</sup> NIL post-injection dose prevented the decrease in successful trials. NIL treatment partially prevented the decrease in retinal nerve fiber layer + ganglion cell layer and inner plexiform layer thickness induced by rotenone and enhanced the *in vitro* rate of oxygen consumption in a dose-dependent manner. The effects of NIL were not due to degradation of rotenone, since NIL-radiated rotenone solutions retained their pro-oxidant properties. The results suggest that photomodulation with near infrared light prevents the neurotoxic effects of mitochondrial dysfunction and might be used in the treatment of neurodegenerative disorders. Supported by NIH grant R01 NS3775 and CONACYT 187413

## **7. Chronic unpredictable stress induces a cognitive deficit and anxiety-like behavior in rats that is prevented by chronic antidepressant drug treatment**

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Chronic exposure to stressful life events is a major risk factor for development of depression in humans. Clinical data suggest that the emergence of cognitive dysfunction and an elevated state of anxiety are major components of both depression and anxiety disorders. In the present study, we subjected rats to a chronic unpredictable stress (CUS) treatment that has been previously shown to induce certain depressive-like behaviors in rats. Rats tested after two weeks of CUS consistently exhibited a cognitive impairment in extradimensional set shifting capability in an attentional set shifting test (AST), suggesting an alteration in function of the medial prefrontal cortex. This chronic stress treatment also increased anxiety-like behavior on the elevated plus-maze (EPM), reflecting altered function in the limbic forebrain. Further, chronic treatment with antidepressants, either the selective norepinephrine reuptake blocker, desipramine (7.5 mg/kg/day), or the selective serotonin reuptake blocker, escitalopram (10 mg/kg/day), beginning one week prior to CUS treatment and continuing through the behavioral testing period, prevented the CUS-induced deficit in extradimensional set-shifting. Chronic desipramine treatment also prevented the CUS-induced increase in anxiety-like behavioral activity on the plus-maze, but escitalopram was less effective on this measure. Thus, CUS induced both cognitive and emotional disturbances that are similar to components of major depression and anxiety disorders. These effects were prevented by chronic treatment with antidepressant drugs, which is consistent with clinical evidence that relapse of depressive episodes can be prevented by antidepressant drug treatment. MH53851, MH72672, MH 57001

## **8. Noradrenergic facilitation of shock-probe defensive burying in lateral septum**

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Acute stress activates norepinephrine (NE) release in regions such as lateral bed nucleus of the stria terminalis and central amygdala, facilitating anxiety-like behavioral responses in the elevated plus-maze and social interaction test, respectively. However, the response to stress in both these tests is reduction of a specific ongoing behavior. To better understand the stress-modulatory effect of NE, it is important to determine if NE also facilitates responses that represent an activation of behavior. Thus, we tested modulation of the shock-probe defensive burying response by NE in the lateral septum (LS) of male SD rats. In experiment 1, we first determined that shock-probe exposure induced an acute 3-fold increase in NE levels measured in LS by microdialysis. Shock-probe exposure also induced a modest rise in plasma ACTH, taken as an indicator of perceived stress, that returned to baseline faster in rats that were allowed to bury the probe compared to rats prevented from burying by providing them with minimal bedding. These findings indicate that the active defensive burying behavior is an effective coping strategy that attenuates the impact of acute shock-probe induced stress. In experiment 2, 5 cm bedding lined the cage to allow burying during the 15 min test. Blockade of either  $\alpha$ 1- or  $\beta$ - receptors in LS by local microinjection of antagonists immediately before testing reduced defensive burying and increased immobility. These results suggest that NE facilitates the active, adaptive behavioral coping response in this test. Together with previous results, we conclude that NE facilitates anxiety-like behavioral responses to stress, whether a reduction of ongoing behavior or an activation of new behavior, whereas blocking NE promotes a passive, immobile response to stress. Support Contributed by NIMH Grant MH53851

