

The Institute for Neuroscience The University of Texas at Austin 14th Annual Neuroscience Symposium

Mission Statement

Welcome to the 14th Annual Institute for Neuroscience Symposium!

For the past fourteen years, graduate students in the Institute for Neuroscience have formed a committee to plan and execute this symposium. It is the goal of this committee to bring the scientific community of our university and surrounding institutions together to share their research in the exciting field of neuroscience. We value the opportunity for students from within the Institute to share their research with individuals from the scientific community through lectures and poster presentations. Our faculty lectures are intended to acquaint others with ongoing research at the Institute for Neuroscience. Each year we also invite a distinguished keynote speaker to share their work with the university. Our student body has consistently chosen prominent scientists with diverse interests from a number of different fields within neuroscience. Keynote speakers from previous years include Drs. Indira Raman, Russell Fernald, Stuart Lipton, Cornelia Bargmann, Bruce McEwen, Daniel Margoliash and William Greenough. We continue the tradition this year by welcoming renowned scientist Dr. Michael Dyer. 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 participating!

Leslie A. Ramsey & Keith W. Whitaker

Symposium Committee Co-chairs

Acknowledgements

Symposium Committee Members:

Leslie A. Ramsey, Co-chair
Keith W. Whitaker, Co-chair
Bailey Kermath
Sachin Vaidya
Brenda Houck
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Neuroscience Graduate Students' Association



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14th Annual Neuroscience Symposium

January 16, 2010

- 8:30-9:00 **Breakfast / Registration**
(Poster session set-up)
- 9:00-9:15 **Opening Remarks**
Dr. Dan Johnston, Director of the Institute for Neuroscience
Leslie A. Ramsey, Co-chair of Symposium Planning Committee
- 9:15-9:45: **Keith W. Whitaker**
Variability in neurobiological mechanisms of behavioral plasticity
- 9:45-10:15: **Brenda Houck**
Forebrain Contributions to Delay Eyelid Conditioning
- 10:15-11:00: **Poster Session A**
- 11:00-11:30: **Brian Bernier**
In vivo drug exposure enhances inositol triphosphate-mediated calcium signaling in ventral tegmental area dopamine neurons
- 11:30-12:00: **Dr. Ila Fiete**
Error-correcting neural codes for 'exact' estimation in the brain
- 12:00-1:00: **Lunch**
- 1:00-1:30: **Eimeira Padilla**
Limbic-Cortical Network Differences between Responders and Non-responders to Fluoxetine Antidepressant Treatment in Rats
- 1:30-2:15: **Poster Session B**
- 2:15-2:45: **Sari Andoni**
Spectrotemporal Feature Selectivity for Conspecific Vocalizations in the Auditory Midbrain
- 2:45 -3:15: **Dr. Jon Pierce-Shimomura**
Neurogenetic analysis of locomotory switching in C. elegans
- 3:15-3:35: **Break**
- 3:35-4:45: **Dr. Michael Dyer**
Retinoblastoma: Bridging Developmental Neurobiology and Cancer Genetics
- 4:45-5:00: **Closing Remarks**
Keith W. Whitaker, Co-Chair of Symposium Planning Committee

Keynote Address

Michael Dyer, PhD

Developmental Neurobiology
St. Jude Children's Research Hospital

Howard Hughes Medical Institute Early Career
Scientist

Pew Scholar

Research to Prevent Blindness Career
Development Award

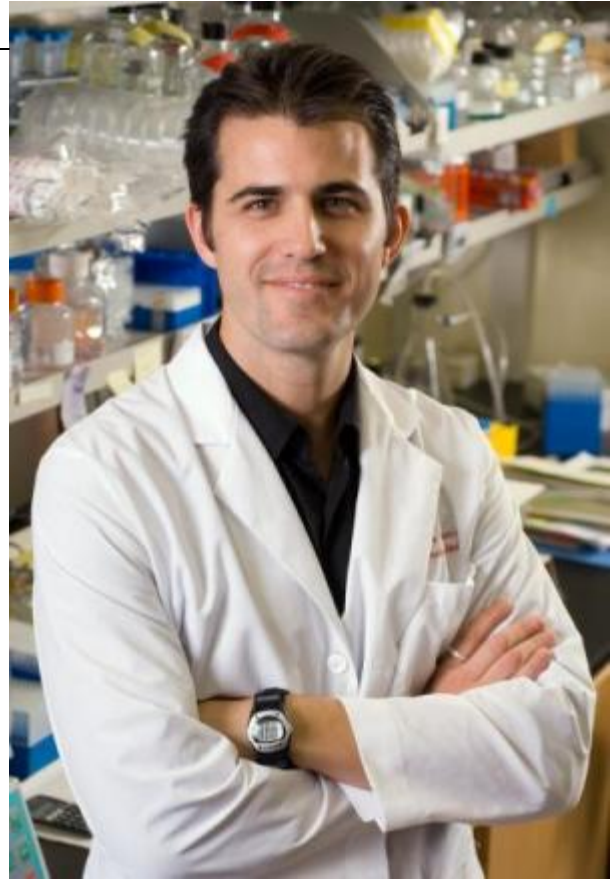
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Laboratory



My laboratory studies the regulation of growth during neural development and disease. Cell division must be carefully regulated during brain development to ensure that the resulting tissue is the appropriate size and contains the correct proportion of each specialized cell type. If the precise balance of cell types were altered in the brain, then the different neurons and glia would not be able to work together to process information. Many of the genes that control growth during development are also involved in regulating cell division following brain injury or in certain degenerative processes. In addition, these genes are often mutated in cancer cells. Therefore, by studying the regulation of growth during development, we can learn about the cause and progression of a variety of diseases in the central nervous system. This may ultimately lead to the design of better treatments for neural injury, degeneration and cancer.

The retina is a specialized region of the central nervous system that receives and processes visual information. Like the rest of the central nervous system, injury, degeneration and cancer involve changes in the growth properties of retinal cells. We use a wide range of experimental approaches to study how cell division is controlled during retinal development and disease. Methods currently being used in the lab include genetically engineered mice, replication incompetent retroviral vectors suitable for in vivo studies, explant culture systems, microarray hybridization, and to extend our observations to human retinopathies we use normal and diseased human tissue and monkey samples. Experimental approaches that are under development include retinal physiology (ERG), electron microscopy, cell sorting, in vivo mouse models of retinoblastoma, and computational modeling of proliferation during development.

Invited Faculty Speakers

Ila Fiete, PhD

Ila Fiete is an assistant professor of neurobiology at UT Austin, a fellow at the Center for Learning and Memory, and an Alfred P. Sloan foundation fellow. She received her Ph.D. in physics/computational neuroscience from Harvard University in 2004, followed by postdoctoral work at the Kavli Institute for Theoretical Physics at UC Santa Barbara and then at Caltech as a Broad Fellow. Her group works on questions of coding and dynamics in neural systems, with the help of computer modeling and theoretical analysis.

Error-correcting neural codes for 'exact' estimation in the brain

Representation and transformation of variables are inherently noisy when performed by neurons. One way to extract a less noisy estimate of the encoded variable is by averaging over neural populations, through population coding. Population coding is widely used by human observers to estimate the encoded variable, and has been interpreted as a model of how downstream brain areas may readout the variable. But population coding leads to only modest estimation improvements as the number of neurons grows.

Is there a better way?

I will show, through the example of the neural code for animal location in space, that in agreement with the results of the field of error correcting codes, it is possible for a finite number of noisy neurons to encode a variable with essentially error-free decoding. This insight helps to explain why position is encoded using the bizzare grid-cell code. It also provides a functionally driven model for interactions and connectivity between the entorhinal grid cells and hippocampal place cells. I will discuss predictions that can be tested within the hippocampal formation, and more generally consider the implications of the existence of exact error correcting codes for the representation and transformation of analog variables in the brain.

Jon Pierce-Shimomura, PhD

Jon Pierce-Shimomura obtained his Ph.D. in Neuroscience at the University of Oregon, Eugene in 2000 studying mechanisms for chemotaxis and taste discrimination in the nematode *C. elegans* with Dr. Shawn Lockery. Dr. Pierce-Shimomura completed post doctoral training at the University of California, San Francisco with Dr. Steve McIntire where he investigated the physiological basis for intoxication in *C. elegans*. He joined the faculty at The University of Texas at Austin in 2008.

Neurogenetic analysis of locomotory switching in *C. elegans*

Our lab seeks to identify genetic mechanisms that govern behaviors. We approach this complex subject by studying how conserved genes contribute to behaviors in the simple but powerful model nematode *C. elegans*. One issue that we study is how the worm switches between distinct forms of rhythmic locomotion: crawling and swimming. Understanding the genes and neural mechanisms that enable this switch has implications for explaining how all nervous systems switch between rhythmic activities such as normal and gasping patterns of respiration, walking and running gaits, and even the unique neural rhythms that underlie forms of higher order cognition. To study conserved genetic mechanisms for switching locomotory rhythms, we combine laser and genetic ablation of identified neurons, pharmacological and optogenetic probing of behaviors of intact animals, and custom image-analysis tools to quantify the behaviors. Our work has recently uncovered a surprising degree of conservation in locomotory switching with relevance to human dystonias such as Parkinson disease.

