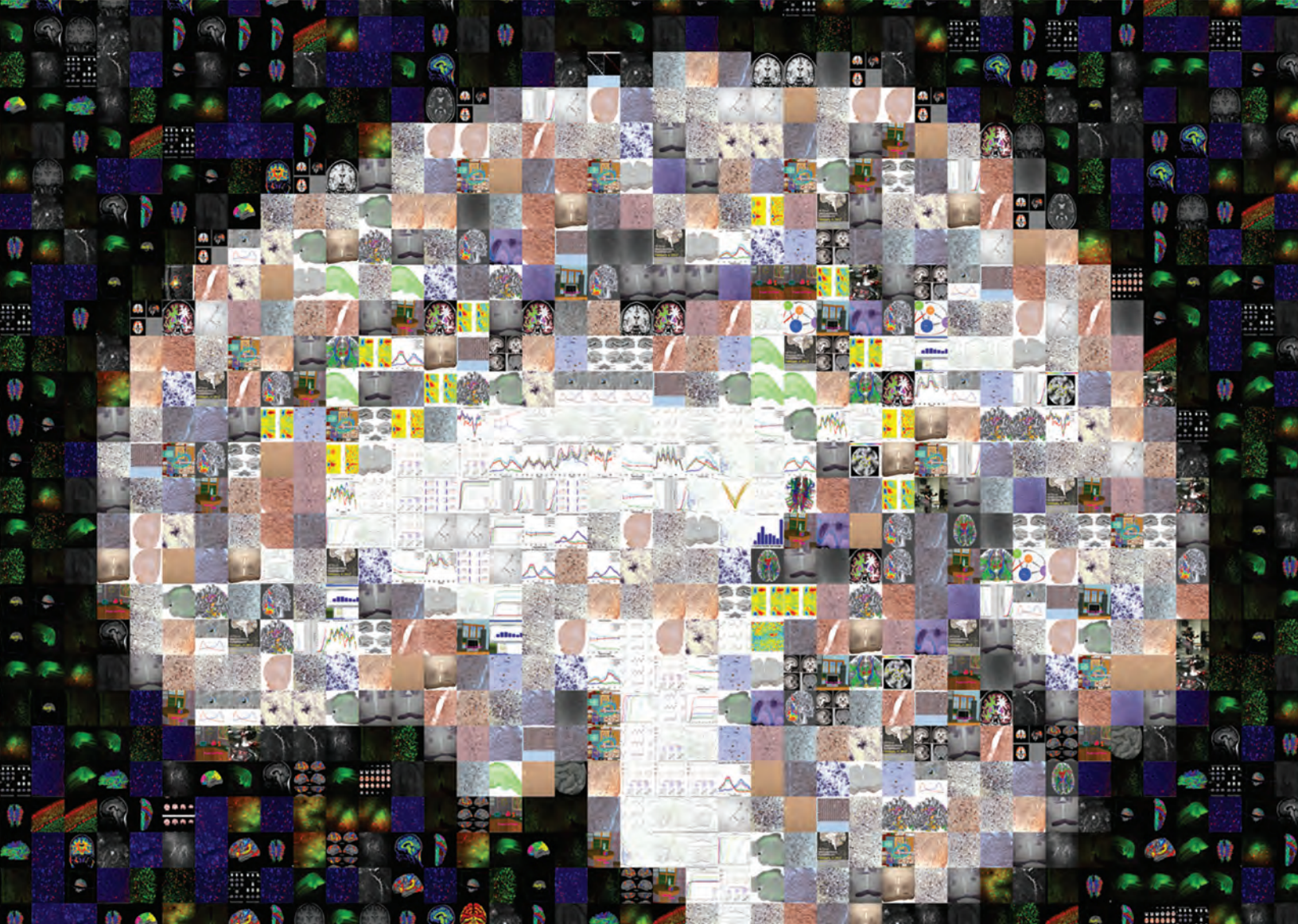




16th Annual Neuroscience Symposium February 4, 2012



THE UNIVERSITY UNIONS
STUDENT EVENTS CENTER
EVENTS COSPONSORSHIP
COMMITTEE

NGSA



UNIVERSITY CO-OP

The Institute for Neuroscience
The University of Texas at Austin
16th Annual Neuroscience Symposium

Mission Statement

Welcome to the 16th Annual Institute for Neuroscience Symposium!

Every year the graduate students in the Institute for Neuroscience organize this symposium with the goal of bringing together the scientific community within and beyond our university to share research in the exciting and rich field of neuroscience. This symposium offers students a unique opportunity to present their research in a familiar setting as well as foster a cohesive and collaborative environment. Our faculty and student lectures demonstrate the quality and breadth of ongoing research at the University of Texas at Austin. Each year we also invite a keynote speaker from outside our institution to share their work with our community. This year we are honored to welcome distinguished neuroscientist Dr. Joshua Gold from the University of Pennsylvania.

We hope you enjoy this year’s symposium and thank you for participating!

Akram Bakkour and Jacob Yates
Symposium Committee Chairs

Contents

Acknowledgements.....2

Schedule.....3

Keynote4

Faculty Speakers5

Student Speakers6

Poster Abstracts9

Symposium Committee Members:

Akram Bakkour
Jacob Yates
Keegan Hines
Bailey Kermath
Dean Kirson
Leor Katz
Nicholas Malecek
Kenneth Latimer
Seth Weisberg
Benjamin Scholl
Miriam Meister

Graduate Program Coordinator:

Krystal Phu

Web Design:

Jason Goltz

Faculty Supervisor:

Dr. Rick Aldrich

Director of the Institute:

Dr. Dan Johnston



NGSA

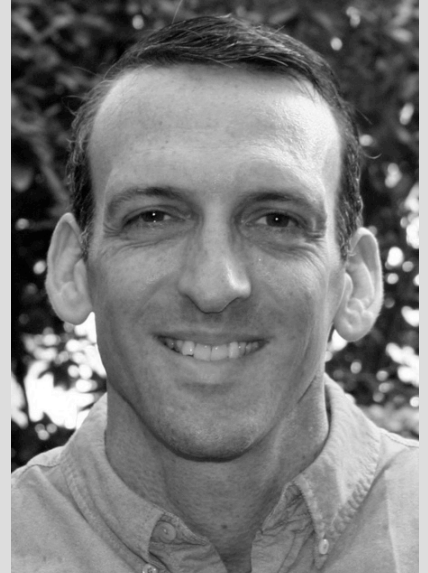


9:30 - 10:00	Breakfast/Registration (Poster presenters put up posters in Ballroom South SAC 2.410)
10:00 - 10:15	Opening Remarks Dan Johnston, Ph.D., Director of the Institute for Neuroscience
10:15 - 10:45	Deena Walker <i>Environmental endocrine disruptors and the brain: Fetal exposures cause lifelong molecular reprogramming of the hypothalamus</i>
10:45 - 11:15	Laura Colgin, Ph.D. <i>Slow and fast gamma rhythms in the hippocampus</i>
11:15 - 12:00	Joshua Gold, Ph.D. <i>Mechanisms of simple learning decisions</i>
12:00 - 1:00	Lunch
1:00 - 1:30	Ann Clemens <i>Age-dependent transformation of store depletion induced intrinsic plasticity in the hippocampus</i>
1:30 - 2:00	Jackson Liang <i>How do we represent the content of experienced events? Neural pattern analysis of the human medial temporal lobe</i>
2:00 - 3:15	Poster Session Ballroom South SAC 2.410
3:15 - 3:45	Brooks Robinson <i>Physiological ethanol dependence in drosophila larvae</i>
3:45 - 4:15	Miriam Meister <i>Decision signals in the parietal cortex</i>
4:15 - 4:45	Bharath Chandrasekaran, Ph.D. <i>How language and musical experience shape early sensory processing of speech</i>

Joshua Gold, Ph.D.

University of Pennsylvania

Dr. Josh Gold is currently an associate professor of neuroscience at the University of Pennsylvania. After completing his undergraduate studies at Brown University, Josh pursued graduate work at Stanford under the guidance of Eric Knudsen. He did post-doctoral research with Michael Shadlen at the University of Washington, Seattle. Josh has served in numerous editorial positions and has won many prestigious awards. Research in the Gold lab is focused on understanding the neural and computational basis of how we make decisions based on sensory stimuli. In particular, Dr. Gold utilizes multi-electrode recordings in awake, behaving monkeys to measure neural activity during perceptual decisions.



Mechanisms of learning simple decisions

Work in my laboratory addresses how the brain learns from experience to deal effectively with the different forms of uncertainty that confront a decision maker. We focus on reinforcement-learning models that describe how past experiences shape predictions used to inform future decisions. These models have typically been applied to value-based decisions in which the perceptual cues are unambiguous but their associated values are uncertain. We recently showed that these models can also account for learning on certain perceptual tasks in which the perceptual cues are uncertain but their associated values are not. In my talk I will describe new theoretical, behavioral, pupillometric, and neurophysiological studies from my laboratory that are beginning to show how the brain deals with yet another kind of uncertainty: the possibility of fundamental shifts in the environment that can render past experiences irrelevant to future decisions. This work represents a novel field of study that is likely to provide far-reaching insights into how individuals make effective decisions in a dynamic world.

Slow and fast gamma rhythms in the hippocampus

Gamma rhythms are seen throughout many regions of the brain. Their occurrence has been linked to functions such as sensory perception, attention, and memory. Gamma rhythm frequencies (~25-150 Hz) vary from one brain region to another and also within a given brain region from one moment to the next. In freely behaving rats, we recently discovered that gamma frequency variations have functional significance in the hippocampus, a brain region critically involved in memory operations. Slow gamma rhythms (~25-50 Hz) in hippocampal subregion CA1 correlate with neuronal activity in CA3, a neighboring hippocampal region necessary for memory retrieval. Fast gamma rhythms (~80-100 Hz) link CA1 to the entorhinal cortex, a region that transmits information to CA1 about current experiences. Slow and fast gamma rhythms do not tend to occur in CA1 at the same time and are correlated with significantly different behaviors. The principal neurons in CA1 are 'place cells', neurons that have spatial receptive fields or 'place fields'. Preliminary analyses suggest that, during slow gamma periods, place cells preferentially code upcoming spatial positions. These findings are in line with the idea that slow gamma rhythms promote recall of memories stored in CA3. During fast gamma rhythms, CA1 place cells code both current spatial location and the location that the animal has just experienced. These findings are consistent with the hypothesis that fast gamma rhythms facilitate encoding of new memories. We propose that the separation of different streams of information to CA1 using different gamma frequencies may help prevent memory retrieval from interfering with memory encoding.

Laura Colgin is currently an Assistant Professor of Neurobiology in the Center for Learning and Memory and the Institute for Neuroscience at the University of Texas at Austin. Her research investigates the effects of brain rhythms on neuronal activity during learning and memory processing. Dr. Colgin's work has been published in high-impact journals including *Nature*, *Neuron*, *Journal of Neuroscience*, and *Journal of Neurophysiology*. She recently received the Peter and Patricia Gruber International Research Award in Neuroscience and the Klingenstein Fellowship Award in the Neurosciences.