## **9. Behavioral characterization of rats before and after learned helplessness training and testing**

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Inescapable electric shock prevents animals from subsequently learning an escape response, a phenomenon which is termed learned helplessness. Learned helpless animals are used as a model of depression and post-traumatic stress disorder. Certain individual differences can predispose subjects to developing learned helplessness; the purpose of this study was to characterize behavioral traits that can lead to learned-helpless behavior. On day 1 of training, male Holtzman rats ( $n = 28$  subjects, 40 days old) underwent open field testing (novel OF). On day 2, subjects were subjected to inescapable shocks (60 minutes session length, with 30 trials of 0.5 mA footshock, 10 second duration). Inter-trial intervals consisted of pseudorandom durations averaging 1 minute. On day 3, rats were tested using escapable shock. Twelve rats underwent 30 trials of a fixed ratio (FR) 1 schedule, in which the escape response was a single jump through a small window eight centimeters from the floor. Sixteen rats also underwent five FR1 trials, followed by 25 FR2 trials, in which the subjects crossed twice in order to terminate the shock. Subjects with high and low latencies to escape were classified as susceptible and resistant (respectively) to learned helplessness. On day 4, rats were re-exposed to the open-field apparatus (familiar OF). To test whether a baseline predisposition towards the development of spontaneous helpless behavior existed in this population, a repeated measures ANOVA was performed on parameters related to open-field behavior. There were no significant main effects of group; however, several Group x Minutes interactions were found. The helpless-susceptible group showed significantly greater stereotypic behavior (e.g., orienting, grooming) in the periphery ( $p = 0.005$ ), especially during the familiar OF. This pattern was not observed in the resistant group. Paired-sample t-tests revealed that helpless-susceptible subjects showed significantly faster rears (both in the total OF and in the periphery) after the stress of helplessness training, while the helpless-resistant subjects did not. Pairwise correlations between escape latency and behavioral measures of activity in the OF were significant for ambulatory parameters in the novel OF only. Both ambulatory distance and ambulatory counts revealed significant pairwise correlations in which the helpless-susceptible group showed increased locomotion, both in total OF and in the periphery. These findings indicate that subjects who showed greater locomotor activity, especially in terms of ambulation, and especially in the perimeter of the open field, were more likely to develop learned helplessness. Interestingly, this predisposition towards increased novelty seeking was present before the stress of learned helplessness training and testing, but not after. These results are consistent with our lab's previous findings of increased baseline locomotor activity in the congenitally helpless rat, prior to exposure to any stressors.

## **10. Possible role for 5-HT in rat orbitofrontal cortex in the impairment of reversal learning induced by chronic intermittent cold stress**

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Chronic stress perturbs brain neuromodulatory transmitter systems, and is a known risk factor in the development of neuropsychiatric conditions such as depression. We have studied the effects of chronic intermittent cold (CIC) stress, a potent metabolic stressor, on cognitive performance of rats on an attentional set shifting test (AST). Male Sprague-Dawley rats exposed to CIC stress (4°C, 6 hr/day x 14 days) exhibited a selective and consistent impairment on the first reversal learning task in the AST (Lapiz and Morilak, 2007, SFN 2007 meeting abstract). This study further characterized the nature of the CIC stress-induced impairment during reversal learning. The orbitofrontal cortex (OFC) has been implicated in reversal learning, which has also been shown to be modulated specifically by serotonin (5-HT). We found subsequently that 5-HT depletion with para-chlorophenylalanine (200 mg/kg/day, i.p.) induced a similar selective deficit in reversal learning on the AST. The CIC-induced impairment in reversal learning was attenuated by acute administration of the 5-HT reuptake inhibitor citalopram (5 mg/kg, i.p.), shown in pilot studies using in vivo microdialysis to produce a 5-fold increase in extracellular 5-HT levels in naïve animals. Microdialysis studies are ongoing to examine differences in 5-HT release in OFC of control and CIC-stressed rats during behavior on the AST. These results suggest that CIC stress-induced impairment of cognitive flexibility may involve alterations of 5-HT function in OFC. Such deficits in cognitive flexibility may thus model relevant symptoms of neuropsychiatric disorders that respond to SSRI treatment, e.g., depression, anxiety disorders and obsessive compulsive disorder. Support: NIMH grant MH72672 (DM), MH52369 (JH) & NARSAD Young Investigator Award (MDLB)

## **11. Changes in brain metabolism associated with fear extinction learning and retrieval**

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One of the questions in learning and memory research has been that of whether learning and retrieval of memory activate the same neurons, and whether the intensity of neural activation correlates with memory strength. By using two complementary metabolic brain mapping techniques to examine fear extinction learning and retrieval, we examined which neuronal populations are associated with both learning and retrieval of extinction memory in unrestrained, intact animals. Specifically, we identified neuronal activation changes in the rat brain associated with extinction memory retrieval using fluorodeoxyglucose (FDG) autoradiography, and then compared those changes with neural activity associated with extinction learning using cytochrome oxidase (CO) histochemistry. We found increased stimulus-evoked neuronal activity and increased state of oxidative metabolism associated with prolonged training in the frontal cortical areas, such as medial, dorsal and lateral frontal cortex, agranular insular cortex, medial orbital cortex and prelimbic cortex in the extinction group as compared to the control pseudorandomly trained group. In addition, we found increased FDG uptake in the auditory system in the extinction group, indicating that tone conditioned stimulus retained its associative properties even after successful extinction training. We also observed increased metabolic capacity in the anterior and lateral hypothalamus in the extinction group, suggesting that the affective dimension of conditioned fear extinction may be differentially processed in an intact brain. Finally, analysis of the brain-behavior correlations showed that strength of retrieved fear extinction memory correlated with intensity of neural activation in a widespread neuronal network encompassing, but not limited to, auditory system and hippocampal formation neurons. This work is supported by NIH grants R01 NS37755 and T32 MH65728 directed by FGL.