Invited Graduate Student Speakers

Sari Andoni

Sari Andoni received his Bachelors degree in Computer Sciences and Mathematics from Brigham Young University. He is currently a PhD candidate at the Institute for Neuroscience in The University of Texas at Austin. After joining the laboratory of Dr. George Pollak in 2004, he was able to combine theory with *in vivo* electrophysiological experiments in order to study the auditory system of bats. His dissertation work focuses on how the brain processes natural sound, such as conspecific vocalizations and human speech. Specifically, his research investigates the neural mechanisms involved in creating response selectivity for complex spectrotemporal features of natural acoustic signals.

Spectrotemporal Feature Selectivity for Conspecific Vocalizations in the Auditory Midbrain

Many studies have shown that response selectivity for conspecific communication signals can be observed as early as the inferior colliculus (IC) in the auditory midbrain. Receiving a convergence of excitatory and inhibitory inputs from the brainstem, it is not surprising that emergent response properties like feature selectivity can arise in the IC. While it has been previously shown that blocking inhibitory inputs greatly reduced response selectivity, it is still unclear which spectral and temporal features of conspecific vocalizations are encoded by an IC neuron and how excitation and inhibition interact nonlinearly with the intrinsic membrane properties of IC cells to produce a feature selective output.

By recording the extracellular response to a large repertoire of bat communication signals we were able to extract the relevant stimulus features (dimensions) that excite or inhibit the response of each neuron. We could then assess the nonlinear relationship between each feature and the spiking output of the neuron. We show that the relevant stimulus features and their respective nonlinearities together define the overall receptive field of the neuron and provide better response predictions than using the spike-triggered average alone. Furthermore, comparing the spectral and temporal modulations found in bat vocalizations with modulation rates IC neurons are tuned for shows that the tuning of the IC avoids spectrotemporal modulations that are redundant across conspecific calls and instead overlaps with modulations that differ most across different vocalizations.

Brian Bernier

Brian Bernier graduated with a bachelor's degree in Cognitive Sciences from the University of Virginia in 2000. He then worked with Dr. Heidi Scrable at the University of Virginia studying neurogenetics before entering graduate school at the University of Texas in 2004. Brian is currently a graduate student in the INS in Dr. Hitoshi Morikawa's lab studying the mechanisms of plasticity and drug addiction in midbrain dopamine neurons.

***In vivo* drug exposure enhances inositol triphosphate-mediated calcium signaling in ventral tegmental area dopamine neurons**

Dopamine neurons of the ventral tegmental area (VTA) are critically involved in reward-based learning and the development of addiction to drugs of abuse. In behaving animals, dopamine neurons "learn" to respond to reward-predicting cues with a burst of action potentials after repeated cue-reward pairing. NMDA-type glutamate receptors are known to play a predominant role in the generation of these bursts. We have recently reported long-term potentiation (LTP) of NMDA receptor-mediated transmission onto dopamine neurons that may contribute to the acquisition of the conditioned burst response. This form of plasticity is induced in a manner dependent on inositol triphosphate (IP₃)-mediated facilitation of burst-evoked Ca²⁺ signals. In this study, we performed patch-clamp recordings and flash photolysis of caged IP₃ in acutely prepared mouse and rat midbrain slices to examine the effects of repeated *in vivo* ethanol or amphetamine exposure on IP₃-mediated Ca²⁺ signaling in VTA dopamine neurons. Flash photolysis of caged IP₃ activates Ca²⁺-sensitive K⁺ currents (I_{IP3}) via release of Ca²⁺ from intracellular stores in dopamine neurons. Repeated ethanol or amphetamine exposure significantly reduced the flash intensity required to elicit half-maximal I_{IP3} without altering the maximal I_{IP3} amplitude, suggesting increased IP₃ receptor sensitivity. Additionally, IP₃-induced facilitation of action potential-evoked Ca²⁺ signals was enhanced in drug-treated mice. Stimulation of the cyclic AMP pathway also increased IP₃ receptor sensitivity, whereas blockade of PKA activity reverses the effect of amphetamine treatment, suggesting that protein kinase A-mediated phosphorylation of IP₃ receptors may underlie the effect of *in vivo* drug treatment. Finally, LTP of NMDAR-mediated transmission is enhanced following repeated amphetamine treatment. These results demonstrate that repeated ethanol or amphetamine exposure enhances the Ca²⁺ signal critical for the induction of NMDA receptor plasticity in VTA dopamine neurons. This may promote the learning of cues associated with drug consumption, thereby contributing to the development of drug-taking behavior and addiction.

Invited Graduate Student Speakers

Brenda D. Houck

Brenda graduated from the University of Texas at Austin with two Bachelors of Science degrees in the fall of 1999. She then took a brief hiatus from academia and ran her own business in the Austin area for six years. However, by 2001 she was certain science was her true passion and returned to the University of Texas to pursue her doctorate degree in the fall of 2004. Brenda is currently a fifth year graduate student in the INS program in Dr. Michael Mauk's lab. She is working to uncover the rules and mechanisms underlying plasticity in the deep nucleus of the cerebellum.

Forebrain Contributions to Delay Eyelid Conditioning

Decades of research have implicated the cerebellum as necessary and sufficient for delay eyelid conditioning. However, current cerebellar theories cannot explain the mechanisms responsible for some behavioral properties seen with conditioned response (CR) expression in delay eyelid conditioning. One such property is savings in which relearning after extinction occurs more quickly than original learning. Savings is expressed when conditioning with the same conditioned stimulus (CS) and even when a separate stimulus is used, referred to as cross-modal savings. For instance an organism trained to a CS (tone), extinguished and then trained to a separate CS (light) will show acquisition of CRs at a much faster rate than original acquisition to the CS (tone). In this situation learning to a new CS occurs faster after an organism has acquired and extinguished responses to a previous CS. We present evidence that savings between different CSs reflects contributions from outside the cerebellum, specifically the pre-frontal cortex (Pfc). To limit extra-cerebellar input that may occur upon presentation of a peripheral CS, we replaced the use of two different tones as separate CSs with stimulation to electrodes in the middle cerebellar peduncle, the source of mossy fibers which carry CS input to the cerebellum. Results of these experiments suggest that savings between different CSs does not reflect processing in the cerebellum but rather from a forebrain input, while savings within a CS is supported by the cerebellum alone. We hypothesize that delay eyelid conditioning involves cerebellar learning in response to inputs driven by the tone CS and inputs from the forebrain. Data from experiments involving electrolytic lesions to the Pfc suggest that these forebrain inputs are localized to the Pfc. Although removal of forebrain inputs does not abolish CRs, it does eliminate specific behavioral properties that includes cross-modal savings.

Eimeira Padilla

Eimeira Padilla was born in Portsmouth, Virginia and grew up in Bayamon, Puerto Rico. She graduated Valedictorian with highest honors from the University of Puerto Rico School of Pharmacy at San Juan in 2004. In that year she became a licensed pharmacist in Puerto Rico and worked as the director of pharmacy at the Millennium Institute for Advanced Nursing Care. In 2005, she joined the Ph.D. program in Neuroscience of the University of Texas at Austin as a member of the Gonzalez-Lima laboratory. She was awarded a Pre-emptive Recruitment Fellowship from the University of Texas at Austin graduate school during 2005 -2006 and has been a fellow of the Texas Consortium for Behavioral Neuroscience since 2006. In 2007, she was certified by the Texas State Board of Pharmacy as a registered pharmacist. During her graduate studies at the University of Texas at Austin, Eimeira has gained experience as a graduate research assistant investigating the mechanisms underlying susceptibility to depression.

Limbic-Cortical Network Differences between Responders and Non-responders to Fluoxetine Antidepressant Treatment in Rats

Neural network effects of antidepressant treatment with the selective serotonin reuptake inhibitor (SSRI) fluoxetine were investigated using Holtzman rats. Animals underwent the forced swim test (FST) and immobility time was scored. On the next day, animals began receiving two weeks of fluoxetine (5 mg/kg) or vehicle and were retested in the FST at the end of treatment. Antidepressant behavioral effects of fluoxetine were analyzed using a ratio of immobility during pre- and post-treatment FST sessions. Brains were analyzed for regional metabolic activity and network interactions using quantitative cytochrome oxidase histochemistry and structural equation modeling. Fluoxetine exerted a protective effect against FST-induced immobility behavior in Holtzman rats. The mean regional metabolism of the nucleus accumbens shell differentiated fluoxetine-treated from vehicle-treated subjects, but not treatment responders from non-responders. The metabolic activities of infralimbic cortex and medial septum were predictive of antidepressant behavioral response, but these regions contributed opposite influences as evidenced by their opposite relationship to FST-induced immobility. A cortico-cortical correlogram revealed complex interactions among frontal cortex regions in fluoxetine responders that were less evident among non-responders and absent in the vehicle-treated group. Structural equation modeling of cortico-subcortical interactions revealed that direct path influences between the dorsal raphe nucleus and the lateral habenula and prelimbic cortex switched from negative to positive between fluoxetine-responders and non-responders, respectively. The observed differences in limbic-cortical interactions may represent an important neural network mechanism mediating the antidepressant SSRI response via modulation of the effective connectivity between the dorsal raphe and the lateral habenula and prelimbic cortex.