Bharath Chandrasekaran is currently an Assistant Professor at The University of Texas Austin and is associated with the Department of Communication Sciences and Disorders, Center for Perceptual Systems, and Institute for Neuroscience. He directs the SoundBrain Lab, which examines the sensory and cognitive processes that underlie speech and music perception. He pioneers the use of multimodal imaging methods—functional neuroimaging and EEG to examine the neural bases of speech perception and auditory learning. Dr. Chandrasekaran has published articles in several high-impact journals including *Nature Reviews Neuroscience*, *Neuron*, *Journal of Neuroscience*, *Journal of Cognitive Neuroscience*, and *Journal of Neurophysiology*. His research work has been featured in various print and television

How language and musical experience shape early sensory processing of speech

In humans, a significant challenge to learning a foreign language is to perceive non-native phonemes. Individual differences in phonetic learning ability have been thus far attributed to cortical circuitry. In this talk, I will discuss a series of studies using multimodal neuroimaging methods (brainstem electrophysiology and functional magnetic resonance imaging, fMRI) that show that sensory encoding in the inferior colliculus (IC), a midbrain structure, contributes significantly to individual differences in learning to use pitch patterns in lexical contexts. Our data reveal that the operational specifics of auditory learning thus cannot be understood by exclusively focusing on cortical circuitry.

Deena Walker

Deena Walker received her B.S. in molecular biology from the University of Texas at Austin in 2002. She began her research career as a cancer biologist investigating endocrine disrupting chemicals (EDCs) and their effects on numerous cancers of the reproductive system. In 2004, she shifted her focus to neuroscience when she began working in Dr. Andrea Gore's laboratory at UT-Austin studying how gestational exposure to EDCs affects the developing hypothalamus. Currently she is a Ph.D. candidate in Dr. Gore's laboratory. While her work focuses on several aspects of endocrine disruption, she is especially interested in epigenetic mechanisms underlying long-term changes in gene expression observed in the brain.

Environmental endocrine disruptors and the brain: Fetal exposures cause lifelong molecular reprogramming of the hypothalamus

Polychlorinated Biphenyls (PCBs) are industrial contaminants and a class of known endocrine disrupting chemicals. Exposure to PCBs during perinatal development results in long-term alterations in numerous reproductive endpoints in rodents such as altering the timing of puberty and reproductive senescence. However, little is known regarding the process by which these long-term alterations occur. We tested the hypothesis that early life exposure to Aroclor 1221 (A1221), a commercially available mixture of PCBs, results in long-term alterations to reproductive parameters and are associated with changes in gene expression in the hypothalamus. *Methods:* Pregnant Sprague Dawley rats were injected on embryonic day 16 and 18 with vehicle (DMSO; N=22) or A1221 (1mg/kg; N=23). Dams were allowed to give birth and developmental milestones such as the timing of puberty and estrous cyclicity were monitored in the pups throughout the life cycle. On postnatal days (P)15, 30, 45, 90 and ~270, 1 male and 1 female from each litter was euthanized. Brains and serum were frozen for mRNA expression and radioimmunoassays respectively. *Results:* There were developmental effects of prenatal EDCs, manifested as age-dependent alterations of gene expression, with effects most profound on P15 (males) and P45 (females). In females, perinatal A1221 exposure also resulted in altered estrous cyclicity in adulthood and in males the timing of puberty was delayed. *Conclusions:* These data suggest that gestational exposure to A1221 has long-term effects on development of the reproductive neuroendocrine system that are associated with altered phenotypes in adulthood.

Jackson Liang

Jackson Liang has a B.A. in Molecular and Cell Biology from the University of California, Berkeley. He is currently a 4th year Ph.D. student in the Institute for Neuroscience at UT Austin, and works in Dr. Alison Preston's lab to understand the function of the human medial temporal lobe.

How do we represent the content of experienced events? Neural pattern analysis of the human medial temporal lobe

The general role of the medial temporal lobe (MTL) in memory is well-established. However, the contributions of individual MTL subregions remains an important open question. Current theories focus on event content as an organizational principle that differentiates MTL subregional function. The perirhinal and parahippocampal cortices are hypothesized to play content-specific roles in memory, whereas hippocampal processing is alternately hypothesized to be content specific or content general. Despite anatomical evidence for content-specific MTL pathways, empirical data for content-based MTL subregional dissociations are mixed. Here, we employ high-resolution fMRI to characterize MTL subregional responses to different classes of novel event content (faces, scenes, spoken words, sounds, visual words). Univariate analyses revealed that responses to novel faces and scenes were distributed across the anterior-posterior axis of MTL cortex, with face responses distributed more anteriorly than scene responses. Moreover, multivariate pattern analyses of perirhinal and parahippocampal data revealed spatially organized representational codes for multiple content classes, including nonpreferred visual and auditory stimuli. In contrast, anterior hippocampal responses were content general, with less accurate overall pattern classification relative to MTL cortex. Finally, posterior hippocampal activation patterns consistently discriminated scenes more accurately than other forms of content. Collectively, our findings indicate differential contributions of MTL subregions to event representation via a distributed code along the anterior-posterior axis of MTL that depends on the nature of event content.

Ann Clemens

Ann is a native of Dallas, TX but found her way to Austin in 2000 to begin college at the University of Texas. During her undergraduate years she discovered the wonders of neurophysiology in a laboratory class taught by Dr. Nace Golding. Unable to escape her newfound fascination with channels and ions, she went on to conduct undergraduate research on heterologously expressed glycine receptors with Dr. John Mihic. After completing her bachelors degree in Neurobiology she decided that she wanted to broaden her research experience before entering grad school. She joined the post-baccalaureate research program at the National Institutes of Health in Bethesda, MD where she worked with Dr. Dax Hoffman on neurophysiology and imaging experiments related to the activity-dependent expression of the Kv4.2 potassium channel and its modulation by DPPX. Despite the many fruitful and eye-opening experiences she had during her brief east coast residence, Ann found it difficult to resist the magnetizing force emitted by the oasis that is Austin. In 2006, Ann returned to sunny skies, warm weather and the Institute for Neuroscience. She is presently a PhD candidate in the laboratory of Dr. Daniel Johnston where she continues to pursue her interest in the neurophysiological workings of the brain.

Age-dependent transformation of store depletion induced intrinsic plasticity in the hippocampus

Disruption of the calcium homeostasis within the endoplasmic reticulum is commonly associated with pathological conditions in the brain. One postulated neuroprotective mechanism to deal with ER calcium disruptions in the hippocampus is Store Depletion Induced (SDI) H-plasticity (Narayanan et al 2010). While the dorsal and ventral regions of the hippocampus are distinct in terms of their susceptibility to multiple neurological disorders, it is unknown whether these two regions are also subdivided in terms of cellular competence for dealing with insults such as calcium store depletion. In this study, we demonstrate that there is an age-dependent emergence of a dorso-ventral gradient in SDI H-plasticity. In young-adult animals, the hippocampus appears homogeneous in its levels of SDI H-plasticity. Into adulthood, SDI H-plasticity dwindles in the dorsal hippocampus while being maintained in the ventral hippocampus. This altered form of plasticity in the adult ventral hippocampus is blocked by the drug ZD7288, indicating that the observed change is also due to altered H-channel activity. We are currently testing whether the observed modification in SDI H-plasticity is due to changes in the somato-dendritic region of the plasticity. These results indicate a region-specific maturation of intrinsic plasticity mechanisms in response to internal calcium store disruptions. We suggest that this dorso-ventral gradient of plasticity may be related to differential susceptibilities to age related diseases in the dorsal and ventral hippocampus.

Brooks Robinson

Brooks is from Santa Fe, NM. He got his B.A. from Colorado College, graduating *cum laude* with distinction in neuroscience. He is currently in his fourth year of graduate school at The University of Texas and studies in the lab of Dr. Nigel Atkinson. Brooks is being funded by an institutional NRSA awarded through the Waggoner Center for Alcohol and Addiction Research. He is seeking to unlock the mysteries of alcohol dependence using the genetic model *Drosophila melanogaster*.

Physiological ethanol dependence in drosophila larvae

Chronic ethanol consumption can cause adaptive physiological responses that produce functional tolerance in the presence of ethanol and withdrawal symptoms when ethanol is withheld. We have developed a model of physiological ethanol dependence in the *Drosophila melanogaster* model system. We demonstrate that ethanol withdrawal negatively effects the performance of larvae in an associative learning assay. *Drosophila* larvae were reared on ethanol-containing food until the 3rd instar developmental stage. Some larvae were then removed from ethanol for a withdrawal period while others continued to consume ethanol. Larvae were then trained in a heat shock olfactory conditioning paradigm in which an aversive heat stimulus was paired with an attractive odorant. Reduced attraction to the odorant indicated that conditioning (learning) had occurred. Interestingly, larvae receiving the chronic ethanol treatment learned equally as well as larvae reared in the absence of ethanol. Conversely, a six-hour period of withdrawal from ethanol significantly reduced levels of learning. This reduction could be rescued by a one-hour reintroduction of ethanol. In short, we have shown that *Drosophila* larvae can adapt to chronic ethanol exposure to the point that performance in a learning paradigm suffers when ethanol is not present. With the unique and unusual genetic toolbox available in *Drosophila*, this model will be invaluable for unearthing the genetic underpinnings of ethanol dependence and withdrawal.

Miriam Meister

Miriam Meister received her B.A. in psychology from Haverford College and then completed several classes of post-baccalaureate work at the University of Pennsylvania while gainfully employed there as a laboratory technician in labs that studied the retina and olfaction. She began as a Ph.D. student at University of Texas at Austin in 2007 and soon joined the lab of Dr. Alex Huk, where she currently studies the electrophysiology of decision formation.

Decision signals in primate parietal cortex

Cells in primate parietal cortex, specifically in the lateral intraparietal area (LIP), are thought to represent the formation of a decision of where to move the eyes. Specifically, firing rate appears to literally be the accumulation of sensory evidence over time for the decision of whether to saccade to the cellular response field (RF). However, these cells are highly responsive to the presence of a visual stimulus in the cellular RF, and it is unknown whether visual stimulation of a cell's RF is necessary for cellular decision signals to be observed. Here, we tested whether decision signals are present despite the lack of visual stimulus in the cellular RF. Spiking activity of single LIP neurons was recorded from two rhesus macaque monkeys during an oft-used decision-making task (discriminating direction of motion in a noisy visual stimulus like TV snow). The monkey indicated his decision at the end of each trial with an eye movement to either the cellular RF or a location diametrically opposite. Trials from this conventional decision task (targets-ON control condition) were interleaved with trials where the choice targets were not present during the motion stimulus, but only flashed at the beginning of the trial (targets-FLASH condition) or, in a minority of experimental sessions, never shown (targets-NONE condition). These two latter conditions thus served to witness neural activity during decisions without visual stimulation in the RF by a choice target. The lack of visual stimuli in the RF systematically lowered the level of the population response by ~25%. Additionally and unexpectedly, we found that in all conditions but targets-NONE, population response was strongly dependent on motion strength, regardless of direction, in an inverse pattern (lowering most strongly firing rate for highest motion strength trials). This novel signal likely emerged in our experiments because, unlike past work, our targets appeared much closer in time to the onset of dot motion, implying further interactions between visual responses and decision signals. The presence of decision-irrelevant visual signals challenges the interpretation of LIP activity as level of accumulated evidence for a decision. Instead, neural responses may be more flexibly interpreted as carrying signals potentially relevant for behavior.