## **12. Search for rough endoplasmic reticulum (RER) in dendrites and spines**

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Evidence is accumulating for presynaptic and postsynaptic structural changes during long-term potentiation (LTP). Glutamate receptors, scaffolding proteins and accessory proteins are required to build synapses and local protein synthesis appears to be crucial following LTP. Recent work has shown that polyribosomes are upregulated in dendritic spines in both young and mature hippocampal area CA1 pyramidal cells specifically in spines with enlarged synapses following LTP (Ostroff et al., 2002; Bourne, Harris et al. 2007). The role of rough endoplasmic reticulum (RER) in dendritic and spine plasticity has not been studied, but since RER translates and processes transmembrane proteins such as synaptic receptors and associated proteins, an upregulation of RER at potentiated spines might be expected. RER has only rarely been described in the vicinity of spines, largely because it hasn't been searched for systematically. Another organelle potentially involved in protein synthesis-dependent plasticity is the spine apparatus which is often found in large spines of mature dendrites and has structural as well as molecular properties similar to the Golgi apparatus. The laminae of smooth ER in the spine apparatus is interspersed with dark staining sheets of the actin-binding protein, synaptopodin. Synaptopodin knockout mice lacked the spine apparatus and had a decreased aptitude for LTP and memory tasks (Deller et al., 2003). Our work analyzed the occurrence of RER-like structures as well as the spine apparatus in the dentate gyrus of a mature rat. One half of the rat's hippocampus underwent robust LTP and the other control side received only test stimulation. Dendrites and spines in these two data sets were systematically searched (blind as to condition) through serial section transmission electron microscopy. The RER was identified as a membranous organelle with 20nm diameter dark particles scattered along its membrane. In a population of 20 dendrites from the first data set (UGSPZ) RER was recognized along the lengths of 18 dendrites; 11 dendrites had RER within one or more spine heads or necks. These observations provide strong evidence that RER extends well into dendrites and some dendritic spines, and may provide a source for local synthesis of integral membrane proteins. Coincident analysis of the same dendrites for spine apparatus revealed 15/20 dendrites to contain SA with the majority, 20/39, located in spine heads. Whether these observations are specific to LTP or control stimulation awaits future decoding.

### **13. Circadian genes are necessary for the acquisition of rapid tolerance to ethanol in *Drosophila***

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Tolerance, defined as a reduced response to an effect of a drug due to previous exposure to the drug, is an important component of addiction. However, the underlying neuronal mechanisms required for the acquisition of tolerance for many drugs of abuse are poorly understood. Our lab investigates rapid tolerance induced by ethanol in the fruit fly, *Drosophila melanogaster*. When exposed to the drug, flies become hyperexcitable before entering a sedative state and will eventually pass out. Flies will take longer to pass out if they have received a single sedative dose of the drug twenty-four hours earlier, thus becoming tolerant to the drug.

Genes modulating circadian rhythms have recently been linked to drug-induced behaviors. In both flies and mammals, mutations in circadian genes alter cocaine sensitization (Andretic et al., 1999; Abarca et al., 2002). We are investigating a role for circadian genes in tolerance to ethanol. Here we show that flies with a loss-of-function mutation for the circadian gene period do not acquire tolerance to the knockdown effects of ethanol. Interestingly, flies with mutations for timeless, cycle, and Clock-- genes that are necessary for a functional circadian clock-- show normal tolerance. These results suggest that some circadian genes are required for the acquisition of tolerance. However, as others are not necessary for tolerance, these genes are most likely acting in a role independent of modulating rhythmicity. Ongoing experiments are being conducted to further elucidate the relationship between circadian genes and drug tolerance.