Invited Graduate Student Speakers

Keith W. Whitaker

Keith earned an interdisciplinary bachelor degree from the University of Florida in the Neurobiological Sciences. His undergraduate thesis with Dr. Don Stehouwer on infant rat vocalizations was presented at the International Society for Developmental Psychobiology. After teaching academically gifted teenagers in Kansas for a summer, he took a research assistant position with Dr. Teresa Reyes at Scripps Florida, a division of The Scripps Research Institute. This led to publications in *Neuropharmacology* and *Journal of Neuroendocrinology*, plus posters at Society for Neuroscience. Keith decided to step down from his lab manager position in order to pursue a PhD at The University of Texas at Austin. Within a year, he was awarded a S.M.A.R.T. scholarship from the Department of Defense. In addition to his graduate work, Keith currently works with the Army Research Laboratory - Human Research and Engineering Directorate's Translational Neuroscience Branch where he has been recognized for his work on the neurobiological mechanisms of multisensory integration.

Variability in neurobiological mechanisms of behavioral plasticity

The neural basis of stimulus-response behaviors has received much attention, yet questions remain about how processes at different levels of biological organization are to generate the decision to initiate a behavior. The startle-escape behavior of *Astatotilapia burtoni* males provides a unique, non-traditional model system for testing hypothesis about how behavioral plasticity is the outcome of the interaction of variability at various levels of biological organization.

In the African cichlid fish *A. burtoni*, males alternate between two social phenotypes: 1) dominant and territorial (T), displaying bright body coloration; or 2) subordinate and non-territorial (NT) with cryptic coloration. Avian predators target mostly T males due to their conspicuousness. In the context of this life history difference, an excitable startle-escape circuit would be beneficial to males when conspicuously colored T, but costly when NT. *A. burtoni* males utilize a startle-escape response that is highly conserved among teleost fishes. This extremely short latency locomotor behavior is governed by two paired reticulospinal neurons (the Mauthner neurons) as well as several interneurons. This simple circuit provides a unique opportunity to uncover how limitations on variability at the cellular and molecular levels alter the decision to initiate an escape behavior.

Notes

Poster abstracts

Decreased synuclein expression following spinal cord injury may contribute to neurological potential for recovery in lampreys [23]

David J. Busch¹, Billy Y. B. Lau¹, and Jennifer R. Morgan^{1,2,3}

¹Molecular Cell and Developmental Biology Dept., ²Institute for Cellular and Molecular Biology, ³Institute for Neuroscience; The University of Texas at Austin

The synucleins are a family of proteins found in vertebrate axons and synapses, best known for toxic aggregation leading to neuronal death in Parkinson's disease. Synucleins also accumulate at neurological sites of injury, yet the cell fates of neurons in which synuclein levels are altered after injury remain unknown. To address this, we used the sea lamprey (*Petromyzon marinus*), a vertebrate in which a subset of descending reticulospinal (RS) neurons is exceptionally large and uniquely identifiable and in which synuclein ($\gamma 1$ isoform) is highly expressed. We used a combination of *in situ* hybridization, immunofluorescence, and histology to identify the giant RS neurons in which synuclein levels were altered after severing their axons and to determine their corresponding fates. We found that $\gamma 1$ -synuclein mRNA expression decreased by 42% in all giant RS neurons by 11 weeks after injury. Likewise, synuclein protein levels also decreased after injury in the majority of giant RS neurons. However, there were occasional giant RS neurons where synuclein protein accumulated in the cell body. Subsequent histology revealed that giant RS neurons in which synuclein accumulated were compromised or dead, as determined by the absence of Nissl staining, whereas those in which synuclein dispersed remained healthy. Interestingly, giant RS neurons in which synuclein accumulated also exhibited poor axonal regeneration. Therefore, synuclein accumulation after injury is a risk factor for poor regeneration and cell death. Conversely, the ability of neurons to maintain low levels of synuclein protein after injury may increase their neurological potential for recovery.

Revisiting the developmental onset of long-term potentiation in rat hippocampal area CA1 [12]

Guan Cao, Kristen M. Harris

Center for Learning & Memory, The University of Texas at Austin

We previously reported that enduring LTP, lasting more than 3 hr, emerges by postnatal day 15 in rat hippocampal area CA1 when LTP was induced using a tetanus stimulation protocol of 2 trains of 100 pulses at 100Hz with a 20s interval (Harris and Teyler, 1985; Jackson et al., 1995). At younger ages, PTP lasting less than 1 minute was first induced at day 4 and short-term potentiation (STP) lasting 1-1.5 hr was first induced at day 11. It has been our hypothesis that enduring LTP requires dendritic spines because mature dendritic spines are first prevalent at day 15 (Harris et al., 1992). However, no systematic analysis of spine formation or alternative LTP induction protocols have been conducted between day 11 and day 15 when spines are presumably generated as well. Here we used theta-burst stimulation (8 bursts with 30s interval, each burst containing 10 trains of 5 pulses at 100Hz, with 200ms intervals between trains) to study LTP endurance at postnatal days 8-15. We confirmed that STP emerges at postnatal day 11, and lasts less than 2 hr, while enduring LTP lasting at least 4 hr first occurs at postnatal day 13. In order to test whether mature dendritic spines are needed for enduring LTP, we are using confocal fluorescence and electron microscopy to investigate dendrites in more detail at all of the ages beginning at day 8 and leading up to the threshold age day 13 for enduring LTP. (This study is supported by NIH grants NS21184, NS33574 and EB002170).

Zebrafish (*Danio rerio*) maze behavioral assays [10]

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²Environmental Science, Baylor University

Behavioral tests involving zebrafish and other small teleost fish are useful for genetic, pharmacology and toxicology screening. Treatments affecting the mesolimbic system can alter fish emotional behavior. To examine this we use two maze-based behavioral tests for zebrafish: a novel light-dark plus maze test of anxiety in a novel environment, and a learning maze task in which a food +/- stimulant reward is associated with colors through operant (Pavlovian) conditioning. We are measuring effects of acute or chronic compound exposures and dose-response relationships in these maze-based behavioral tests. In the aquatic plus maze, we found that with acute bath exposure to the GABAA agonist chlordiazepoxide (5mg/L), 0.5% ethanol, or 1 week dietary exposure to cannabinoid agonist WIN 55,212 (1 ug/d) zebrafish spent more time in white arms and/or entered white arms more often than controls (ANOVA and Fisher's LSD $p < 0.05$, $N=6-8$). Nicotine (50 mg/L) exposure increased fish locomotion in the plus maze. Sub-chronic dietary exposure of zebrafish to pesticides dieldrin or chlorpyrifos (10 ug/d) produced immobility and a trend toward

less time spent in white arms ($p < 0.08$, $N = 4-6$). In the associative learning maze, we found that with caffeine pre-administration (50 mg/L) and the color purple, hungry zebrafish acquired association of a food reward with a color (+ purple vs. - green) in fewer rounds than controls. Most of the results presented are the product of student research involvement, and were conducted in adult zebrafish. The maze can be scaled down to accommodate juvenile fish.

Near-infrared light induces muscle cytochrome oxidase and aerobic phenotype [9]

Christopher R. Hayworth, Ph.D.^{1,2}, Julio C. Rojas, M.D., Ph.D.², Eimeira Padilla, Pharm.D.³, Genevieve M. Holmes², Eva C. Sheridan², F. Gonzalez-Lima, Ph.D.^{2,3}

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Near-infrared light therapy (NILT) increases survival of cultured cells, improves behavioral recovery from neurodegeneration, and speeds wound healing. These beneficial effects are thought to be mediated by upregulation of mitochondrial proteins, especially the respiratory enzyme cytochrome oxidase. However, the effects of in vivo NILT on cytochrome oxidase in intact striate muscle have not been previously investigated. Quantitative enzyme histochemistry of cytochrome oxidase and metabolic fiber type composition were examined in the rat temporalis muscle after in vivo NILT. NILT induced a dose-dependent increase in cytochrome oxidase activity and a remarkable shift of intermediate muscle fibers towards a stronger aerobic phenotype. These findings suggest that NILT enhances muscle oxidative energy metabolic capacity, and that it may not be necessary for muscles to contract to build their aerobic capacity. NILT may have potential applications to support motor rehabilitation under conditions where muscle contraction and movement are compromised.