Searching for objects in a virtual apartment: the effect of experience on scene memory [1]

Leor Katz¹, Dmitry Kit², Brian Sullivan³, Kat Snyder³, Mary Hayhoe³

¹Institute for Neuroscience, ²Computer Science Dept.,

³Psychology Dept., Center for Perceptual Systems,
University of Texas

How do we form memories for real-world environments, and how do these memories influence gaze? Most investigations of memory for natural environments have used static 2D images usually involving multiple unrelated scenes. Natural experience, however, entails immersion in a limited number of 3D environments for extended periods of time. To investigate scene memory development in natural settings we recorded the sequences of saccades and body movements while observers searched for and touched a series of different objects in a 3-room virtual apartment, over 30-minute periods on two consecutive days. Subjects rapidly learnt the global layout of the apartment and restricted gaze to likely target locations such as counters. For objects designated as search targets on repeated occasions, both search time and number of fixations diminished gradually over repeated search episodes (by factors of 3 and 2, respectively). Thus, the binding of particular objects to particular locations is learnt fairly slowly, despite the presence of a constant context. Surprisingly, learning appeared to require active search. When an object first became a search target there was no measurable reduction in the amount of time or number of fixations required to locate it, even if it had been spontaneously fixated upon multiple times (~40) before. This lack of passive learning may be a consequence of the highly task-specific processing that occurs when engaged in search, which might suppress the encoding of task-irrelevant distracters. Thus, visual search in natural environments appears to be guided by memory representations that are dependent upon attentional constraints.

Expectations about memory items modulate the parietal old/new effect in ERPs [2]

Emily E. Knight¹, Ian G. Dobbins², Logan T. Trujillo¹, Antonio Jaeger², David M. Schnyer¹

¹UT Austin, ²Washington University in St Louis

Considerable human memory research has focused on finding a reliable neural correlate of the recollective experience. Previous investigations have revealed a parietal “old/new effect” - old items previously presented at study elicit larger amplitude signals in the electrophysiological event-related potential (ERP) or greater activation in functional magnetic resonance imaging (fMRI) relative to new items. Explanations for this effect have repeatedly cited its apparent indexing of recollective processes; it has been found to scale with experimental manipulations of encoding and source memory. However, significant evidence from the attention and perception literature indicates that specific parietal regions respond to perceptual response conflict and stimulus probability, and as a result, Cabeza and Moscovitch (2008) reason that it is likely parietal memory processing contains both top-down monitoring and bottom-up orienting elements. Through the use of ERPs, we sought to confirm the results of a recent fMRI study (O'Connor et al 2010) which found that some parietal areas were sensitive to expectations about the memory status of an item as well as the episodic content related to that item. Examining a late ERP component from 400-600ms representing the traditional “old/new” effect, we found an interaction between the ERP response to the status of a target in memory and the ERP response to prior expectations about that target. This finding suggests that the ERP “old/new” effect may not be a pure neural correlate of episodic recollection, but rather reflects cognitive control/monitoring as well as recollective processing.

Boosting skill learning by hypnosis [3]

Bertalan Polner, Karolina Janacsek, Zoltan Ambrus Kovacs, Dezso Nemeth

Institute of Psychology, University of Szeged, Hungary

Human learning and memory depend on multiple cognitive systems related to dissociable brain structures. These systems interact not only in cooperative but sometimes competitive ways in optimizing performance. It has been previously demonstrated that functional brain connectivity is reduced in hypnosis, and this is especially typical for frontal areas. We compared learning in hypnosis and in the alert state and found that hypnosis boosted basal ganglia-dependent sequence learning. This result implies that disconnecting competitive brain systems can improve human learning and memory performance.

Keywords: memory systems, hypnosis, sequence learning, functional connectivity, prefrontal cortex, striatum

**Belief-directed Exploration in Human Decision-Makers:
Behavioral and Physiological Evidence [4]**

**A. Ross Otto, W. Bradley Knox, Tyler H. Davis, Arthur B.
Markman, Bradley C. Love**
University of Texas at Austin

Decision-making in uncertain environments poses a conflict between the goals of exploiting past knowledge in order to maximize rewards and exploring less-known options in order to gather information. This work presents an Ideal Actor model that prescribes an optimal incremental belief-update procedure and payoffs-maximizing pattern of choice in a simple decision-making task. By comparing human choice dynamics to those prescribed by the Ideal Actor, we evaluate the notion that people explore in a reflective, belief-directed fashion rather than according to a reflexive and stochastic account. Further, we examine how decision-makers' beliefs are indexed by anticipatory autonomic arousal (measured using skin conductance) and choice reaction times, suggesting that people engage in a belief-directed choice process similar to that prescribed by the Ideal Actor and that choice latencies and arousal register these beliefs. Additionally, I show that manipulating concurrent working memory load provides clear evidence for the involvement of central executive resources in carrying out belief-directed as opposed to naïve exploratory choice strategies.

**Study-test representational similarity within hippocampus
demonstrates reactivation of integrated representations
during novel inference [5]**

**Margaret L. Schlichting^{1,3}, Dagmar Zeithamova^{1,4}, Alison R.
Preston¹⁻⁴**

*¹University of Texas at Austin, ²Center for Learning and Memory
³Department of Psychology and ⁴Institute for Neuroscience*

The ability to infer relationships among discrete events may rely on retrieval-based processes, wherein elements from individual memories are retrieved and flexibly recombined in novel situations. However, flexible memory expression may also rely on hippocampal encoding processes that integrate information across events during learning, thereby eliminating the need for recombination at retrieval. Using high-resolution fMRI and representational similarity analysis, the present study tested these alternative accounts of mnemonic flexibility. Participants learned overlapping associations (AB and BC) and were then tested on inferential relationships about the two events (AC). Retrieval-based recombination predicts that representations retrieved at test would be similar to representations of both AB and BC during learning, as both must be accessed and recombined at test. Integrative encoding, however, suggests that successful inference results from direct expression of relational knowledge formed by binding new events with existing memories. Thus, the representation retrieved during novel AC inference would be more similar to overlapping BC pairs than to initially encoded AB pairs, as new information about BC is encoded in the context of AB. We compared neural patterns evoked during AC inference with patterns elicited during learning in hippocampus. Within CA1, RS between BC encoding and AC inference during test predicted successful inferential performance. However, CA1 RS between initially learned AB pairs and AC test responses did not predict performance. These results suggest that representations formed through CA1 integrative encoding processes are retrieved at test to support novel inferences about relationships among discrete events.

**Representational connectivity analysis between regions of the reward-based decision-making network [6]
Tom Schonberg¹, Jeanette A. Mumford², Akram Bakkour¹, Emily Barkley-Levenson³, Russell A. Poldrack^{1,2,4}**

¹Imaging Research Center, University of Texas at Austin, ²Department of Psychology, University of Texas at Austin, ³Department of Psychology, University of California, Los Angeles, CA ⁴Section of Neurobiology, University of Texas at Austin

Animal and human studies alike have implicated a network of brain regions involved in reward-based decision-making (DM). In the current study we used representational connectivity analysis to describe the similarity patterns between regions of this network. We used the results of a previous fMRI study with a mixed gambles DM task (Tom et al., 2007, sample S1, 16 subjects) to create 8 masks of distinct regions of interest (ROIs) involved in reward-based DM. We reanalyzed the individual trials of the task and extracted individual beta parameters (Rissman et al., 2004) for each trial for each of the voxels in each of the 8 ROIs. We followed the representational similarity analysis (RSA) scheme proposed by Kriegeskorte et al. (2008) and computed representational dissimilarity matrices (RDMs) within each of the regions. We performed a representational connectivity analysis and used a permutation test to determine the significance of the group averaged connectivity matrices. The correlation between the vmPFC and striatum ($r=0.36$, $p<0.002$) was significant. We applied the same ROI masks on an independent sample (S2). In S2 significant connectivity was found between the striatum and vmPFC ($r=0.33$, $p<0.0005$) and also between other frontal regions (r 's 0.18-0.21, $p<0.01$). We found highly similar results in the representational connectivity matrices between the 2 studies (r (S1-S2)= 0.96); alluding to the robustness and consistency of this analysis. Interestingly this pattern of results was consistent with the results of a probabilistic white matter connectivity analysis performed on 21 subjects of S2.

The relationship between sleep-wake cycles and associative memory performance in young adults. [7]

Stephanie M. Sherman and David M. Schnyer
University of Texas at Austin, Psychology Department

Previous research suggests that there is a relationship between sleep and episodic learning. The purpose of the current study is to investigate the relationship between aspects of the sleep-wake cycle and associative memory performance. College-aged adults were asked to wear an actigraph continuously for 3 weeks. Actigraphs are small, motion sensitive devices that record objective measures of sleep-wake patterns under normal environmental conditions. Following the 3-week session, participants returned to the laboratory and completed a word-pair associates task to obtain a measure of associative memory performance. Data from the actigraphs were used to calculate standard sleep measures (i.e. total sleep time, sleep onset latency, and sleep efficiency) and three non-parametric circadian rhythm variables including *intradaily variability* (the extent to which the sleep-wake cycle is fragmented), *interdaily stability* (the stability of the rhythm from one day to the next) and the *amplitude of the rhythm* (difference between the least and most active hours). We hypothesized that lower performance on memory tasks would be associated with more variable sleep-wake patterns. The results were in line with our predictions suggesting that memory performance was related to the variability in the sleep-wake cycle. We found a negative relationship between interdaily stability and false alarm rate ($r = -.43$, $p = .013$), meaning that the less consistent the sleep-wake cycle, the higher the false alarm rate. We conclude that poorer associative memory performance is related to more fragmentation in circadian rhythm patterns.

Individual differences in reward-based modulation of memory are reflected in hippocampal subregional engagement both prior to and during episodic encoding [9]

Sasha M. Wolosin^{1,2}, Dagmar Zeithamova¹⁻³ and Alison R. Preston¹⁻³

¹Center for Learning and Memory, ²Department of Psychology, and ³Institute for Neuroscience, The University of Texas at Austin, Austin, TX

Emerging evidence suggests that medial temporal lobe (MTL) memory processing is modulated by reward, resulting in enhanced encoding of episodic information, long-term memory for events. Recent neuroimaging research has further revealed activation in hippocampus prior to stimulus presentation that predicts later memory performance, suggesting that modulatory processes such as reward may influence encoding processes in anticipation of upcoming events. Using high-resolution functional magnetic resonance imaging (fMRI), the present study examines (1) how cues indicating future rewards influence MTL subregional activation prior to associative encoding and (2) how individual differences in reward sensitivity are reflected in MTL subregional activation. A high-value or low-value monetary cue preceded a pair of objects indicating potential reward for successful retrieval of the association. Memory was tested using a two-alternative forced-choice paradigm. Behaviorally, memory was superior for high-value associations relative to low-value associations. fMRI analysis revealed anticipatory responses within the MTL that were modulated by reward, with greater activation for high-value compared to low-value cues. Reward-sensitive dentate gyrus/CA_{2,3} and subiculum regions additionally showed activation during stimulus encoding that predicted subsequent memory for high-value, but not low-value associations, suggesting that the anticipatory engagement of these regions impacts successful memory formation for high-value events. Finally, the degree of reward modulation in midbrain predicted reward modulation of subsequent memory effects in anterior regions of the MTL. These findings suggest that reward-based motivation influences memory by facilitating hippocampal processing both prior to and during stimulus encoding.