### **14. The development of a semi-automated phototaxis assay to identify genes responsible for ethanol tolerance**

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According to NIDA statistics in 2007, the consequences of drug abuse costs Americans over half a trillion dollars each year. Our lab studies the effect of ethanol on the *Drosophila* model system. We have developed an assay to measure ethanol tolerance. We define tolerance as ethanol-induced resistance to the effects of ethanol. The assay is based on phototaxis, the movement towards a light source. The flies are sedated and an automated camera system takes pictures at defined intervals. The images are then processed by programs as described in Ramazani et al. and then the number of recovered flies are counted. We have identified a deficiency mutant, df-7589, that does not acquire tolerance. The deficiency deletes a portion of the 3L chromosome, encompassing nine genes. After measuring gene expression of these nine genes, we identified candidate genes that may be responsible for the lack of tolerance phenotype. Using gene knockdown and P-element induced mutations specific to these genes, we are currently studying the effects of these candidate genes on ethanol tolerance.

### **15. Dynamic reproductive decision-making in túngara frogs**

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In anuran amphibians, acoustic communication is a central component of reproductive behavior. A wealth of behavioral studies of mate choice in frogs and toads has explored the acoustic signal parameters essential for species recognition and mate preferences. Typically, laboratory playback experiments simplify the social conditions under which animals make decisions, such as with whom to mate. One example of this simplification is that mate choice studies use static playbacks – usually two-choice tests where each speaker broadcasts an unchanging train of a single stimulus. However, in nature, a receiver processing signals in real-time is faced with temporally varying signals. Here we investigate the mate choices of female túngara frogs when they are subject to dynamic playbacks of male advertisement calls. The results demonstrate that females are sensitive to the position of preferred call types on a moment-to-moment basis, and reactive responses are modulated by sound pressure level (SPL) and the intrinsic attractiveness of the individual male calls. Finally, based on repeated testing of individual subjects, females can be classified as either reactive or non-reactive in this temporal updating task.

## **16. Noradrenergic modulation of the hypothalamic-pituitary-adrenal axis in the bed nucleus of the stria terminalis**

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The lateral bed nucleus of the stria terminalis (BSTL) is a component of the extended amygdala that modulates stress-activation of the hypothalamic-pituitary-adrenal (HPA) axis. We have shown previously that stress-induced release of norepinephrine (NE) activates  $\alpha$ 1-adrenergic receptors in BSTL and other hypothalamic and extrahypothalamic limbic regions to facilitate the HPA response to acute stress. We have also shown that this modulatory function is enhanced following chronic intermittent cold stress, contributing to sensitization of the HPA response to novel acute stress. After mild cold stress, NE release was elevated in BSTL of stress-vulnerable WKY rats but not Sprague-Dawley rats. We have since shown that adrenergic receptor sensitivity is enhanced after cold stress in the paraventricular nucleus of Sprague-Dawley rats, accounting for some of the HPA sensitization. Thus, in this study, we have begun to investigate pre- and post-synaptic mechanisms in BSTL whereby changes in noradrenergic modulatory function contribute to changes in the acute HPA stress response following chronic intermittent cold stress. In this initial study, we first characterized the ACTH response elicited by direct local application of the  $\alpha$ 1-adrenergic receptor agonist phenylephrine into BSTL, as a way to assess changes in post-synaptic receptor sensitivity following cold stress, as done previously in PVN. Animals were implanted stereotaxically with bilateral guide cannulae aimed at the BSTL, and with indwelling jugular catheters for repeated blood sampling in awake, behaving animals. On the day of the experiment, saline vehicle or phenylephrine (50 nmole/0.2 ml/side), were microinjected bilaterally into BSTL. Phenylephrine induced a 8-fold increase in plasma ACTH, peaking 15 minutes post-injection (from 88 pg/ml to 716 pg/ml), returning toward baseline over the next 60 min. No change in plasma ACTH was seen in vehicle-injected controls. Full dose-response studies to address potential changes in  $\alpha$ 1-receptor sensitivity in BSTL of rats subjected to chronic intermittent cold stress are ongoing, as are in situ hybridization and radioligand binding experiments to assess corresponding changes in  $\alpha$ 1-receptor expression in BSTL.

## **17. Vasopressin associated with play fighting in golden hamsters**

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In hamsters, play fighting precedes adult aggression and has been interpreted as a juvenile form of agonistic behaviors. This behavior is initiated before puberty, peaks in early puberty, and then gradually matures into adult aggression. A recent study in my lab indicates that play fighting and adult aggression are controlled by a common neural circuitry in golden hamsters. The goal of the present study was to further test if the vasopressin system, a neural system facilitating adult aggression in hamsters, is associated with play fighting as well. Juvenile male golden hamsters were tested in early puberty. In the first experiment, experimental animals were sacrificed after attacking a smaller intruder. Control animals were sacrificed after exposure to a woodblock carrying the odor of an intruder. The woodblock triggered behaviors related to agonistic behavior (e.g. flank marking behavior) without attacks. Double-labeling c-Fos and vasopressin were performed in both groups to identify the sub-populations of the vasopressin cells associated with play fighting. In the second experiment, two groups of juvenile hamsters with the age difference of one week were sacrificed and the vasopressin fiber density was quantified. Interestingly, vasopressin cells in the nucleus circularis and the medial division of the supraoptic nucleus, which have been associated with offensive aggression, also showed increased c-Fos labeling after play fighting. In addition, the vasopressin fiber density in the medial amygdala doubled from P-28 to P-35, which is positively correlated with the increased intensity of play-fighting attacks in early puberty. Together, our results indicate that the vasopressin system is associated with play fighting in golden hamsters. Supported by NSF IOB 0516272