Testosterone level is associated with a social effect on morphine sensitization [6]

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¹Department of Psychology, Texas A&M University; ²Department of Psychiatry and Biobehavioral Sciences, UCLA

Drug use during early adolescence is a key predictor of later drug abuse and dependence during adulthood. Given that social influences are among the strongest predictors of adolescents' drug use, this study examines the effect of social interaction on morphine's effect on locomotion and plasma testosterone levels in both adolescent and adult mice. Three experimental groups were examined for each age group: 1) morphine-treated mice (twice daily, 10-40 mg/kg, s.c.), 2) saline-injected mice housed together with the morphine-treated mice ('saline cage-mates'), and 3) saline-injected mice housed physically and visually separated from the morphine-treated mice ('saline alone'). Nine days after the last dose of morphine (withdrawal day 9, WD9), mice were tested individually for their locomotor response to 10 mg/kg morphine. Additionally, blood was collected from separate mice on WD1 and WD9 to examine plasma testosterone levels. Adolescent saline cage-mates, though administered morphine for the very first time, exhibited an enhanced hyper-locomotion response similar to the locomotor sensitization response exhibited by the morphine-treated mice. Paralleling the behavioral sensitization, a decrease in plasma testosterone levels was observed in both the morphine-treated adolescent mice as well as in their saline cage-mates, as compared to plasma testosterone levels in the control saline alone mice. These phenomena were not observed in adults. In adults, there were no significant differences between saline alone and saline cage-mates in either morphine induced hyper-locomotion or plasma testosterone levels. Thus, these results demonstrate a vulnerability to social influences in adolescent mice which does not exist in adult mice.

Functional and Structural Basis for Alcohol Modulation of GLIC Channels [11]

Rebecca J. Howard, Kathryn E. Ondricek, R. Adron Harris

Waggoner Center for Alcohol and Addiction Research, The University of Texas at Austin

The recent publication of the atomic-resolution structure of GLIC, a prokaryotic proton-gated homolog of cys-loop receptors, poses a novel opportunity to characterize the structural basis for alcohol modulation of an ion channel. To validate GLIC as a structurally accessible model system for alcohol modulation, and reveal critical details of alcohol binding to ligand-gated ion channels, we are harnessing the electrophysiological properties of GLIC expressed in frog oocytes. Functional analysis allows us to explore alcohol modulation of GLIC in detail, identify specific GLIC sites associated with alcohol binding, and design GLIC mutants with enhanced alcohol modulation. Preliminary results reveal bimodal modulation of GLIC by short- and long-chain n-alcohols, and support a role for specific residues in the transmembrane domain in mediating alcohol binding.

mTOR-dependent Translational Repression: A Novel Mechanism for Regulating Ion Channels and Dendritic Excitability [28]

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Nora I. Perrone-Bizzozero² and Kimberly Raab-Graham¹

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Mammalian target of rapamycin (mTOR) kinase plays an important role in neuronal signaling including synaptic plasticity and local protein translation. While much is known about mTOR dependent translational activation, little is known about mTOR dependent translational repression. Here we reported the first mechanistic insight into the newly discovered role for mTOR signaling in inhibiting the local translation of the voltage-gated potassium channel Kv1.1. We have discovered that the 3'UTR of Kv1.1 mRNA is required for its mTOR dependent repression. Overexpression of the 3'UTR of Kv1.1 in cortical neurons outcompetes endogenous factors that suppress Kv1.1 mRNA translation, resulting in an increase of Kv1.1 surface expression. In order to identify those suppressing factors, we have implemented an in vitro RNA affinity capture method. We have identified a microRNA, miR-129, that binds the 3'UTR of Kv1.1 mRNA when mTOR is active. When miR-129 was knocked down in cortical neurons, a significant increase of Kv1.1 expression was observed in dendrites, confirming the translational repression role of miR-129. Additionally, we have identified an RNA binding protein, HuD, that binds Kv1.1 mRNA only when mTOR is inhibited. Furthermore, transgenic mice overexpressing HuD showed marked increase of Kv1.1 expression in hippocampus, suggesting HuD promotes Kv1.1 expression *in vivo*. Moreover, HuD transgenic mice had reduced back-propagating action potential in dendrites, indicating that increased local expression of Kv1.1 channels would decrease dendritic excitability. We thus propose that activated mTOR through synaptic excitation causes a suppression of dendritic Kv1.1 mRNA translation via miR-129 mediated translational repression, which results in fewer channels on the surface and higher neuronal excitability. When mTOR is inhibited, HuD binds Kv1.1 mRNA and activates its local translation, resulting in an increase of Kv1.1 channels on the surface and a decrease of neuronal excitability. These results demonstrate a novel mechanism for regulating ion channels and dendritic excitability which are important during learning and memory.

Molecular and Neuroendocrine Mechanisms of Social Transition [14]

Lin S. Huffman¹, A. Lauren Munchrath¹, Carly D. Kenkel¹, Hans A. Hofmann^{1,2,3}

¹Institute for Cellular and Molecular Biology, ²Section of Integrative Biology, ³Institute for Neuroscience,
The University of Texas at Austin

How do animals respond to an opportunity to become dominant? What are the neuroendocrine and molecular mechanisms underlying this transition from socially subordinate to dominant (or *vice versa*)? We examine these questions using the highly social African cichlid fish *Astatotilapia burtoni*. In this species, males express either a dominant or subordinate phenotype, but will switch phenotypes depending on the relative size and aggression of conspecific males. We are using this remarkable plasticity to study the neuroendocrine and molecular processes associated with social transition with unprecedented temporal resolution. We find that, when given an opportunity to ascend, males will increase their aggressive behavior and androgen levels within minutes, yet sexual behaviors do not emerge until five days after the onset of the transition. Within two weeks, the new phenotype appears to stabilize.

The neuropeptide arginine vasotocin (AVT), a key regulator of social behavior in all vertebrates, is highly expressed in the pre-optic area, a forebrain region that integrates and controls social behavior. Using pharmacological manipulations, we show that in males AVT facilitates the transition to dominance, likely via the V1a receptor. We are currently analyzing (by quantitative *in situ* hybridization) the distribution of AVT and the V1a receptor in the brains of males as they are becoming dominant. Finally, we have cloned and sequenced the cichlid homologs of the neuropeptide isotocin (oxytocin) and its receptor, a pathway considered complementary to AVT. This will allow us to simultaneously examine the roles of the AVT and IT pathways – and their possible interaction – in regulating transitions in social status.

Hyaluronan and Laminin Hydrogels for Repair Strategies after Cervical Spinal Cord Injury [27]

Zin Z. Khaing*¹, Sydney A. Geissler*¹, Timothy Schallert², Raymond J. Grill³, Christine E. Schmidt¹

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Cervical spinal cord injuries (SCIs) can result in loss of hand functions, which are among the most devastating deficits in patients. Impairment is typically chronic because adult mammalian axons in the CNS do not normally regenerate after injury. This regeneration failure is attributed in substantial part to components of the scar tissue and myelin-associated inhibitors within the injury site. Previously, we have shown that degradation-resistant hyaluronic acid (HA) hydrogels can inhibit astrocyte activation and proteoglycan deposition after SCI in adult rats. It is not known whether the modified scar tissue afforded by the presence of HA hydrogels can support axonal growth and functional improvement. HA alone is generally non-cell adhesive. Therefore, here we examined the effects of unmodified HA hydrogels compared to HA hydrogels modified with laminin (HA/LN) after acute lateral hemisection of the cervical spinal cord in adult rats. A gelfoam-only group was included as control. A number of behavioral tests (limb use during vertical-lateral rearing and exploration of the wall of a cylindrical enclosure, vibrissae-elicited forelimb placing, and grid walk tests) were used to assess forelimb function for 6 weeks after SCI. All tests readily detected SCI-induced deficits relative to non-injury over the 6-week period. Using the cylinder test, we found that animals treated with HA/LN hydrogel reached higher and explored more using their affected forepaw than HA or gelfoam-only animals. This improvement in the HA/LN implant group was statistically significant starting at week 2 and escalated through week 4. Relative to gelfoam-only SCI rats, no significant beneficial effects were detected in the HA or HA/LN groups in the grid walk or vibrissae-elicited forelimb placing tests. Histological and axon tract tracing analyses are currently underway to determine the type and extent of axonal regeneration. Results presented here suggest that HA-based scaffolds, modified with cell adhesive proteins, may hold great potential for repair strategies after spinal cord injury. This work was supported by The Gillson Longenbaugh Foundation and The David Van Wagener Spinal Cord Fund of the Joy to The World Foundation to CES.