Perceptual Criteria in the Human Brain [8]

Corey N. White, Jeanette A. Mumford, Russell A. Poldrack
University of Texas at Austin, Departments of Psychology and Neurobiology, Imaging Research Center

Perceptual decision making is thought to involve the accumulation of evidence toward boundaries representing the possible choices. We employed cognitive modeling and functional magnetic resonance imaging to explore this process with emphasis on the perceptual criterion that is used to transform perceptual information into decision evidence. Participants performed perceptual discrimination tasks in the scanner in which two types of stimuli, lines or patches of dots, were identified as large or small. The size of the stimulus criterion (midpoint) was manipulated between blocks. The data were modeled with a drift-diffusion model and the parameters were used to create modulated regressors corresponding to decision evidence, difficulty, and the size of the decision rule. Distinct regions of cortex were identified that corresponded to the stimulus size, decision rule size, decision evidence, and motor response. Stimulus processing was associated with activation in occipital cortex whereas criteria processing was reflected in inferior temporal cortex. These values were combined to form the decision through processing in a front-parietal network of neural systems. The results provide insight into the neural systems involved in transforming perceptual information into decision-related action.

Fluctuations in attractor networks [10]

Michael A. Buice and Ila Fiete

UT-Austin, Center for Learning and Memory

Noise correlations, which can provide information about functional connectivity between neurons and significantly alter estimates of the information carried in neural populations, are of burgeoning interest in neuroscience with the advent of simultaneous in-vivo recordings from multiple neurons. However, the theory of fluctuations in neural networks has not kept pace. We present a theory of fluctuations in general, non-linear recurrent neural networks of Poisson neurons with rates given by their time-varying synaptic inputs. The theory uses a path integral approach, enabling a systematic and analytic evaluation of fluctuation effects beyond mean field. For concreteness and comparison with existing work, we consider (continuous) attractor networks. The path integral mean-field theory gives the standard rate-based result for a given network, while allowing us to compute noise correlations as a function of connectivity, the feedback of fluctuations on the firing rates, the loss of persistence through diffusion, and the effects of input correlations on the network. We illustrate these results in a simple 1-dimensional ring-attractor network that underlies models of visual orientation tuning. Finally, our results are instrumental for accurately estimating the Fisher Information in population codes, because they specify the actual correlations that will be present in network models of population tuning. We show that, surprisingly, although neural correlations grow vanishingly small in increasingly large networks, their contribution to Fisher Information remains finite. We also show that this effect cannot exist in the corresponding Mutual Information, and thus contribute to growing evidence that Fisher Information is a flawed proxy for information.

Electrical coupling of inferior olive neurons: A mechanism of cerebellar homeostasis [12]

Michael D. Mauk

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

Inferior olive (IO) neurons provide the teaching input to the cerebellum. IO neurons are electrically coupled. Mice absent this coupling display cerebellar ataxia and yet it is not known how this electrical coupling between IO neurons contributes to the computational properties of the cerebellum. Current theories each fail to provide computational insight and each are contradicted by experimental data. Based on results from large-scale simulations, I propose that electrical coupling of IO neurons provides a necessary form of homeostasis for the cerebellum. Previous work has identified a system-level homeostasis in the olivo-cerebellar system: IO neurons induce long-term depression at synapses onto Purkinje cells, Purkinje cells inhibit cerebellar deep nucleus cells, and these deep nucleus neurons inhibit IO neurons. This negative feedback enforces a specific level of spontaneous activity in IO neurons that prevents spontaneous drift of the strength of synapses onto Purkinje cells. The connectivity of this pathway, however, ensures that each IO neuron is influenced by Purkinje cells (via deep nucleus cells) that the IO neuron does not influence. Simulation results show that this incomplete closure in connectivity means that the systems-level equilibrium can only enforce an average level of activity for all IO neurons. Over long periods of time individual IO neurons diverge from this average, which causes spontaneous drift in the strengths of synapses onto Purkinje cells and “ataxic” behavior in the simulation. I show that adding electrical coupling between IO neurons acts to prevent this drift and maintain proper long-term equilibrium in the cerebellum.

Modeling simple decisions in the parietal lobe with hidden Markov Models [11]

Kenneth Latimer, Jacob Yates and Jonathan Pillow

Institute for Neuroscience, University of Texas at Austin

Neurons in the lateral intraparietal sulcus (LIP) are thought to encode perceptual decisions involved in the planning of eye movements. LIP neurons are studied with extracellular recordings from single neurons while a monkey performs a perceptual decision task. Traditionally, the neural computations underlying LIP activity have been examined by comparing the responses of single cells averaged across multiple trials. Several models have been proposed to explain how these decisions are represented by single neurons. However, average firing rate analysis offers only indirect metrics of distinguishing between these models and cannot reveal how the decision occurs on a single trial. We modeled the monkey’s decision as a hidden state linked to a spike generation process using Markov Chain Monte Carlo (MCMC) methods to estimate how the decision state evolved through each trial. In particular, we compared a discrete decision state model with a drift-diffusion process. These decision processes are vastly different over the course of a single trial, but result in identical average firing rates. We not only demonstrate the feasibility of using MCMC methods to compare existing models of decision-making without relying on indirect statistical metrics, but also extend this framework to fit a single decision state to multi-neuron recordings.

Stochastic encoding model of LIP spike trains and decoding choices [13]

I. Memming Park, Miriam L. Meister, Alex C. Huk and Jonathan W. Pillow

The University of Texas at Austin

A central problem in systems neuroscience is to decipher the neural mechanisms underlying sensory-motor decision-making. The lateral intraparietal area of parietal cortex (LIP) forms a primary component of neural decision-making circuitry, but its exact role in choice behavior is hotly debated. Here we describe an analysis of the neural code in LIP using advanced statistical methods for modeling the detailed structure of neural spike trains. We obtained single-neuron recordings from LIP in monkeys engaged in a 2AFC motion discrimination task. Variability in the task and behavior allowed us to disentangle the relationship between various extrinsic variables and neural responses. First, we fit each neuron with a stochastic encoding model, which describes the time-varying firing rate as a function of the external task and decision variables, and recent spike-history. The model allowed us to quantify the relative influence of sensory, motor, and reward variables on the response, and to generate spike train predictions on single trials. We found these predictions to be surprisingly accurate, revealing more precise time structure than the averaged response (PSTH), and capturing non-Poisson variability that varied substantially across neurons. Second, we used the model to perform decoding choices from the LIP responses on single trials. This allowed us to quantify the information carried about choice, and to compare the performance of various hypothesized LIP coding schemes. Third, we analyzed the optimal decoding weights of a diverse population, and found a common low dimensional temporal basis. We further analyzed the population decoding performance under the independence.

Spike time-dependent synaptic plasticity can organize a recurrent network to generate grid cell responses

John Widloski and Ila Fiete [15]

UT Austin, Center for Learning and Memory

We describe a biologically plausible model for the development of a network that, after learning, reproduces the spatially periodic patterns of activity characteristic of grid cells. Further, the formed network can integrate velocity input to estimate animal location. The formed network displays the low-dimensional continuous attractor (CA) dynamics of models that successfully predict many features of the grid cell response. Our model uses a spike-time-dependent plasticity (STDP) rule with both symmetric and asymmetric components, applied to an initially unstructured network of spiking neurons that receive different velocity inputs and also randomly receive spatially local place cell-like inputs. The symmetric STDP term causes neurons firing at short time-lags to become recurrently connected, and those firing at intermediate time-lags to become negatively coupled. If the neurons are rearranged topographically according to their place inputs, this connectivity produces grid-like patterns on the neural sheet. The antisymmetric STDP term enhances connectivity in the movement directions of a simulated trajectory, causing slight asymmetries in the network weights based on both the location and velocity tuning of the cells. These asymmetries cause velocity inputs to drive movement of the network activity pattern in proportion to animal velocity, enabling path integration. The simplicity and plausibility of the developmental model should lay to rest critiques about the complexity of wiring in grid cell CA models. The model explains why the network need not be topographic, and generates predictions about inputs to and maturation of responses in the grid cell network during development.

Phase precession through intrinsic neural resonance in continuous attractor models of grid cells [14]

Sean Trettel and Ila Fiete

Center for learning and memory, University of Texas at Austin

With one notable exception, the features of grid cells are remarkably well-modeled by recurrent network models (called continuous attractor or CA models) whose weights stabilize a restricted set of patterns in the neural population. The exception is a feature ubiquitous in layer II entorhinal grid cells: phase precession. As an animal moves through a grid cell's activity field, the neuron's spikes precess, or are emitted at progressively earlier phases of the oscillating local field potential (LFP).

We show here that if a simple model of the resonant properties of layer II entorhinal neurons is included in CA network neurons, with appropriate phase coupling, the resulting grid cells will phase precess. We consider a 1-dimensional CA grid cell model network with center-surround connectivity in which the neurons are intrinsic oscillators, with frequency f_0 Hz. Neural spiking leads to perturbations in the phase of synaptic target neurons based on the phase difference between neurons and the sign of their interaction (excitatory or inhibitory). As the animal moves through a chain of grid fields, the phases of cells along this chain are progressively retarded, resulting in an LFP with lower frequency, $f_0 - \delta$, in addition to phase precession.

The model predicts that phase precession depends on location rather than time spent in the response field, unlike models based on cellular processes with fixed time-constants. Further, the model makes testable predictions about how the precession rate varies with peak neural firing rates and animal velocity.

Optimal tuning curve widths for multi-periodic neural population codes [16]

Yongseok Yoo and Ila R. Fiete

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

Motivated by the unusual response properties of grid cells, here we analyze the mutual information between a stimulus and a neural population code consisting of periodic responses with multiple periods. The grid population code (GPC) has recently been shown to have remarkable intrinsic error-correcting properties, and thus to define a new class of neural population codes called exponentially-strong population codes (EPCs). Unlike classical population codes (CPCs), strong error-correcting codes exhibit an interesting nonlinearity: below a threshold noise, they are able to nearly exactly correct errors, but above a threshold, they tend to fail catastrophically. In the neural context, this threshold depends on tuning curve width. We show that unlike CPCs, the GPC has a finite optimal tuning curve width with respect to mutual information, regardless of the dimensionality of the coded variable. The multi-periodic nature of the GPC counters the pressure found in CPCs against broadening tuning curve widths in 1-2 dimensions: narrow tuning curves increase the probability that small noise will produce a large error in the decoded estimate. Thus, broader tuning curves increase the probability of remaining in the strong error-correction regime with larger noise, albeit at the cost of some resolution loss at low noise. Our results predict that the optimal tuning curve width should be similar to the size of the expected errors per grid network. We discuss this prediction in the context of the wide tuning curves found in neural recordings.

Are grid-cell responses very low-dimensional? [17] **KiJung Yoon¹, Caswell Barry^{2,3}, Michael Buice¹, Neil Burgess^{2,4}, Ila Fiete¹**

¹Center for Learning and Memory, The University of Texas at Austin, Austin, TX;

²UCL Institute of Cognitive Neuroscience, London, United Kingdom; ³UCL Institute of Behavioural Neuroscience, London, United Kingdom; ⁴UCL Institute of Neurology, London, United Kingdom

What mechanisms could underlie grid cell activity in rodents is the subject of debate, with different models positing starkly divergent neural architectures and dynamics. One model class is based on the conversion of cellular temporal oscillations into spatially periodic responses, while another is based on strong lateral network connectivity that leads to low-dimensional periodic pattern formation in the neural population. Despite these differences, current analyses of experimental data have not ruled out either model.