## **18. Serotonin 1A receptors in an animal model of impulsive aggression**

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In hamsters, individual differences in offensive aggression are correlated with differences in impulsivity, as well as a difference in serotonin (5-HT) innervation. Aggressive animals are impulsive and have decreased 5-HT innervation in various parts of the brain. As 5-HT<sub>1A</sub> receptors participate in the inhibitory effects of serotonin on aggression and impulsivity, we hypothesized that individual differences in behavior are also associated with differences in the expression of this receptor subtype. In particular, we predicted decreased expression of 5-HT<sub>1A</sub> receptors in the High-Aggression group. The density of 5-HT<sub>1A</sub> receptor-immunoreactivity was compared between Low- and High-Aggression animals in various aggression and impulsivity-related brain areas. Interestingly, our results showed a 30-50% greater density of 5-HT<sub>1A</sub> receptor-immunoreactivity in aggressive animals within the anterior hypothalamus, lateral septum and prelimbic cortex. However, at least in the anterior hypothalamus, this increase was associated with a 30% decrease in the number of immunoreactive perikarya. While there can be several explanations to this outcome, we are currently addressing the possibility that these differences in receptor immunoreactivity reflect differential release, activation and/or internalization of serotonin receptors. Although further studies are necessary to identify the dynamics of these receptors in highly aggressive individuals, our data point to serotonin function as a common underlying mechanism for this convergence of aggressive and impulsive characteristics.

## **19. Semantic processing in Hindi-English bilinguals using functional neuroimaging**

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Neuroimaging research on bilinguals has focused on trying to elucidate whether similar or spatially segregated neural substrates subservise two languages. While some studies provide evidence for anatomically separate mental lexicons (Ding et al., 2003; Pillai et al., 2003), others have shown common regions of activation for both languages (Chee et al., 2000; Illes et al., 1999). There are a number of potential reasons why some studies may have found similar regions of activation, and why some studies failed to find an overlap in activation. These include the proficiency in second language and orthographic similarities between first language and second language. To date, there is no conclusive evidence on cortical representation of semantic processing in bilinguals. The aim of this study was to investigate the patterns of cortical activation in early proficient bilinguals during processing of Hindi and English. 10 Hindi-English proficient bilinguals in the age range of 20-30 years residing in Austin took part in the study. All participants were right handed. The experiment consisted of two tasks semantic judgment in Hindi and English and size judgment. A visual fixation condition for 0.5 seconds served as the baseline before each stimulus was presented for 3 seconds. A block design paradigm was utilized and each block comprised of eight stimulus triplets totaling 28 sec in duration. The experiment consisted of 12 blocks of semantic judgment (6 blocks in English and 6 blocks in Hindi) and 12 blocks of size judgment. Data was acquired on a 3T GE scanner. A gradient-echo EPI with the following parameters were used TE=40ms, TR = 2000ms, FOV = 24x24cm, a 256x256 pixel matrix. 31 axial slices with 3 mm thickness and 0.3 mm gap in A-P direction were acquired. Functional MRI data for the three subjects were preprocessed and analyzed in FSL ([www.fmrib.ox.ac.uk/fsl/](http://www.fmrib.ox.ac.uk/fsl/)). Contrasts examined differences in activation between semantic and size decisions in Hindi and English. Images were thresholded using clusters determined by  $Z > 2.3$  and a (corrected) cluster significance threshold of  $p = 0.05$ . For reaction time, there was a main effect for task  $F(2, 188) = 24.69, p = .$  Semantic judgment was significantly slower than size judgment and Semantic Judgment in Hindi was significantly slower than semantic judgment in English. There was greater activation for semantic judgment relative to nonsemantic judgment in the left frontal and temporal regions (figure 1). Semantic processing in English (relative to size decisions) activated the left frontal region (figure 2). However, semantic processing in Hindi yielded greater activation in the left frontal and temporal regions compared to English (figure 3). Greater activation during the Hindi task could be because the less frequently used native language required increased processing demands or the process of extracting the meaning from script could be harder in Hindi as opposed to English. The results of this study suggest that language proficiency, orthographic structure and language use are important in determining bilingual neural organization.