A distinct subset of transcripts that encode for synaptic vesicle associated-proteins increases in the lamprey brain during functional recovery from spinal cord injury [22]

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Molecular and cellular mechanisms underlying recovery of synaptic function after spinal cord injury (SCI) remain unclear because recovery is inefficient in most vertebrate models. Therefore, we are using sea lamprey (*Petromyzon marinus*) to study synapse recovery after SCI because axon and synapse regeneration readily occur, as does behavioral recovery, implying a return of synaptic function. To begin, we have focused on synapse-based molecular and structural changes that occur after SCI in the midbrain and hindbrain, which contain the cell bodies of reticulospinal (RS) neurons, the major class of descending neurons that are severed upon injury. Using semi-quantitative reverse transcriptase-PCR (RT-PCR) and *in situ* hybridization, we examined relative changes in mRNA levels of synaptic vesicle associated-genes at 1, 3 and 11 weeks post-transection. Using these approaches, mRNA levels for most genes remained unchanged after SCI (CSP, rab3, synaptogyrin, synaptophysin IIa, synaptotagmin, VAMP2 and vGlut). However, synapsin and SV2 were upregulated by >150% at 3 weeks post-transection and beyond. Preliminary immunofluorescence results suggested an increased level of synapsin protein in individual synapses of midbrain and at 11 weeks post-transection. Furthermore, the number of synapsin positive puncta increased at 11 weeks post-transection, suggesting that synaptic sprouting occurs in response to injury. Taken together, our data identified synapsin and SV2, as well as increased synaptic sprouting, as potential molecular and cellular targets for restoring greater synaptic function after SCI.

Neuregulin1-induced remodeling of mouse neuromuscular junction [1]

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The morphology of a vertebrate neuromuscular junction (NMJ) - and its components: precise apposition of the postsynaptic acetylcholine receptor (AChR) aggregates with the presynaptic motor nerve terminal capped by non-myelinating terminal Schwann cells (tSCs) - appears mostly stable once the synapse has reached its mature state approximately 2 weeks after birth. However, we have observed marked changes in the morphology of junctions when motor axons overexpress a ligand (neuregulin1-type III, “NRG”) known to signal to SCs. In these mice, all three components of transgenic MNJs are dramatically altered. tSCs are increased in number and send out processes absent from control NMJs. AChR aggregates are found, not in smooth and continuous gutters, but in small islands with matching presynaptic nerve terminal boutons/varicosities connected by thin neurites. Additional features of the junctions in these overexpressing mice suggest dynamism of synaptic components: including the presence of “aneural” islands of AChR; some of these sites have dimmed receptor staining. These observations suggest that synaptic contacts are being broken, leaving denervated receptor aggregates that then gradually disappear, and that tSCs, expressing receptors for NRG, may actively remodel synaptic morphology/connection at vertebrate NMJs.

Vital imaging of synaptic remodeling at a vertebrate neuromuscular junction [29]

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A mammalian neuromuscular junction (NMJ) is comprised of three cellular components: presynaptic axon terminal, postsynaptic muscle fiber which expresses acetylcholine receptors (AChRs) on its surface, and the unmyelinated glial cells/terminal Schwann cells (TSCs) that cover the nerve terminal. Extensive studies have focused on the axon-muscle relationship of the NMJ, but recent work also revealed critical roles of the TSCs in its maintenance and repair. We have found that in mice whose motor axons overexpress neuregulin 1 type III (NRG1-III) all three components of NMJs are dramatically altered from those in normal mice. I have used vital imaging to examine the dynamics of the components of NMJs in these mice. I find that nerve terminal branches withdraw from contact with the muscle fiber. The vacated receptor sites usually become dim over time and disappear eventually. However, the withdrawn terminal can extend again to re-innervate the unoccupied receptor sites. TSCs have changed dramatically too. They proliferate and extend numerous fine processes forming a cloud over the nerve terminal. SC bodies also migrate at the junction. In addition, SC processes wrap the nerve terminal except the synaptic sites. I conclude that overexpression of NRG1-III in the axon activates TSCs and causes disruption of the normal synaptic connection and constant modification of the NMJ.

Content-sensitive novelty encoding in the medial temporal lobe: Insights from high resolution fMRI and distributed pattern analysis [25]

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The ability to distinguish between novel and familiar stimuli plays a critical role in orienting toward behaviorally salient and rewarding events. Current theories of medial temporal lobe (MTL) function propose that distinct MTL regions may differ in their sensitivity to novelty based on information content. For example, the anatomical projections between sensory processing regions and perirhinal and parahippocampal cortices suggest that these regions are sensitive to visual object and visuospatial content respectively. However, the representation of different stimulus content need not be modular and may instead be distributed in a graded manner both within and across subregions. To answer this question, we employed high-resolution functional MRI and an incidental novelty detection task using five stimulus classes (faces, scenes, visual words, spoken words, sounds). Univariate statistics revealed a graded distribution of face and scene novelty responses along the anterior-posterior axis of MTL cortex. Novelty responses in hippocampus were isolated to the anterior subfields and were similar across content. Additional multivoxel pattern analyses revealed that despite overall sensitivity to specific content, MTL cortical regions maintained an ability to classify information of nonpreferred content. In contrast, hippocampal subfields DG/CA3 and CA1 failed to accurately discriminate between different content types, though subiculum demonstrated significant classification accuracy for faces and scenes. Together, these findings support a graded distribution of content-sensitive novelty responding along the anterior-posterior axis of MTL cortex and provide evidence for content general novelty encoding in the hippocampus.

Disease severity induced by gene/environment synergy [5]

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Disease phenotypes are typically highly variable with some of this variability attributable to gene/environment interactions. However, due to their complexity, we know virtually nothing about these interactions. We chose Fetal Alcohol Syndrome (FAS) as a model for gene/environment interactions, because it has variable craniofacial phenotypes, including cleft palate and jaw hypoplasia; a known environmental cause, ethanol; and there is clear evidence that FAS is genetically modulated. We reasoned that at least some genes that interact with alcohol would have craniofacial defects when mutated. Therefore, we screened known zebrafish craniofacial mutants for enhanced susceptibility to ethanol-induced craniofacial disease. Here, we provide a novel example of gene/environment synergy that leads to variable craniofacial defects in zebrafish, mimicking those found in FAS. Untreated *platelet-derived growth factor receptor alpha* (*pdgfra*) mutants have cleft-palate, caused by defective neural crest cell migration (ref). Mutants treated with 1% ethanol have profound craniofacial phenotypes not observed in untreated mutants, including upper jaw hypoplasia. Additionally, ethanol treatment unmasks latent haploinsufficiency in *pdgfra* heterozygotes; 66% of treated heterozygotes have palatal defects distinct from those in untreated mutants. These unique interaction phenotypes suggested that migration might not cause the ethanol-induced defects. Indeed, we found a significant increase in neural crest cell death in ethanol-treated heterozygotes and mutants, but not their untreated siblings. Blocking apoptosis with a caspase inhibitor rescues the ethanol-induced craniofacial defects in mutant and heterozygous embryos, verifying that neural crest cell death causes the interaction phenotype. Our results demonstrate that gene/environment interactions can be synergistic, adding great complexity to the etiology of human disease.

A Transmembrane mutation in the Neuregulin 1 gene is associated with alterations in cytokine levels in-vitro [31]

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The Neuregulin 1 (NRG1) gene, one of the strongest schizophrenia candidate genes so far reported, has been recently implicated in immune system regulation. We hypothesized that a schizophrenia-associated missense mutation (Valine to Leucine) we identified within the transmembrane region of NRG1 would be involved in regulation of cytokine gene expression and may thereby contribute to schizophrenia development. We used EBV-transformed B cells from unaffected heterozygous mutation carriers and wild type individuals to evaluate protein and mRNA cytokine expression *in vitro* using quantitative PCR and ELISA assays. We observed a significant increase in protein secretion levels of IL-6, TNF- α , and IL-8 in mutation carriers compared to controls. At the mRNA level we observed a significant increase in IL-6 expression, while IL-4 levels appeared to be down regulated in heterozygous individuals compared with wild-type controls. Elevated levels of pro-inflammatory cytokines are often associated with schizophrenia. We believe our data supports a novel role for NRG1 as a regulator of cytokine gene expression. The NRG1 Valine to Leucine mutation may contribute to altered cytokine levels and possibly schizophrenia development.