We examine spikes from multiple simultaneously recorded grid cells, with the aim of elucidating the dynamics underlying grid cell activity. We demonstrate evidence of a 2-dimensional continuous attractor in the response of grid cells to animal location. The responses of grid cells with similar spatial period are identical, differing from each other along only 2-dimensions of their response, through translations of their preferred spatial phases. The *relationships* between grid cell responses, their relative spatial phases, remain absolutely stable over time, even if the responses themselves do not. Relative phases remain absolutely stable when the grids are significantly deformed by anisotropic stretching in response to a rapid resizing of the environment, as well as when the grids uniformly expand in novel environments. The stabilization of relative phase during dramatic changes in single-cell responses cannot be ascribed to input from external cues or from the hippocampus, because we ascertain that relative phases are stable even when these inputs are not. The findings together provide unequivocal support for the hypothesis that the brain computes using low-dimensional continuous attractors.

Thalamocortical Dynamics of Spontaneous and Stimulus-evoked Activity in the Rat Visual System [18]

Sari Andoni and Nicholas J. Priebe

Section of Neurobiology, Institute for Neuroscience and Center for Perceptual Systems

Spontaneous activity in the visual cortex of rodents is usually characterized by slow oscillations featuring membrane depolarizations (up-states) separated by silent hyperpolarized periods (down-states). These oscillations are typically found during slow-wave sleep, anesthesia, as well as behavioral quiescence in awake animals. Here we investigated the role of the lateral geniculate nucleus (LGN) in the thalamus in affecting cortical states and how these spontaneous states interact with visual stimulation. We performed *in vivo* whole-cell recordings in the primary visual cortex (V1) of urethane-anesthetized rats, paired with local field potential (LFP) and multi-unit (MU) recordings both in V1 and LGN. Spontaneous activity in LGN and V1 showed strong coherence at low frequencies below 5 Hz. However, our analysis suggests that the thalamus might be involved in triggering cortical up-states but not necessarily down-states during spontaneous activity. While visual stimulation with brief flashes triggered a transition from the down- to up-state in most neurons, surprisingly, a visual stimulus also triggered a transition from the up- to down-state with a high probability. Similarly, we were able to trigger cortical state transitions in both directions by electrically stimulating LGN. Our results suggest a strong role for the thalamus in modulating spontaneous activity in the cortex, and they also indicate that stimulus encoding strongly depends on thalamocortical state.

Phase Change in the Cortical Field Potential Marks the Onset of Epileptiform Activity [19]

D. Benites^{*2}, R. J. Buchanan^{1,2}, J. Shen^{1,3}, M. R. Lee¹, D. L. Nelson¹, D. F. Clarke^{3,4}, Z. Nadasdy^{1,2}

¹Seton Brain and Spine Inst., Univ. Med. Ctr. At Brackenridge, Austin, TX; ²Dept. of Psychology, Univ. of Texas at Austin, Austin, TX; ³UT Southwestern, Austin, TX; ⁴Dell Children's Comprehensive Epilepsy Program, Seton Family of Hosp., Austin, TX

Large amplitude high frequency hypersynchronous activity is a hallmark of epileptiform EEG. In practice, combined ECoG and depth electrode recordings are applied for seizure localization where channels of hypersynchronous activity point to the origin of seizures in the brain. We hypothesized that the times when the hypersynchronous activity starts to depart from the ongoing normal EEG are predictive of ictal/interictal seizures. We developed a new method to detect and analyze phase transitions between ECoG channels and correlate these phase transitions with seizure episodes. We first filtered the EEG at gamma and theta frequency bands and detected seizure episodes based on the EEG spectrum. We then quantified inter-channel phase transitions by: computing continuous phase differences between electrodes pairs, extracting time points of phase reversals on the first derivative of phase differences in 500 ms bins, averaging the number of phase reversals over channel pairs, identifying the time point corresponding to the major phase transition around the time of seizure onset or interictal spike, and defining the statistics of phase transitions relative to seizure events. The algorithm was validated on surrogate data sets. Our preliminary results suggest that phase transitions most likely occur 100-300 ms before seizure onset and 100-300 ms after seizure offset, which implies a phase decoupling and re-coupling between seizure-related pathological oscillations and normal oscillations. We propose to utilize the early phase decoupling as a trigger to start closed-loop deep brain stimulation as a prospective technique for therapeutic seizure control.

Intravenous Isotonic and Hypotonic Ethanol Increases Dopamine in the Medial Prefrontal Cortex of the Long Evans Rat [21]

Dilly, G.A., Schier, C.J., Lee S., Gonzales, R.A.

University of Texas, Department of Pharmacology and Toxicology

The prefrontal cortex is a component of the mesocorticolimbic dopaminergic system. Dopamine transmission in this system is believed to mediate reward and motivational behavior involved in the consumption of ethanol. In this study, microdialysis was used to examine dopamine release in the medial prefrontal cortex of Long-Evans rats during the acute intravenous administration of ethanol. A rapid bolus infusion (~2.7ml/min) of 1.0g/kg ethanol produced a significant $55 \pm 9\%$ increase in dialysate dopamine relative to basal levels. A slow 1.0 g/kg infusion experiment (~0.6ml/min) was also performed to eliminate confounding factors associated with the rapid iv infusion. The slow infusion of ethanol resulted in a significant $63 \pm 15\%$ increase in dialysate dopamine, suggesting that pharmacological rather than physiological factors associated with the method of drug administration caused the post-infusion dopamine increase. An additional experiment was performed in which four infusions of ethanol were administered sequentially, resulting in cumulative doses of 0.25, 0.75, 1.5, and 2.25g/kg. A non-significant $17 \pm 5\%$ increase resulted from the 0.25g/kg infusion, and significant $36 \pm 15\%$, $68 \pm 19\%$ and $86 \pm 20\%$ increases resulted from each respective dose. Hypotonic and isotonic salt concentrations were used in each ethanol infusion experiment, and no significant difference was found. Additionally, all ethanol infusions were paired with saline controls, none of which significantly increased dopamine. These results show that iv ethanol administration results in a dose-dependent increase in dopamine in the medial prefrontal cortex of the Long-Evans rat.

Modeling habitual alcohol-seeking in rats [20]

Roberto U. Cofresí¹, Regina A. Mangieri², and Rueben A. Gonzales²

¹College of Natural Sciences, Department of Chemistry and Biochemistry, ²College of Pharmacy, Division of Pharmacology and Toxicology, the University of Texas at Austin

While commonly described as a "bad habit," whether and under which conditions alcohol-seeking may be driven predominantly by learned stimulus-response, as opposed to action-outcome, associations has remained largely unexplored. The extent to which an instrumental behavior is "habitual," i.e., driven by the former, is gauged by its *insensitivity* to outcome devaluation. It was predicted that seeking behavior by rats trained to self-administer an ethanol-containing reinforcer under a variable interval (VI), but not variable ratio (VR), schedule of reinforcement would be *insensitive* to devaluation, and that seeking behavior by sucrose-administering VI trained rats would be sensitive to reinforcer devaluation. Male Long-Evans rats were trained in MedAssociates operant chambers to lever press for 10 sec access to a 10% sucrose (10S) drinking solution. After 2-3 daily 20-min sessions with 10S, ethanol-administering groups received 10% ethanol/10% sucrose (10S10E) reinforcement under either a VI or VR schedule for ≥ 20 or ≤ 9 sessions (extended and limited training cohorts, respectively). Sucrose groups received equivalent duration VI training with 10S. Outcomes were devalued via a single pairing with lithium chloride-induced malaise. Sensitivity of lever pressing to outcome devaluation was tested in an 8 min extinction session 24 hr later. A reacquisition session 24 hr thereafter confirmed successful devaluation. After extended training, seeking behavior was insensitive to outcome devaluation across groups. However, after limited training, *only* 10S10E VI seeking behavior was insensitive to outcome devaluation, suggesting that either over-training or variable interval schedules of reinforcement may be capable of producing "habitual" alcohol-seeking in rats.

A Model for Bone Repair in Mammals and the Potential Role of Hh Signaling [22]

J.L.Fogel, M. Srour, K. Yamaguchi and F. Mariani

Broad Center for Regenerative Medicine and Stem Cell Research, Keck School of Medicine, University of Southern California

The regeneration of whole skeletal elements is a feature typical of some amphibians. In humans and other mammals, repair is very limited although there are reported cases of digit tip and rib regeneration. In order to better understand how skeletal repair can be enhanced in mammals, our lab has established a model for rib repair in the mouse. We have found that when a large portion of the rib is removed, new cartilage and/or bone forms as nodules which appear to join together over time. We are currently studying this repair in greater detail to determine if the endochondral process is recapitulated and to determine the role of the surrounding periosteum.

In addition, we are taking advantage of the genetic tools and strains available in the mouse to understand the molecular control of bone repair in this system. Furthermore, our studies on development during embryogenesis confirm that *Shh* is expressed in the developing rib and that Shh signaling is required for rib patterning. Since, the molecular and cellular events that drive embryogenesis are often found to reoccur during regeneration and healing in the adult organism we suggest that Hh signaling will be important for rib repair. We are therefore stimulating or blocking Hh signaling using several approaches (small molecules, genetically modified mouse strains) during rib repair. Our hope is that these studies will lead to not only to an increased understanding of bone repair but also to clinical treatments of severe skeletal injury.

NFIA inhibits oligodendrocyte differentiation during development and white matter injury [23]

Stacey Glasgow ^{2,5}, Stephen P. J. Fancy ^{1,5}, Meggie Finley ², David H. Rowitch ^{1,3}, and Benjamin Deneen ^{2,4}

¹ *Departments of Pediatrics and Neurosurgery, Eli and Edythe Broad Institute for Stem Cell Research and Regeneration Medicine and Howard Hughes Medical Institute, University of California, San Francisco, California, USA.*

² *Center for Cell and Gene Therapy, Baylor College of Medicine, One Baylor Plaza, Houston, Texas 77030, USA*

³ *Division of Neonatology, University of California, San Francisco, California, USA*

⁴ *Department of Neuroscience, Baylor College of Medicine, One Baylor Plaza, Houston, Texas 77030, USA*

⁵ *Equal Contribution*

Chronic demyelination can result in axonopathy and is associated with human neurological conditions such as multiple sclerosis (MS) in adults and cerebral palsy in infants. In these disorders myelin regeneration is inhibited by impaired differentiation of oligodendrocyte progenitors (OLPs) into myelin-producing oligodendrocytes (OLs). However, regulatory factors relevant in human myelin disorders and in myelin regeneration remain poorly understood. Here we report that the transcription factor Nuclear Factor I-A (NFIA) is expressed in OLPs, but not differentiated OLs. Functional studies reveal *NFIA* is necessary and sufficient to suppresses OLP differentiation, and suggest this occurs through direct repression of myelin genes. Furthermore, *NFIA* expression and function is recapitulated during remyelination. Examination of *NFIA* expression in white matter lesions of human newborns with neonatal hypoxic-ischemic encephalopathy (HIE), as well as in active MS lesions in adults revealed that it is similarly expressed in OLPs. These observations, coupled with our functional studies, suggest that *NFIA* participates in the inhibition of remyelination in these disorders.