## **20. Mechanisms underlying ethanol enhancement of GABAergic transmission on VTA-Dopamine neurons**

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Activation of the dopaminergic neurons of the VTA by ethanol has been implicated in its rewarding and reinforcing effects. Long-lasting potentiation of GABAergic synapses has been observed in mice after a single *in vivo* ethanol exposure (Melis et al 2002). This observation suggests that ethanol may directly modulate GABAergic transmission in the VTA. Therefore, here we examined changes in GABAergic transmission in rats after acute ethanol exposure *in vitro*. We used conventional whole-cell recording techniques and pharmacologically-isolated spontaneous GABAergic IPSCs. We observed little difference within the event population between mIPSCs (in TTX) and sIPSCs in both amplitude and frequency in the presence of ethanol (50 mM); therefore hereafter measured sIPSCs. Acute exposure to ethanol (25, 50 mM) significantly increased sIPSC frequency ( $31 \pm 5\%$  (n=25) and  $47 \pm 8\%$  (n=12), respectively) and amplitude ( $5.4 \pm 1.5\%$  and  $8.5 \pm 2.3\%$ , respectively). These results show an apparent pre- and postsynaptic site of action for ethanol in the VTA. sIPSC frequency was suppressed by the GABA<sub>B</sub> agonist, baclofen and enhanced by the antagonist, SCH50911; however, neither appeared to modulate or occlude the effects of ethanol suggesting that GABA<sub>B</sub> receptors are not involved in ethanol modulation of GABA release onto VTA neurons. The presynaptic action of ethanol was further demonstrated as application of 50 mM ethanol resulted in a shift towards paired-pulse depression as manifested in a decrease in the paired-pulse ratio. Taken together, these findings indicate an ethanol-induced enhancement of GABA release onto VTA-DA neurons, which is independent of voltage-gated Na channel, ionotropic glutamate receptor, and GABA<sub>B</sub> auto-receptor activation. Although this effect seems to be independent of neuron excitability, the involvement of intracellular Ca<sup>2+</sup> stores in mediating this ethanol effect cannot be ruled out. Intracellular Ca<sup>2+</sup> stores can be activated via several mechanisms such as GPCR activation and recent evidence has linked the GPCR, 5-HT<sub>2C</sub>, to VTA-GABA transmission (Bankson and Yamamoto, 2004), and thus may serve as a potential site of action for ethanol in mediating the effects presented here. (Support: Jones Fellowship to JWT; R01AA14874 to RAG and R01A15677 to RAM).

## **21. Conversion of synaptic depression to potentiation after intermittent ethanol exposure in the nucleus accumbens**

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The mesolimbic dopamine system is the primary location for the rewarding actions of drugs of abuse. The nucleus accumbens (NAc) is an important site of convergence for several different inputs from limbic structures. GABAergic medium spiny neurons (MSNs) in the NAc receive glutamatergic input from the prefrontal cortex, amygdala, thalamus, and hippocampus. Alterations in glutamatergic synaptic transmission are believed to underlie the neural adaptations that contribute to the development of alcohol dependence. Our goal is to determine the effects of multiple bouts of ethanol exposure and withdrawal on glutamate-dependent synaptic plasticity in the NAc. Therefore, we investigated N-methyl-D-aspartate (NMDA) dependent long-term synaptic plasticity in the NAc of C57/BL6 mice that underwent three intermittent 16-hour ethanol exposures *in vivo*. Our *in vitro* whole-cell patch clamp recordings indicate that conditioning stimuli induce synaptic depression ( $59.7 \pm 11.7\%$  of baseline) in ethanol-naive mouse MSNs that is blocked by the NMDA receptor antagonist, DL-APV ( $94.8 \pm 15.9\%$ ). Acute exposure of NAc slices to 40 mM ethanol throughout the recording completely abolishes the synaptic depression ( $103.6 \pm 12.4\%$ ). However, the same conditioning stimuli induce a remarkable conversion from synaptic depression to synaptic potentiation ( $155.1 \pm 46.6\%$ ) in MSNs following intermittent ethanol exposure. We conclude that this form of intermittent ethanol exposure causes a significant change in glutamatergic transmission within the NAc. The conversion from synaptic depression to synaptic potentiation of the major projection neurons in the NAc could be a crucial component to the expression of neural adaptations that inevitably occur during repeated ethanol exposure and withdrawal.