Integrated Microscopy Techniques Allow Targeted 3-d Ultrastructural Modeling of the Neuromuscular Junction [30]

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The mammalian neuromuscular junction (NMJ), comprised of a postsynaptic acetylcholine receptor apparatus, a presynaptic motor neuron, and non-myelinating Schwann cells, is a large and easily accessible neuron-target synapse making it an excellent subject for the study of development, maintenance, and disease. We can observe the NMJ using fluorescence microscopy with the aid of transgenic markers, but the resolution of this technique is limited in spite of advances in recent years. Electron microscopy (EM) offers remarkable detail and resolution, but is limited in its usefulness when used alone. Serial EM and the 3-d models rendered from it can reveal detail previously invisible in fluorescence microscopy. We propose to image a NMJ with fluorescence microscopy, create an identifiable landmark in the near vicinity of the NMJ of interest, prepare and embed the tissue for EM, then locate the mark and therefore the junction. We have performed each of these steps, but not in the same tissue, and are currently testing marking methods. Our objective is to create fluorescence images using transgenic markers followed by the creation of a 3-d model from serial TEM images of the same junction. The EM images will provide detailed information about the synaptic components and their relationships to one another in normal and mutant NMJs.

Using *C. elegans* to understand Down Syndrome [18]

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Down syndrome (DS) is the number one genetic cause of mental retardation, affecting 1 in 733 live births. People with DS suffer from many neurological and neuromuscular symptoms including congenital heart disease, hypotonia, and early-onset dementia resembling Alzheimer disease. DS is caused by trisomy of chromosome 21 (HSA21), but the mechanism by which the extra copy of HSA21 leads to DS is unknown. We are exploring the current theory that single or small groups of HSA21 genes contribute to specific DS phenotypes. Studying DS is slow in mouse models, so we take advantage of the powerful genetics of *C. elegans* to rapidly elucidate which equivalent genes might be involved in DS. First, we identified all HSA21 gene equivalents in *C. elegans* through BLAST comparison. We next performed an RNAi screen to systematically determine which of these genes might function in muscle and/or the nervous system. Knock-down of gene expression through RNAi produced qualitative defects in locomotory and/or feeding behaviors in approximately half of the 170 tested genes. To test which subset of these genes might cause dysfunction in nervous system or muscle in DS, we have begun to generate transgenic worms that overexpress single copies of these genes and assay for defects in behaviors. Future research will identify DS-relevant gene pathways by screening for mutants that suppress/enhance the behavioral phenotypes of transgenic worms. Identification of the complete set of candidate genes that contribute to DS phenotypes could lead to novel gene-targeting strategies to improve the lives of people with DS.

Evolution of the vertebrate social decision-making network [13]

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The dopamine reward system and Newman's social behavior network in the vertebrate fore- and midbrain are fundamental in the regulation of social behavior. We propose that brain nuclei in these circuits are part of a social decision-making network that provides a powerful framework for understanding the evolution of social behavior. As little is known about this network in teleosts, we examine it in the highly social African cichlid fish, *Astatotilapia burtoni*, which has become a model system for the study of social decisions in the context of dominance and mate choice. Using immunohistochemistry on tyrosine hydroxylase (TH) and dopamine receptor D1 *in situ* hybridization, we mapped the dopamine system and found that *A. burtoni* have TH-ir cell bodies or fibers and/or D1 receptor expression in nuclei putatively homologous to those of the reward system and Newman's social behavior network. This pattern is consistent across teleosts, with a few exceptions in area Vs (putative medial amygdala/BNST homolog) and DI (putative hippocampus homolog). We then compared the dopaminergic system across teleosts, amphibians, reptiles, birds and mammals. To complement this analysis, we also mapped the distributions of the sex steroid and neuropeptide hormone receptors in brain nuclei of the proposed social decision-making circuitry across vertebrate classes, as these hormones are thought to regulate social behavior via this network. Finally, although the dopaminergic system has been mapped in teleosts, there is contention as to whether this system is functionally homologous to structures in other vertebrates, and specifically if the posterior tubercle is functionally similar to the mammalian ventral tegmental area as a main source of ascending dopaminergic input. To address this, we are currently examining the DA motif in cis-regulatory regions of genes associated with dopamine neurons in three species of teleosts and the spatial expression of transcription factors that regulate dopaminergic neuron specification and maintenance in other vertebrates. We conclude that the social decision-making network exhibits a large degree of conservation across vertebrates and that it likely arose from an evolutionarily ancient core network of brain nuclei.

Evidence for decreased sensitivity to amphetamine in BACE1 knock-out mice [32]

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B-Site APP-cleaving Enzyme 1 (BACE1) knock-out (k/o) mice display a schizophrenia-like behavioral phenotype including novelty-induced hyperactivity, cognitive deficits, and impaired prepulse inhibition. Here we provide evidence that BACE1 ko mice display hyposensitivity to amphetamine (AMPH). 24 wild-type (wt) and 24 BACE1 ko mice were treated with either 3.2 mg/kg AMPH, 10 mg/kg AMPH, or saline vehicle (eight mice per group) and subjected to a locomotor activity test for 45 min. During the first 15 minutes of baseline testing, conducted 24 h before drug testing,

we observed significantly less locomotor activity in k/o compared to wt mice, with no significant differences observed after that period. In addition, we observed a significant interaction between the effect of genotype and amphetamine dose on locomotor activity. Compared with their respective saline-treated controls, both wt and k/o mice treated with 3.2 mg/kg AMPH exhibited higher locomotor activity, with a significantly greater increase in wt compared to k/o mice. In contrast, k/o mice treated with 10 mg/kg AMPH exhibited significantly higher locomotor activity than the wt mice. These differences in locomotor activity response to amphetamine may indicate differences in sensitivity to amphetamine. Compared with wt mice, the reduced response of the k/o mice to 3.2 mg/kg AMPH and the increased response of the k/o mice to 10 mg/kg AMPH suggest a shift to the right of the dose-response curve for amphetamine in the k/o mice. These studies add to the evidence that alterations in BACE-1 function may be relevant in schizophrenia and other psychiatric disorders.

Strain, Sex, and Open-Field Behavior: Factors Underlying the Genetic Susceptibility to Helplessness [7]

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Learned helplessness represents a failure to escape after exposure to inescapable stress and may model human psychiatric disorders related to stress. Previous work has demonstrated individual differences in susceptibility to learned helplessness. In this study, we assessed different factors associated with this susceptibility, including strain, sex, and open-field behavior. Testing of three rat strains (Holtzman, Long-Evans, and Sprague-Dawley) revealed that Holtzman rats were the most susceptible to helplessness. Holtzman rats not only had the longest escape latencies following inescapable shock, but also showed spontaneous escape deficits in the absence of prior shock when tested with a fixed-ratio 2 (FR2) running response. Moreover, when tested with fixed-ratio 1 (FR1) running—an easy response normally unaffected by helplessness training in rats—inescapable shock significantly increased the escape latencies of Holtzman rats. Within the Holtzman strain, we confirmed recent findings that females showed superior escape performance and therefore appeared more resistant to helplessness than males. However, regression and covariance analyses suggest that this sex difference may be explained by more baseline ambulatory activity among females. In addition, some indices of novelty reactivity (greater exploration of novel vs. familiar open-field) predicted subsequent helpless behavior. In conclusion, Holtzman rats, and especially male Holtzman rats, have a strong predisposition to become immobile when stressed which interferes with their ability to learn active escape responses. The Holtzman strain therefore appears to be a commercially available model for studying susceptibility to helplessness in males, and novelty-seeking may be a marker of this susceptibility.

Circadian Genes Differentially Affect Tolerance to Ethanol in *Drosophila* [2]

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Alcoholism is a prominent and devastating disease that has large societal and financial costs. However, the molecular mechanisms that underlie this addiction are poorly understood. Tolerance, defined as a reduced response to an effect of a drug due to a previous exposure, can lead to addiction as the user requires more drug to reach their desired state. The fruit fly, *Drosophila melanogaster*, has been a useful model system in understanding ethanol behaviors. Like in mammals, large doses of the drug cause an initial hyperactive phase before sedating the animal. Using an automated knockdown assay, we have found that flies receiving their second dose show a delay in both the hyperactive and sedative phase compared to naïve animals, demonstrating clear tolerance.

Circadian genes have been shown to play a role in drug-induced behaviors. It has been demonstrated, in both flies and mammals, that animals lacking specific circadian genes fail to show normal sensitization to cocaine. Here we show that circadian genes are differentially involved in tolerance to ethanol. Backcrossed *tim⁰¹*, *cyc⁰¹*, and *Clk^{JRK}* mutants show wildtype sensitivity to ethanol, but differentially affect tolerance. *tim⁰¹* mutants show reduced tolerance to both the hyperactive phase and the sedative phase, whereas *cyc⁰¹* mutants show reduced tolerance only to the hyperactive phase. *Clk^{JRK}* mutants do not appear to affect the acquisition of tolerance. Ongoing experiments are looking further into the relationship between circadian genes and the fly's response to ethanol.