Molecular Profiles and Evolution of Dopaminergic Cell Populations in the Vertebrate Brain [24]

Miles R. Fontenot, Lauren A. O'Connell, Hans A. Hofmann

Section of Integrative Biology, Institute for Neuroscience, UT Austin

The mesolimbic reward system encodes stimulus salience, which provides the basis for adaptive decision-making. Numerous mental disorders, such as drug addiction and depression, are commonly associated with a dysfunction of this system, and dopamine is generally considered the neurotransmitter most relevant to its function. Although brain regions in the dopaminergic reward system have been well characterized in mammals, homologizing these brain areas with structures in teleost fishes has been difficult. However, a recent synthesis by O'Connell & Hofmann (2011) suggested that this brain system is indeed highly conserved across vertebrates. Nevertheless, the evolutionary antecedents of the ventral tegmental area (VTA) in particular – which serves the main source of dopamine in the reward system – remain unclear.

Here we use the highly social cichlid fish *Astatotilapia burtoni* to examine the neurochemical profiles of five dopaminergic groups: the ventral subpallial division of the telencephalon (Vc; putative homolog of the striatum), the preoptic area (POA), the rostral periventricular pretectal nucleus (PPr), the posterior tuberculum (TPp; putative VTA/substantia nigra), and the posterior tuberal nucleus (pTn; putative substantia nigra). To better understand the putative homologies between fish and mammals for these brain regions, we have characterized the expression patterns of five genes (*Etv5*, *Nr4a2*, *Pitx3*, *GRP*, *Otx2*) in these five dopaminergic cell groups in *A. burtoni* and compared these patterns to those in the mammalian brain. We find high concordance despite 450 million years of divergent evolution. Our results suggest that many of these dopaminergic cell groups are evolutionarily ancient.

Changes in Gene Expression in the Median Eminence During Natural Reproductive Aging in Female Rats [25]
**Bailey A. Kermath^{1,2}, Deena M. Walker^{1,2}, Penny D. Riha³,
Andrea C. Gore^{1,2,3}**

¹University of Texas at Austin, ²Institute for Neuroscience,
³College of Pharmacy

The complex mechanisms underlying menopause are unclear. The purpose of this experiment was to characterize neuroendocrine mechanisms that underlie the transition to acyclicity in a middle-aged female rat model of natural reproductive senescence. During this life transition, GnRH release begins to diminish, and there is a failure of GnRH neurons to drive ovulatory processes. Here, we examined changes in gene expression in the median eminence (ME), the site of GnRH neurosecretion. Middle-aged rats were regularly cycling (MA-Reg, n=9), irregularly cycling (n=11), or acyclic (n=10). We tested the hypothesis that natural reproductive decline at middle age is associated with changes in gene expression of a subset of neuroendocrine molecules known to be critical to reproductive function. Using real-time PCR, ten neuroendocrine genes that modulate GnRH release and reproductive function were quantified including sex steroid hormone receptors, kisspeptin, and NMDA receptor subunits. Interestingly, preliminary data analysis revealed changes in gene expression in the MA-Reg group compared to the other groups. The MA-Reg animals are at the beginning of the transition to reproductive senescence before loss of reproductive function but during loss of GnRH activation and release prior to ovulation. Thus, we interpret the gene expression changes to reflect altered neurotransmitter and steroid inputs to GnRH cells. As there are few neuronal cell bodies in the ME, many of these changes are likely occurring on glial cells. Considering our recent reports for substantial structural changes in nerve terminals and glia in the aging rat ME [Yin et al. 2009 (J Comp Neurol, Endocrinology)], this is a brain area that merits future research in the context of reproductive aging. Grant support: NIH 5R01 AG028051

Who's watching? Endocrine and neural substrates of context-dependent social behavior [27]

Sean M. Maguire¹, Joshua Stevens-Stein and Hans A. Hofmann^{1,2,3}

¹ Section of Integrative Biology, ² Institute for Cellular and Molecular Biology, ³ Institute for Neuroscience UT Austin

Classically, biologists have studied social behavior mostly by using dyadic paradigms, even though they do not accurately reflect the rich context in which social interactions are embedded in nature. In a social network multiple individuals can interact and observe the interactions of others, and they often adjust their behavior in response to social context. However, the proximate mechanisms underlying this behavioral plasticity are poorly understood.

The African cichlid fish *Astatotilapia burtoni* has become an important model system in social neuroscience and is ideally suited to investigate the proximate mechanisms of socially contingent behavioral plasticity. Members of this species readily form naturalistic social hierarchies in the lab and exhibit remarkable abilities in social cognition.

In the present study we used a triadic design where focal males and females were presented with another male, another female or both stimuli at the same time. Both males and females showed a significant increase in social displays when presented with both stimuli over either stimulus alone. Furthermore males showed a significant increase in courtship behavior towards females when another male was present and a trend of increased aggression towards other males when a female was present. Females also showed a trend of increased receptive behaviors when another female was present. We are currently investigating hormonal and neural correlates of the behavioral differences we have observed.

Daam2 is required for dorsal patterning via modulation of canonical Wnt signaling in the developing spinal cord [26]

Hyun Kyoung Lee and Benjamin Deneen

*Center for Cell and Gene Therapy, Department of Neuroscience,
Baylor College of Medicine, One Baylor Plaza, Houston, Texas
77030, USA*

The Daam family of proteins consists of Daam1 and Daam2. While Daam1 participates in non-canonical Wnt signaling during gastrulation, Daam2 function remains completely uncharacterized. Here we describe the role of Daam2 in canonical Wnt signal transduction during spinal cord development. Loss-of-function studies revealed that Daam2 is required for dorsal progenitor identities and canonical Wnt signaling. These phenotypes are rescued by Δ -catenin, demonstrating that Daam2 functions in dorsal patterning through the canonical Wnt pathway. Complementary gain-of-function studies demonstrate that Daam2 amplifies Wnt signaling by potentiating ligand activation. Biochemical examination found that Daam2 association with Dvl3 is required for Wnt activity and dorsal patterning. Moreover, Daam2 stabilizes Dvl3/Axin2 binding, resulting in enhanced intracellular assembly of Dvl3/Axin2 complexes. These studies demonstrate that Daam2 modulates the formation of Wnt receptor complexes, revealing new insight into the functional diversity of Daam proteins and how canonical Wnt signaling contributes to pattern formation in the developing spinal cord.

Aging influences mating-induced activation of estrogen-sensitive cells in the medial preoptic area [28]

**Victoria L. Nutsch¹, Tomoko Hattori², Daniel Tobiansky²,
Andrea C. Gore^{1,3}, Juan M. Dominguez^{1,2}**

¹*Inst. Neurosci, Univ Texas Austin, TX, USA*, ²*Dept Psychol, Univ Texas Austin, TX, USA*, ³*Div of Pharm. And Toxicology, Univ Texas Austin, TX, USA*

Testosterone, the main circulating steroid hormone in males, acts to facilitate sexual behavior via both reduction to dihydrotestosterone (DHT) and aromatization to estradiol. One way estradiol facilitates sexual behavior is through binding estrogen receptor alpha (ER α) in the medial preoptic area (mPOA). The MPOA is important for male sexual behavior, and expresses a high concentration of ER α . Compared to young animals, aged males show increased levels of sexual dysfunction, and a decreased facilitation of behavior by steroid hormones. We examined whether age-related changes in ER α activation in the mPOA modulates these behavioral changes. To this end, young (4-5 months) and middle-aged (11-12 months) males were allowed to copulate to one ejaculation, before being sacrificed one hour later. Histochemistry was used to visualize Fos- and ER α -containing cells in the MPOA. Quantification of immunolabeled cells revealed significant differences between the two groups ($p < 0.05$), such that mating induced activation of ER α cells in the MPOA increased from 30.09% (+/- 0.04) in young animals to 38.44% (+/- 0.05) in middle-aged animals. Additionally, ER α activation negatively correlated with intromission latency in young animals ($p < 0.05$), but not in middle-aged males. One possible explanation for this increased activation of ER α is that it may be a compensatory mechanism necessary to maintain sexual behavior, as in the case of decreasing facilitation of excitatory transmission. While this requires further investigation, current results support an important role for ER α in the regulation of male sexual behavior, particularly the regulation of erectile function.

Comparison of Macular Pigment Optical Density Spatial Profiles Measured Using Two-Wavelength Autofluorescence with Foveal Pit Morphology [29]

G.M. Pocock^{1,2}, D.M. Snodderly¹, M. Malania¹, W.H. Bosking¹

¹*The University of Texas at Austin*

²*Air Force Research Laboratory, Brooks City-Base, TX*

We compared macular pigment optical density (MPOD) spatial profiles measured by customized heterochromatic flicker photometry (CHFP) and two-wavelength autofluorescence (AF) imaging. Spectral domain optical coherence tomography (SD-OCT) was used to compare the MPOD distribution with foveal architecture. Thirty healthy subjects were recruited to measure their MPOD spatial profiles out to 7° retinal eccentricity using CHFP and two-wavelength AF methods (Heidelberg HRA MP). Measurements of central foveal thickness, width of the foveal pit, and arrangements of the foveal layers were extracted from OCT scans in a subset of the subjects to investigate relationships to the MPOD distribution using the Heidelberg Spectralis SD-OCT. OCT B-scans and corresponding infrared fundus images were co-aligned with MPOD spatial profiles to examine MPOD with respect to foveal location. Our preliminary results support the idea that a wider fovea is associated with a wider macular pigment spatial profile that can include a central peak and flanking peaks. A narrow fovea is likely to have a steeper macular pigment distribution that more closely approximates an exponential spatial profile. OCT raster scans of the foveal pit are being co-aligned with MPOD spatial profiles for more detailed comparison of spatial features.

Whole cell intracellular recordings in primary visual cortex of awake behaving macaque [30]

Eyal Seidemann, Yuzhi Chen, Benjamin Scholl, Andrew Y. Y. Tan, Nicholas J. Priebe

University of Texas at Austin

Intracellular recordings from anesthetized animals play a crucial role in constraining current models of visual cortical function, but these recordings are limited by unknown effects of anesthesia and the lack of behavior. We have therefore developed a method to perform stable whole cell intracellular recordings from the cortex of awake, behaving monkeys, providing access to subthreshold and suprathreshold neural responses as well as precise control of behavior and behavioral states. We used this technique to record from V1 of a fixating monkey while presenting drifting gratings with varied orientation and direction. Our records revealed both simple and complex cells: simple cells were characterized by modulations in both membrane potential and spike rate at the temporal frequency of the drifting gratings (F1), whereas complex cells were characterized by sustained depolarization to the drifting gratings (F0). Both simple and complex cells exhibited orientation selectivity for subthreshold membrane potential modulations as well as suprathreshold spiking responses. Orientation and direction selectivity were systematically broader for membrane potential responses than spiking responses. We next considered membrane potential fluctuations during blank trials. All cells showed clear spontaneous fluctuations containing power over a broad range of frequencies, but the degree and nature of these fluctuations were diverse. In all neurons, however, these fluctuations were affected by visual stimulation and on average show an increase in subthreshold variance evoked by visual stimuli. These observations represent a novel perspective on the function of V1 in the awake, behaving animal.