## **22. Burst-dependent plasticity of NMDA receptor-mediated transmission in midbrain dopamine neurons**

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Midbrain dopamine (DA) neurons play critical roles in reward processing and addictive behaviors. In awake animals, DA neuron firing switches from low frequency, single-spike activity to phasic bursts (2-10 spikes at 10-50 Hz) in response to unexpected rewards. These bursts are thought to be triggered primarily by NMDA receptor (NMDAR) activation. Intriguingly, the phasic burst response transfers from primary rewards to reward-predicting cues with repeated cue-reward pairing. Bursting produces large, phasic transients of DA in target areas of the striatum and prefrontal cortex, where it mediates motor output and reinforcement learning. However, the locus of neural plasticity underlying the conditioning of DA neuron responses to reward-predicting cues remains unclear. It is possible that Hebbian synaptic plasticity at DA neurons themselves may mediate this form of reward learning. Here, we have used patch-clamp electrophysiology in acute brain slices from rats to investigate synaptic plasticity of NMDAR-mediated transmission in midbrain DA neurons as a putative cellular substrate for reward-dependent reinforcement learning. We find that facilitation of calcium release from intracellular stores in response to bursts of action potentials via activation of postsynaptic phosphoinositide-coupled receptors in DA neurons drives a novel form of long term plasticity of NMDAR-mediated transmission.

## **23. Mechanisms of receptor and channel-specific modulation of neuronal ion channels by phosphoinositides**

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A major focus of our work investigates the molecular mechanisms linking  $G_{q/11}$ -coupled receptors to several different ion channels responsible for the M-type  $K^+$  and N-type  $Ca^{2+}$  currents of neurons. In sympathetic ganglia, agonists of  $M_1$  muscarinic and  $AT_1$  angiotensin II receptors depress both currents by depletion of  $PIP_2$ ; however, stimulation of bradykinin  $B_2$  or purinergic P2Y receptors only modulates M channels, but not  $Ca^{2+}$  channels. The striking receptor specificity correlates with the selective induction of intracellular  $Ca^{2+}$  signals by  $B_2$  and P2Y, but not by  $M_1$  or  $AT_1$ -receptor stimulation. Based on electrophysiology,  $Ca^{2+}$  imaging,  $PIP_2$  hydrolysis reporter experiments and pharmacology, we suggest that  $B_2$  and P2Y receptors stimulate  $PIP_2$  synthesis concurrently with its hydrolysis, compensating for reduction in  $PIP_2$  abundance that would otherwise occur. Thus, bradykinin and purinergic agonists do not modulate the  $PIP_2$ -sensitive  $Ca^{2+}$  channels, and depress M current via  $IP_3$ -mediated  $Ca^{2+}$  signals, in concert with calmodulin (CaM). In contrast, muscarinic agonists and angiotensin II do not concurrently stimulate  $PIP_2$  synthesis, membrane  $[PIP_2]$  is strongly lowered, and the  $PIP_2$ -sensitive channels are modulated. Our data suggest that receptor-specific  $Ca^{2+}$  mobilization is key, but our modeling suggests other receptor-specific intracellular pathways that stimulate PI kinases are involved. We seek to discover the molecular players in these pathways, and to understand the mechanisms conferring receptor specificity in their action. A related focus of the lab is to understand the mechanism of differential sensitivity of the Kv7.2-7.4 M-type channels to  $PIP_2$ . Using chimeras and point mutants, we are elucidating the site(s) of action of  $PIP_2$  on channels studied at the single-channel level. Our initial focus has been on Kv7.3 and Kv7.4, which previous work has identified as having high, or low, apparent affinities for  $PIP_2$ , respectively. Our work suggests a domain between the two CaM binding sites within the carboxy termini to be a primary  $PIP_2$  binding site. Here, we show data from several sets of chimeras between Kv7.3 and Kv7.4 that implicate this domain, as well as results from point mutants in this domain at residues that are conserved between Kv7.2, 7.3 and 7.4. We also find a marked similarity of this domain to a similar putative  $PIP_2$  binding domain on inwardly-rectifying (Kir)  $K^+$  channels, and use the published crystal structure of Kir2.1 channels to perform homology modeling and energy minimization of  $PIP_2$  docking, to predict the effect of mutations in this part of the channel on phosphoinositide binding.