Long-term Epigenetic Modifications linked to the production of Drug Tolerance in *Drosophila* [3]

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Drug-induced tolerance is widely thought to be an adaptive mechanism meant to counteract repeated exposure to a substance. In the model organism *Drosophila*, tolerance lasting over a week can be induced from a single exposure to the anesthetic benzyl alcohol. An increase in the expression of a Ca²⁺-activated BK-type K⁺ channel encoded by the *slo* gene is responsible for this adaptation. Altered Gene expression can be modulated by epigenetic modifications made to the promoter region of a gene. These modifications are plastic and can change over time. In order to gain an understanding of the molecular process leading to the increased transcription of *slo* and resulting long-term reaction to benzyl alcohol seen in *Drosophila*, we are studying the time course of epigenetic marks throughout the promoter of *slo*. Using the chromatin immunoprecipitation assay, we are exploring the acetylation and methylation states of certain histone residues and how they change through the extent of induced tolerance.

Near-infrared light therapy facilitates fear extinction [8]

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Near-infrared light therapy (NILT) enhances the metabolic capacity of neurons in culture through stimulation of the mitochondrial enzyme cytochrome oxidase, but the *in vivo* effects of NILT on brain and behavior have not been extensively analyzed. This study tested the hypothesis that transcranial NILT could facilitate fear extinction and prevent the reemergence of extinguished conditioned fear responses *via* enhancement of brain metabolic capacity in rats. Animals were trained in a Pavlovian fear-conditioning paradigm consisting of two sessions of four tone-foot shock presentations. Subsequently, animals underwent extinction training in sessions occurring one every day for four days. Freezing behavior was used as a measure of fear. NILT was delivered at $\lambda = 660$ nm, 5 J/cm², 15 min after each extinction session and freezing scores were compared to those of control rats (undergoing fear-conditioning training but no NILT). NILT-treated rats showed an enhanced rate of extinction, with freezing levels 59 and 70% lower than control, after the 2nd and 3rd extinction sessions. After the 4th extinction session, NILT-treated rats showed a paradoxical increase in freezing, compared to control. However, NILT-treated rats showed decreased rates of renewal and spontaneous recovery, compared to controls. Also, NILT induced a hormetic dose-response effect on the metabolic capacity of the frontal cortex, as quantified with cytochrome oxidase histochemistry, with a dose of 10.9 J/cm² NILT at $\lambda = 660$ nm showing the largest (12%) increase as compared to control. The data demonstrate that *in vivo* transcranial NILT can be used to enhance the metabolic capacity of the brain and to facilitate retention of fear extinction memories, and implicate NILT as a potential intervention to augment exposure therapy in humans.

The impact of neuronal activity on cytosolic pH in *Drosophila* motor nerve terminals as revealed by a genetically encoded pH indicator [33]

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Many studies show the importance of Ca²⁺ in regulating release from nerve terminals but the impact of pH changes on neurotransmission is not well understood. Most biochemical reactions are pH dependent and pH may also modulate presynaptic machinery. It is therefore necessary to systematically examine the effects of pH on neurotransmission. To study the impact of pH changes on neurotransmission we engineered several transgenic animals with genetically encoded pH indicators (GEpHI's) which have revealed presynaptic cytosolic acidification in response to stimulation of *Drosophila* motor neurons. The GEpHI cytopHlourin was used to characterize pH changes in terminals under varying stimulation conditions. The magnitude of the acidification is positively associated with both the frequency and duration of stimulation while the decay constant of the change in fluorescence is independent of both the frequency and duration of stimulation. The pH changes in nerve terminals measured using the GEpHI cytopHlourin were consistent with changes measured with the synthetic pH indicator seminaphthorhodafluor-1 (SNARF-1), but the source and clearance mechanisms of the H⁺ ions contributing to the acidification are still unknown. The GEpHI

Ptilosarcus green fluorescent protein (PtGFP) was not responsive to pH changes in the range observed. The pH responses were quantified using calibration techniques in an in situ preparation and comparison of the pH responses at different extracellular Ca^{2+} concentrations revealed the acidification to be Ca^{2+} dependent. GEpHI's are essential tools required to measure pH changes under physiological conditions and elucidate the likely modulatory influences of pH changes on neurotransmission and synaptic plasticity.

Osmotic potentiation of hygrotaxis in *C. elegans* [17]

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Moisture is essential for life. As such, many animals have adapted different behavioral mechanisms to detect moisture (hygrosensation) and migrate toward their preferred moisture level (hygrotaxis). While the molecular basis for sensory modalities such as photosensation and mechanosensation has been intensely investigated, hygrosensation remains poorly understood. To study the molecular mechanisms for hygrosensation, we developed the first paradigm for hygrotaxis in *C. elegans*. Worms are transferred to a hypoosmotic agarose pad contained in a gel apparatus. A desiccant is placed on one side and water on the opposite; neither directly contacting the pad. The container is sealed to allow a moisture gradient to form. The hypoosmotic challenge causes animals to hygrotax to the dryer side of the pad. Animals assayed in a mock gradient show no preference. The migration to the dry side does not appear to be an olfactory response to the desiccant because worms migrated to the wet side when assayed on hyperosmotic agar. We have begun to evaluate extant mutants including TRP channel, sensory cilia, and chemosensory defective strains to identify the moisture signaling pathway. Determining the molecular basis for moisture sensation in *C. elegans* will provide the groundwork for understanding this sense in other organisms.

Genomic Signatures of Social Evolution in East African Cichlid Fish [15]

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We study the evolutionary transitions of brain transcriptomes that control social organization in the monophyletic Ectodini (Tanganyikan cichlid fishes), where species vary according to mating (monogamy vs. polygamy) and parental care systems (biparental vs. maternal). This clade originated from a polygynous ancestor ca. 1 MYA.

We inferred their phylogenetic relationships using AFLPs and found that there have been ≥ 4 independent transitions from polygamy to monogamy. We collected the brains of wild-caught, sexually mature males and females of four species ($n=5$ per sex and species) – representing two independent transitions to monogamy and their respective polygamous sister species – and determined neural transcript profiles using a custom-made cDNA microarray (~19,000 features). Our study is the first to analyze mating system evolution on a genomic scale.

Of the 3127 genes with species-specific regulation patterns in males, most (95%) were associated with lineage and only a small portion (5%) were regulated according to mating system. For females, the results were similar. Interestingly, while many of the lineage-specific genes are common to both sexes, there are few, if any, sex-invariant mating system-specific genes. These results suggest that (a) despite dramatic differences in social behavior between sister species, brain transcriptomes reflect phylogenetic inertia; (b) changes in the activity of only a small number of genes may be necessary to facilitate the transition from polygamy to monogamy; and (c) the molecular basis of monogamy differs between males and females. Using comparative genomic hybridizations we are currently determining to which extent sequence variation could explain these results.

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Prefrontal cortex and lateral pontine neurons display tone-evoked persistent activity during trace eyelid conditioning [20]

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The prefrontal cortex (PFC) is essential for learning tasks that incorporate a delay period between cue presentation and behavioral response. Trace eyelid conditioning, in which a conditioned stimulus (500 ms tone CS) and unconditioned stimulus (50 ms eyeshock US) are separated by a delay interval (500 ms trace), requires an intact medial PFC and cerebellum. Cerebellar learning requires near overlap between the CS and US. We hypothesize that tone-evoked persistent input to the cerebellum is the neural basis for bridging the delay period between the CS and US. To test this hypothesis, we recorded single-unit activity from the mPFC during trace eyelid conditioning and observed neurons that displayed tone-evoked increases in activity that persisted through the delay interval, similar to that reported during non-match to sample tasks. We also recorded neurons from the pontine nuclei, which receives mPFC input and projects to the cerebellar cortex, to determine if a persistently active signal is relayed to the cerebellum. Pontine neurons also displayed persistent activity in response to the tone CS.

The data support the hypothesis that the mPFC provides the cerebellum, via the pontine nuclei, with a tone-evoked persistent input. Such activity is thought to function as a working memory of the stimulus until a behavioral response is made. In trace eyelid conditioning, such activity provides the cerebellum with an input that overlaps in time with the US, enabling cerebellar learning and the eventual expression of conditioned responses.