Reassessing the role of inhibition in the MSO [31]

Michael T. Roberts and Nace L. Golding

Section of Neurobiology, The University of Texas at Austin

Principal neurons in the medial superior olive (MSO) respond to the source of a sound by comparing the timing of excitatory inputs received from pathways originating at both ears. In vivo recordings suggest that inhibitory inputs to the MSO shift the temporal dynamics of interaural time difference (ITD) detection, but the biophysical mechanisms underlying this are not understood. We have investigated these mechanisms using two approaches. First, in recordings from a novel brain slice preparation that retains the input circuitry to the MSO, we found that direct stimulation of the auditory nerve evoked inhibitory responses in MSO neurons that preceded excitatory responses by up to several hundred microseconds. Second, in conventional brain stem slices we investigated the effects of preceding inhibition on coincidence detection in MSO neurons using dynamic clamp recordings. ITD response functions were simulated by independently stimulating ipsilateral and contralateral excitatory afferents to evoke EPSPs with relative time differences covering the range of ± 0.6 ms. The ITD protocol was then repeated using the dynamic clamp to simulate an IPSP preceding the contralateral EPSP by 0.3 ms. Inhibition decreased the halfwidth and the peak amplitude of the ITD response function without shifting the mean and median mass of the response function with respect to interstimulus timing. Together, these results suggest that coincidence detection in the MSO remains remarkably linear in the presence of inhibition. Thus, we propose that inhibition on its own cannot account for the shift in ITD response function timing observed in in vivo recordings.

Reduced ethanol preference and consumption in cocaine- and amphetamine-regulated transcript (CART) knockout mice [32]

Armando Salinas, Chinh T. Q. Nguyen, Dara Ahmadi-Tehrani, and Richard A. Morrisett

Division of Pharmacology & Toxicology, College of Pharmacy, The University of Texas at Austin

Cocaine- and amphetamine-regulated transcript (CART) is a neuropeptide implicated in addiction. Several studies have characterized the role of CART in psychostimulant addiction, but few have examined the role of CART in alcohol use disorders including alcoholism. The current study utilized a CART KO mouse model to investigate what role, if any, CART plays in ethanol appetitive behaviors. CART KO and WT mice were produced by crossing heterozygotes and weaned at 3 weeks. The mice were then genotyped and at 14 weeks a two-bottle choice, unlimited ethanol access paradigm was used to compare ethanol preference and consumption between genotypes. The mice were presented with escalating concentrations of an ethanol solution (3%-21%) and water, each for four days. Preference for quinine and saccharin solutions was also measured. Body weights were measured every other day and the position of the ethanol (or tastant) and water bottles was alternated daily to avoid a position preference. Ethanol metabolism rates and ethanol sensitivity were examined following i.p. ethanol administration with an enzyme assay and the loss-of-righting-reflex assay, respectively. CART KO mice consumed and preferred ethanol less than their WT counterparts. This genotype effect could not be attributed to differences in bitter/sweet taste perception or ethanol metabolism rates. There was also no difference in ethanol sensitivity in males; however, CART KO females showed a greater ethanol sensitivity than the WT females. Together, these data demonstrate a role for CART in ethanol appetitive behaviors and as a possible therapeutic drug target for drug addiction and abstinence enhancement.

Functional imaging reveals a lack of columnar organization for simple and complex cells in mouse visual cortex [33]

Benjamin Scholl and Nicholas J. Priebe

University of Texas at Austin

Neurons of primary visual cortex (V1) are highly organized into anatomical and functional columns and layers. In cat and monkey V1, orientation selectivity and ocular dominance are shared across cortical layers, but vary over the cortical surface. Simple and complex cells, however, vary across cortical layers within a column and this feature is shared across the cortical surface. It is unclear whether this columnar organization of simple and complex cells exists in rodent V1, given that other aspects of columnar organization such as orientation selectivity and ocular dominance are absent (Ohki et al, 2004). To address this question we characterized simple and complex cells in mouse V1 using in-vivo two-photon calcium imaging and measured the responses from hundreds of neurons from cortical depths of 200 to 450 microns. Responses were evoked by reverse-contrast square-wave gratings presented in the receptive field for each cortical area. Simple cells were characterized as responding to a single contrast polarity, while complex cells were characterized as responding to both contrast polarities. At each depth we characterized the distribution of simple and complex cells based on these responses. Our data suggest there is no discernible laminar organization of simple and complex cells in mouse V1. Similarly, we found no significant clustering of cell types across different layers imaged. Our results suggest that the architecture of rodent V1 is functionally different from that of cat or monkey V1.

**Impaired unfolded protein response to sleep deprivation
in mice with diminished chaperone levels [34]**

**Kris Singletary, Marishka Brown, Mary Yu and Nirinjini
Naidoo**

University of Pennsylvania, Philadelphia, PA

Sleep/wake quality and rhythms change as humans age, characterized by increased nighttime awakenings and daytime somnolence. This is likely attributed to age related neuronal dysfunction. Expression of BiP/GRP78, an endoplasmic reticulum (ER) chaperone in wake-active neurons, decreases over age, yielding accumulation of misfolded proteins and an increase in apoptotic factors. Additionally, a 30% reduction in BiP protein levels is seen in the cerebral cortex of aged mice. Low levels of BiP reduces the capacity of the ER to handle protein load. In young animals, but not aged animals, BiP levels increase in response to an acute stressor such as sleep deprivation.

We predicted that young transgenic mice with a reduced BiP (+/-) genotype would have a diminished response to sleep deprivation similar to responses seen in aged wild type mice.

In 3 month old BiP (+/-) and wild-type mice, EEG recordings and/or beam breaks monitored baseline activity. Animals were sleep deprived by gentle handling for 6hrs. or undisturbed during the lights-on period. Westerns were used to compare ER stress and apoptotic markers in cortex and pancreas between groups of mice.

In young BiP (+/+) animals, but not young BiP (+/-) animals, BiP levels increase in response to sleep deprivation. In BiP (+/-) mice wakefulness impairments were also seen. Interestingly, these young mice with a BiP (+/-) genotype exhibit a similar sleep/wake phenotype to wild type aged mice.

**Co-variability of spontaneous synaptic excitation and
inhibition in visual cortex [35]**

Andrew Y. Tan and Nicholas J. Priebe

*Center for Perceptual Systems, Section of Neurobiology, School
of Biological Sciences, College of Natural Sciences, The
University of Texas at Austin*

Spontaneous activity may be a signature of neural circuitry, is modulated by behavioral state, and affects stimulus encoding and synaptic plasticity. Here we estimate the co-variability of spontaneous synaptic excitation and inhibition in pentobarbital-anesthetized rat visual cortex. We measured synaptic currents at various membrane potentials with in vivo whole cell voltage clamp recordings. Assuming a linear current-voltage relation yields a quadratic relation between current variance and membrane potential whose coefficients are excitatory and inhibitory conductance covariances. Fits of the current variances to the quadratic relation provide 90% confidence lower limits for the cross-correlation coefficient, averaged across the population, of 0.2 ± 0.1 (std). The upper limits for the cross-correlation coefficients are sensitive to the assumed reversal potential and only weakly constrained. We estimate stronger upper limits to the cross-correlation coefficients by further assuming that the currents are filtered Poisson processes, which is consistent with the exponential distribution of inter-event intervals of the currents. Across neurons the excitatory rate of a neuron was 2.7 times greater than its inhibitory rate. We estimate the maximum cross-correlation given a greater excitatory rate via a model in which the inhibitory rate is entirely due to a filtered Poisson process that is also a source of the excitatory rate, with the remainder of the excitatory rate provided by another filtered Poisson process. In this model an excitatory to inhibitory rate ratio of 2.7 corresponds to a maximum cross-correlation coefficient of 0.6. The greater excitatory rate suggests that inhibitory neurons spike less frequently or more synchronously.

CREB, BK channels and drug Tolerance [36]

Benjamin Troutwine and Nigel Atkinson

University of Texas Institute for Neuroscience and Institute for Cellular and Molecular Biology

Drug tolerance is an adaptive response to drug exposure that reduces an effect of the drug. *Drosophila* acquire functional tolerance to anesthetics and alcohol after a single sedation. This response is mediated by the induction of *slowpoke*, the *Drosophila* BK channel gene. Increased BK channel expression counteracts the sedative effects and allows for faster neuronal firing. CREB family transcription factors have been implicated in a variety of drug responses, and function in the regulation of *slowpoke* following sedation. Our lab has previously shown that *Drosophila Creb2* is necessary for the acquisition of tolerance and that induction of a dominant negative *Creb2* isoform blocks the acquisition of tolerance and the induction of *slowpoke*. Here we show that *Drosophila CrebA*, a gene previously thought to only function in development, plays a role in the acquisition of tolerance and that transgenic *CrebA* induction phenocopies tolerance.

The medial preoptic area modulates cocaine-induced reward [37]

Daniel J. Tobiansky¹, Peter G. Roma², Tomoko Hattori¹, Victoria Nutsch³, Frank Puga¹, Juan M. Dominguez^{1,3}

¹Dept of Psychology, Univ of Texas at Austin, ²Dept of Psychiatry and Behavioral Sciences, Johns Hopkins Univ School of Medicine, ³Inst for Neuroscience, Univ of Texas at Austin

The present study examined whether the medial preoptic area (mPOA) of the hypothalamus influences cocaine-induced reward via interactions with the mesocorticolimbic system [ventral tegmental area (VTA) and nucleus accumbens (NAcc)]. Five experiments were performed that determined: (1) the extent and distribution of anatomical interactions between the mPOA and the VTA using tract tracing techniques; (2) hormone receptor colocalization of cells in the mPOA that project to the VTA; (3) the influence of cocaine on cellular activity in the mPOA; (4) whether the mPOA influences cocaine-induced activation in the mesocorticolimbic system by comparing levels of Fos-immunoreactivity in animals with lesions of their mPOA versus shams, and (5) whether the mPOA influences behavioral expression of cocaine reward by comparing place conditioning to cocaine in animals with lesions of their mPOA versus shams. Results revealed anatomical interactions between the mPOA and the VTA; in particular, mPOA to VTA efferents that contain high concentrations of progesterone receptors and moderate concentrations of estrogen receptor α and androgen receptors. Furthermore, there was cocaine-induced cellular activity in the rostral mPOA. Finally, lesions of the mPOA enhanced cocaine-induced activation of the VTA and NAcc, pointing to the directionality of this interaction, and also enhanced cocaine-induced conditioned place preference. Structural equation modeling supported the existence of this modulation by placing the mPOA as a central node with direct influences on cocaine-induced activity in the VTA and NAcc. Together these data suggest that the mPOA interacts with the mesocorticolimbic system to modulate cocaine-induced neurobiological activation and behavioral expression of reward.

Possible Influences of Glia in the Preoptic Area on Male Copulation [39]

Ryan G. Will¹, Victoria L. Nutsch², and Juan M. Dominguez^{1,2}

¹Department of Psychology, ²Institute for Neuroscience University of Texas at Austin, TX, USA

While sexually experienced male animals copulate at a higher frequency than sexually naïve animals, there is still a great deal of variability in their sexual behavior. Glutamate acting in the medial preoptic area (mPOA) of the hypothalamus may modulate this variability. Microdialysis studies have shown glutamate levels increase during sexual behavior, peaking with ejaculation and falling precipitously with the post-ejaculation interval. Additionally, lower glutamate levels after ejaculation translates to longer post ejaculatory intervals. Administration of a glutamate uptake inhibitors into the mPOA during copulation increases the number of ejaculations a male rat achieves over an hour-long mating bout, as well as reducing the time it takes to reach ejaculation once mating begins. Since neuroglia are involved in the uptake and production of glutamate, we hypothesized that differential glial density in the mPOA may modulate observed variability in male sexual behavior. To this end, glial density in the mPOA of sexually experience male rats was assessed through immunohistochemistry. Analyses revealed a significant negative correlation between the time required to reach an ejaculation and the concentration of glial in the mPOA; namely, as glial numbers increased time to reach ejaculation decreased. These findings suggest that animals with a greater number of astrocytes in their mPOA may more efficiently recycle glutamate and produce glutamate at a faster rate thus increasing sexual efficacy.