## **24. Repetition priming in a response learning task using novel objects**

M. Saggarr, M. Sathishkumar, R. Miikkulainen and D. M. Schnyer

Repeated classification of visual stimuli can result in a shift of attention from higher-level information extraction processes towards more automatic retrieval of associations between a stimulus and previous classification decisions. Research utilizing fMRI (Dobbins, et al, 2004) and MEG (Ghuman, et al, 2006) has revealed that prefrontal (PFC) and ventral temporal (VT) neural activity reductions associated with repetition priming can be linked to decision learning (DL). These previous studies have examined the phenomenon of DL with common, well-known objects and it remains unclear the extent to which the process is dependent on preexisting knowledge structures. Moreover, some of the activity reductions may be specific to stimulus type, particularly with respect to the changes observed in VT cortex. In the current work, participants made judgments about the occupied area while viewing visually presented novel objects (Slotnick & Schacter, 2004). In a study phase participants were asked to indicate whether the stimuli is fat (occupying more area) while viewing novel objects repeated 1 to 2 times. In a test phase, new objects and objects repeated from the study phase for a third time were presented. During this phase, participants were asked either to continue with the same decision or to switch their decisions to indicate whether the stimulus is slim (occupying less area). Functional EPI images were collected covering the entire head during both study and test phases.

Both behavioral and functional imaging data revealed interesting results, namely reduced response times during the study phase only and not in the test phase accompanied by neural activity reductions in Lateral Occipital and Temporal Fusiform cortex again only in study phase. Additionally, there was no activity reductions associated with repetition in the PFC in either the study or test phases. These results indicate that although there is clear priming, it is relatively short lived and does not benefit from multiple repetitions.

Additionally, the lack of evidence for DL indicates that there may need to be well-learned object representations in order to get DL. Further, a computational model has been proposed to understand the underlying mechanisms and streamline future experiments.

## **25. Activity-dependent expression of kv1 channels in the hippocampus and the visual cortex**

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The properties of intrinsic neuronal excitability, the duration and frequency of action potentials and the efficiency of neurotransmitter release are functionally linked to the expression of a heterogeneous population of voltage-gated potassium channels. Recently, our knowledge as to the role of potassium channels in the brain has expanded to reveal that voltage-gated potassium channels are dynamically regulated by the activity state of the neuron. Here, we show that the expression of the voltage-gated potassium channel Kv1.1 is regulated by activity both in the hippocampus and in the visual cortex. In the hippocampus, NMDA receptors activate the mTOR pathway to suppress Kv1.1 local protein synthesis in dendrites. We hypothesize that NMDA receptor mediated suppression of Kv1 in the dendrites would lower the threshold required to fire an action potential. We are beginning to test this hypothesis by examining visual experience-dependent expression of Kv1.1 using the light reared/dark exposed mouse model. We have found that in the visual cortex light deprivation suppresses the expression of Kv1.1 in synaptoneuroosomes which is rapidly reversed with exposure to light. Furthermore, endogenous Kv1.1 mRNA isolated from synaptoneuroosomes is upregulated by sensory deprivation and remains elevated when exposed to light.

## **26. Regionally-specific enhancement by ethanol on cocaine- and amphetamine-regulated transcript and peptide expression in mesolimbic structures**

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Cocaine and amphetamine-regulated transcript (CART) has been implicated in drug reward and reinforcement mechanisms, particularly in the mesolimbic dopamine (DA) system. CART mRNA and peptide are highly expressed in the Nucleus accumbens (NAc) and CART immunoreactivity (CART-IR) is found in terminals in the ventral tegmental area (VTA). In the NAc, CART is found in medium spiny GABAergic neurons with projections to many brain regions, including the VTA. Evidence suggests that ethanol owes its reward, reinforcing or abuse potential, in part, to activation of the mesolimbic DA system. Presently, the significance of CART in ethanol-induced DA neurotransmission is unknown. This study measures CART peptide in the NAc and the VTA using PCR and immunohistochemistry techniques. Male rats received a single i.p. dose of saline, 1, or 3.5 g/kg ethanol. One hour later the animals were sacrificed by transcardial perfusion with paraformaldehyde for immunohistochemistry or rapid tissue extraction for PCR studies. CART mRNA was found to dose dependently increase in the NAc in response to systemic ethanol. Baseline CART immunofluorescence intensity was determined for the shell and core regions of the NAc of the saline-treated animals. In section-matched slices, CART immunofluorescence was markedly and significantly increased in the shell and core following 1 or 3.5 g/kg ethanol compared to controls. In the VTA, CART-IR fiber length and optical density were increased in ethanol treated animals at the 1 g/kg dose. This effect was not observed at the 3.5 g/kg dose. These studies are the first to demonstrate a link between ethanol and CART. The ethanol-induced increases in NAc CART mRNA and peptide, as well as, the increases in CART-IR in terminal VTA fibers suggest that CART may function as a retrograde signal from the NAc to the VTA. The nature of this signal is likely inhibitory, given the observed co-expression of CART and GABA.

# NOTES

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