Tone-evoked hippocampal theta reset precedes the acquisition of conditioned responses in trace eyelid conditioning [21]

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Several studies indicate that the hippocampus is important for the learned association of stimuli that span space and/or time. As a result, a number of theories exist regarding what role the well-described theta rhythm may play in modulating hippocampal function. We report here that the repeated presentation of paired stimuli evoked a robust pause and restarting of hippocampal theta rhythm (i.e., theta reset), specifically in association with learning. During trace eyelid conditioning (500 ms tone CS followed by a 500 ms stimulus-free interval and terminating with a 50 ms eyeshock US) we observed the development of a robust tone-evoked theta reset in the hippocampus of rabbits during the acquisition of conditioned responses (CRs). Hippocampal field potential activity revealed a time- and phase-locked reset of theta in response to tone presentation. Rabbits displayed a significant increase in the robustness of tone-evoked theta reset in the 2 sessions prior to the expression of CRs (2-5 fold power increases from baseline; Friedman, corrected $p = .002$; Wilcoxon signed rank as post hoc, $p < .05$), independent of the number of sessions the rabbit required to learn. Subsequent to the acquisition and expression of CRs, the incidence of tone-evoked theta reset decreased to baseline. Extinction and reacquisition of the expression of CRs did not result in the same increases observed during the initial acquisition. The data strongly suggest that the pause of hippocampal theta, rather than the presence of ongoing theta modulation, may be an important network condition during the learned association of stimuli.

cAMP-dependent pathways increase plasmalemmal sealing of transected neurites of hippocampal B104 cells [4]

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Neuronal survival and eventual axonal regeneration depends upon rapid sealing of plasmalemmal damage after axonal transection (Yoo *et al.*, 2004). Plasmalemmal sealing occurs by an accumulation of intracellular vesicles that often arise from nearby undamaged membranes (Detrait, *et al.*, 2000a) and requires increased intracellular $[Ca^{2+}]$, calpain, syntaxin, SNAP-25, synaptobrevin, synaptotagmin, and PKA (Krause, *et al.*, 1994; Bi, *et al.*, 1995; Yoo, *et al.*, 2003; Shen and Steinhardt, 2005). The effect of cAMP-dependent pathways, through PKA and Epac, on plasmalemmal sealing has not been studied before.

We used exclusion of extracellular dye (Texas-red) at 5 minutes post- Ca^{2+} addition to assess sealing of B104 neurites transected in Ca^{2+} -free saline. Cells with neurites transected farther ($>50 \mu m$) from the soma sealed more rapidly than cells with neurites transected nearer to ($<50 \mu m$) the soma. Most cells transected farther from the soma completed

plasmalemmal sealing by 5 minutes post- Ca^{2+} addition. When added to the bath solution the following substances decreased the percent of cells that sealed plasmalemmal damage: **1)** KT5720 and PKI, which inhibit PKA activity; **2)** tetanus toxin and Botulinum toxin B, which cleave synaptobrevin; **3)** Botulinum toxin A, which cleaves SNAP-25; **4)** Botulinum toxin E, which cleaves SNAP-25 and syntaxin; and **5)** N-ethylmaleimide (NEM), which blocks activity of the NEM sensitive factor (NSF). The following substances increased the percent of cells that sealed plasmalemmal damage: **1)** db-cAMP, a membrane permeant cAMP analog; **2)** cBiMPS, a cAMP analog specific for PKA; and; and **3)** 8CPT-2Me-cAMP, a cAMP analog specific for Epac. Neither PKA-specific activation nor Epac-specific activation could overcome the NEM-dependent decrease in plasmalemmal sealing.

In summary, our data show plasmalemmal sealing is increased by two distinct cAMP pathways, activated by either PKA or Epac. Furthermore, PKA and Epac dependent sealing pathways converge on the NEM-sensitive factor (NSF), an ATPase involved in membrane fusion in many intracellular compartments. All these data suggest a common role for cAMP/PKA in membrane fusion and/or vesicle/plasmalemmal interactions that initially evolved for plasmalemmal sealing and were then co-opted for Golgi trafficking and exocytotic release of synaptic transmitters.

Dopaminergic control of locomotory switching in *C. elegans* [19]

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A key component of the study of rhythmic behaviors is characterization of the underlying neural circuit. The nematode *C. elegans* offers an excellent model for studying neural basis for rhythmic behaviors because it displays alternate forms of locomotion and has a completely characterized nervous system. We find that *C. elegans* crawls on firm substrates and swims in liquid environments. Moreover, worms continually switch between crawl- and swim-like motions in certain viscous media suggesting that the worm “chooses” to move with a particular form of motion. Neuromodulators, such as dopamine, have conserved roles in switching locomotory rhythms. We tested whether dopamine is involved in switching between swim and crawl in *C. elegans* through light-activation of channel rhodopsin in dopamine neurons. Swimming worms switched to crawl-like movement for the duration of dopamine neuron activation suggesting that dopamine may be sufficient to induce crawling. Consistent with this hypothesis, we found that immersing worms in liquid dopamine also induced crawl-like behavior. To test whether dopamine signaling is required to switch from swim to crawl, we investigated how dopamine receptor mutants behaved as they emerged from liquid. Worms lacking a D1-like receptor displayed defective switching, while those which lacked D2-like receptors did not. Together, our results indicate that release of dopamine by dopaminergic neurons is sufficient for worms to switch from swimming to crawling, and that D1-like dopamine receptors are necessary for this transition. This work represents a major step forward in understanding the locomotory system of *C. elegans*.

Deletion of TRIP8b decreases I_h in hippocampal CA1 pyramidal neurons [16]

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Hyperpolarization-activated Cyclic nucleotide gated Non-selective cation channels (I_h , HCN) are important regulators of neuronal physiology as they contribute not only to key membrane parameters like resting potential (V_M), input resistance (R_N) and the membrane time constant, but also to intrinsic oscillatory activity and synaptic integration. Although I_h is plastic and modulated in response to increased neuronal activity including patterns that induce LTP and LTD, the mechanism underlying the change is not known. A clue to this regulation may lie in the observation that loss of dendritic I_h in CA1 pyramidal neurons following status epilepticus is accompanied by a decrease in the interaction between HCN subunits and the auxiliary protein TRIP8b (TPR – containing Rab8b interacting protein). TRIP8b and its isoforms are known to interact with the C-terminal domain of the HCN1 subunit and regulate the activity and distribution of HCN channels. To determine the physiological role of TRIP8b, we measured physiological parameters sensitive to I_h in CA1 pyramidal neurons from mice that had the TRIP8b gene deleted. Deletion of TRIP8b resulted in hyperpolarization of V_M , increase in R_N and temporal summation, and a decrease in resonance frequency (f_r) and voltage sag, suggesting that the absence of TRIP8b resulted in downregulation of I_h . In addition, we show that deletion of TRIP8b does not impair synaptic plasticity but abolishes I_h mediated changes in intrinsic plasticity associated with LTP. Our results indicate that TRIP8b is essential for the normal function of dendritic I_h and may be a regulatory target for intrinsic plasticity.

Reward modulation of hippocampal subregions during motivated associative encoding [26]

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Emerging data suggest that hippocampal memory processing is modulated by midbrain regions under conditions of reward resulting in enhanced encoding of episodic information—long-term memory for events. Current theories further suggest that hippocampal subregions may have distinct roles in episodic memory formation, and may be differentially influenced by dopaminergic midbrain inputs. Using high-resolution functional magnetic resonance imaging (fMRI), the present study investigated hippocampal subregional function as well as activation in surrounding medial temporal lobe (MTL) cortex during associative encoding under varying conditions of reward. A high-value or low-value monetary cue preceded a pair of objects indicating potential reward for successful retrieval of the association. At test, participants performed cued recall followed by match (correct association) or mismatch (incorrect association) probe decisions and received feedback on their performance. Behaviorally, cued recall performance was superior for pairs preceded by high reward cues at encoding relative to pairs preceded by low reward cues. FMRI analysis revealed regions within hippocampus, parahippocampal cortex, and midbrain showing subsequent memory effects (greater encoding activation for remembered, compared to forgotten items). Within these regions, reward-related individual differences in encoding activation were correlated with the degree of the behavioral reward effect (better memory for high reward compared to low reward pairs). Moreover, hippocampal activation, but not parahippocampal activation, was correlated with midbrain activation across participants. These findings suggest that reward-based motivation influences memory formation through interactions between dopaminergic midbrain and hippocampus.

Bayesian methods for electrode artifact compensation and noise removal in intracellular recordings [24]

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Intracellular recording techniques provide a fundamental tool for understanding the functional properties of excitable cells. However, substantial measurement artifacts arise when current is injected through the same electrode used for recording membrane potential, due to the electrode's resistance and capacitance. Traditional compensation methods (e.g., "bridge" compensation) assume a linear RC-circuit description of the electrode, which is not accurate for most electrodes.

Here we develop a recursive Bayesian filtering approach to electrode artifact compensation. We model the electrode as an arbitrary linear filter, and show that this filter can be estimated using a brief recording of the neuron's voltage response to a white noise current. We also include an explicit model of measurement noise, which allows for Bayesian denoising of voltage traces. Our approach relies on the fact that the sub-threshold dynamics of a hyperpolarized neuron can be approximated as a linear dynamical system with Gaussian noise, for which powerful statistical methods have been developed. We use EM to perform maximum likelihood estimation of the electrode kernel, noise variances, and passive neural response properties, and perform Kalman filtering/smoothing to obtain estimates of true membrane voltage. We apply these methods to simulated data from a Hodgkin-Huxley neuron and to real data recorded in vitro. Fitting is robust to noise level and accurate even with small amounts (~500ms) of data. We show that the resulting estimates of membrane voltage are more accurate than those obtained by previous methods, particularly for large measurement noise.