***C. elegans* selects distinct crawling and swimming gaits via dopamine and serotonin [38]**

Andrés Vidal-Gadea¹, Stephen Topper¹, Layla Young¹, Scott Davis¹, Lindsay Beckman¹, Ashley Crisp¹, Leah Kressin¹, Erin Elbel¹, Thomas Maples¹, Martin Brauner², Karen Erbguth¹, Abram Axelrod³, Alexander Gottschalk², Dionicio Siegel³, and Jonathan T. Pierce-Shimomura¹

¹Section of Neurobiology, Waggoner Center for Alcohol and Addiction Research, and ³Department of Chemistry and Biochemistry, University of Texas at Austin, Austin, TX 78712; and ²Institute of Biochemistry and Frankfurt Institute for Molecular Life Sciences, Johann Wolfgang Goethe Universität, 60438 Frankfurt am Main, Germany

For animals inhabiting multiple environments, the ability to select appropriate behaviors is crucial as their adaptability is often context dependent. The nematode *Caenorhabditis elegans* is adapted for locomotion on land and in water and is likely required to transition between these sub-niches in nature. However, it remains controversial whether swimming and crawling are distinct gaits in *C. elegans*, and if so, how animals transition between them. Answering these questions could enable the use of this powerful model system to study the mechanisms underlying locomotory transitions. We used a multifaceted approach to test whether the worm uses distinct gaits and to determine how they transition between them. We show that in *C. elegans* crawling and swimming are distinct gaits. Dopamine is necessary and sufficient to initiate and maintain crawling by a pathway activating D1-like receptors. Conversely, serotonin is necessary and sufficient to initiate and maintain transition from crawling to swimming and to inhibit a set of crawl-specific behaviors. We found these transitions to be modulated by the balance between dopamine and serotonin. These amines have been found to play crucial roles in transition between alternate locomotory forms in diverse species stressing the importance locomotor transitions have for survival. Further study of locomotory switching in *C. elegans* and its dependence on dopamine may provide insight into comparable motor deficits observed in Parkinson's disease.

Heterogeneity in synaptic vesicle release at developing neuromuscular synapses [40]

Christopher R. Hayworth, Etan Aber & Rita Balice-Gordon
*Department of Neuroscience, University of Pennsylvania
School of Medicine*

The mammalian neuromuscular junction is a useful model synapse to study the relationship between synaptic structure and function, although these have rarely been studied together. To do this, we previously generated transgenic lines of mice in which the Thy1.2 promoter drives motor neuron expression of synaptopHluorin (spH), a pH-sensitive variant of GFP tethered to the luminal domain of the vesicular protein VAMP2 (Miesenbock et al., *Nature*, 1998) as a means of optically measuring synaptic vesicle release and total vesicle pool size, among other properties, in motor nerve terminals. Previous work showed that:

- SpH is co-localized with other synaptic vesicle proteins in motor nerve terminals;
- SpH does not alter normal synaptic function in developing or adult mice;
- Nerve stimulation leads to readily detectable and reproducible fluorescence changes that vary with stimulus frequency and are reliable indicators of neurotransmitter release;
- There is a surprising amount of heterogeneity in evoked release within individual presynaptic motor axon terminals regardless of stimulation frequency that is correlated with total vesicle pool size. These regions have been called “hot spots” (Tabares et al., *J. Neurosci.* 2007; Wyatt and Balice-Gordon, *J. Neurosci.* 2008; Gaffield et al., *J. Neurosci.* 2009)

We have now extended these studies to developing neuromuscular junctions in mice ranging in age from postnatal day 6 to 70 (P6 – P70). The goal of our work is to understand how synaptic vesicle release and total vesicle pool size dynamically mature, and how release properties change during the developmental period of activity-dependent synapse elimination.

An Optogenetic Approach to Studying Climbing Fiber Connectivity in the Cerebellar Cortex [42]

P. Mathews, K .H. Lee, T. Otis

Integrative Center for Learning and Memory, Department of Neurobiology, David Geffen School of Medicine, University of California Los Angeles

Information within the brain is thought to be represented by spatiotemporally correlated activity, but it is unclear how neural circuits decode such activity. In cerebellum, synchronous climbing fiber (CF) activity conveys an instructive signal important for associative motor learning. Utilizing optical methods to synchronously activate channelrhodopsin2 expressing CFs, we show that CFs cooperate to recruit a network of feed-forward inhibitory neurons. Through volume transmission this unique form of inhibition transiently silences spontaneously active Purkinje neurons (PNs). CF-driven inhibition broadly influences PN activity, impacting even PNs that do not receive direct CF input. Our results identify a mechanism by which CF-dependent, instructive signals synchronize inhibitory elements across the cerebellar network, thereby expanding the associative control exerted by CFs over cerebellar learning.

Schwann cell mediated remodeling of mouse neuromuscular junctions [41]

Young il Lee, Michelle Mikesh, Ian W. Smith

MCDB Section, School of Biological Sciences, University of Texas at Austin

The morphology of an adult rodent neuromuscular junction is well described and highly stable, with its acetylcholine receptor (AChR) aggregates in the postsynaptic muscle fiber precisely apposed by a presynaptic nerve terminal and capped by non-myelinating terminal Schwann cells (tSCs). NMJs of transgenic mice whose motor axons overexpress a membrane-tethered isoform of neuregulin1 (type III; NRG1-III), however are dramatically altered: AChRs aggregate in small islands rather than smooth and continuous “gutters” with matching varicose nerve terminal branches. tSCs, expressing ErbB receptor tyrosine kinases that bind and activate in response to axonal NRG1-III, are increased in number and send out fine processes not produced by their control counterparts. Ultrastructural examination revealed more frequent intrusions of these tSC processes into the synaptic cleft at NMJs of NRG1-III overexpressing mice when compared to control synapses. These findings suggest that tSCs are capable of sculpting synaptic morphology. Unlike in adults, NMJs are highly plastic during early postnatal development, undergoing significant morphological alterations as well as loss of initial supernumerary innervation until each fiber is singly innervated – a process called “synapse elimination.” The time-course of neuromuscular synapse elimination is accelerated in NRG1-III transgenic neonates. Together, our results suggest activated tSCs mediate morphological and functional synaptic remodeling of NMJs.

Schwann cells degrade nerve terminals at polyneuronally innervated, neonatal neuromuscular junctions in the mouse [43]

Ian Smith, Michelle Mikesh, Young il Lee

MCDB Section, School of Biological Sciences, University of Texas at Austin

Newborn rodent neuromuscular junctions are polyneuronally innervated by several motor axons. Over the 1st week and a half after birth all but one of these axonal inputs is removed by “synapse elimination”. By serial electron microscopy, we have reconstructed the inputs at individual junctions in the mouse sternomastoid muscle at postnatal day 3. We show, in confirmation of the images obtained by light microscopy, that individual axons branch on the muscle surface and contact the muscle at non-overlapping sites within the nascent endplate. By exploiting the higher resolution possible in the electron microscope, we show that all of the terminals are being “attacked” by processes of Schwann cells that reside at these early synaptic contacts. These processes separate the terminals from the muscle fiber. Moreover, the Schwann cells send finger-like processes into the nerve terminal and isolate small pieces of terminal axoplasm that then appear to be degraded within Schwann cell cytoplasm. We conclude that the process of synapse elimination is accompanied by active Schwann cell degradation of terminal components. This suggests that synapse elimination occurs by the balance between active terminal growth and terminal destruction.

Relative location of transmembrane regions of GABA_A receptors probed by cysteine substitution and crosslinking [44]

Jessica A. Hicks¹, Cecilia M. Borghese¹, James R. Trudell², R. Adron Harris¹.

¹Waggoner Center for Alcohol and Addiction Research, The University of Texas at Austin, Austin, TX 78712, ²Dept. of Anesthesia & Beckman Program for Molecular and Genetic Medicine, Stanford University, CA 94305

The GABA_A receptor is a likely target for alcohols and volatile anesthetics. The transmembrane regions (TMs) 1, 2 and 3 provide one amino acid each that line a putative alcohol and volatile anesthetic binding site. However, the relative position of these amino acids is still uncertain, as the pocket they line could be located between or within receptor subunits. Introducing cysteines in key TM locations, we tested the proximity of cysteine pairs by applying reducing and oxidizing agents that may break or form disulfide bridges between cysteines that are close enough, usually altering GABA-induced currents through the receptor. Wild-type and cysteine mutant $\alpha 1$ and $\beta 2$ GABA_A receptor subunits were expressed along with wild-type $\gamma 2$ in *Xenopus laevis* oocytes. A cysteine located in either $\alpha 1$ TM1 or $\beta 2$ TM2 was paired with a cysteine in different positions along $\beta 2$ TM3. EC₅₀ GABA-induced currents were recorded before and after application of dithiothreitol or copper:phenanthroline. Three pairs of cysteines appeared to crosslink. We will test alcohol and volatile anesthetics in GABA_A receptors containing these cysteine combinations, before and after application of reducing or oxidizing agents. We expect that, if the cysteines that crosslink are located in the drug binding site, the drug's effect will be decreased. The results will be used to inform structural models based on recent high-resolution structures of related channels.

Understanding calcium activation of calmodulin [45]

Keegan Hines, Tom Middendorf, Richard Aldrich

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

Calmodulin (CaM) is a ubiquitous calcium binding protein that transmits calcium signaling in many important biochemical pathways including ion channel modulation, protein expression, and synaptic plasticity. In order to understand how Ca²⁺ binds to CaM, three things must be determined: the specific affinity of each of CaM's four Ca²⁺ binding sites, the cooperative effects that binding sites may have on one another, and the effects that global conformational changes may have on affinities and cooperativities. The binding of Ca²⁺ to CaM has been extensively studied both structurally and functionally. However, Ca²⁺ binding models are, as yet, constrained by experimental manipulations that report only total ligand binding, which is insufficient to discern unique solutions to even moderately sophisticated models. Here we demonstrate the advantages to be gained if models are constrained by (i) site-specific binding data and (ii) site-conditional binding data. The information gained by using these methods is quantified by estimating the posterior distribution over parameters (for each data type) using Markov Chain Monte Carlo (MCMC) simulation. We demonstrate that total binding type data is insufficient to uniquely constrain models; that is, parameter values can vary by many orders of magnitude and still fit data well. In contrast, once site-specific type data is considered, models parameters are tightly constrained and the addition of site-conditional type data further improves parameter estimation. Thus, using MCMC to estimate posteriors of different data types, we conclude that the use of site-specific and site-conditional data is necessary to accurately understand calcium binding to calmodulin.

Structural basis for alcohol modulation of a pentameric ligand-gated ion channel [46]

Rebecca J. Howard¹, Samuel Murail², Kathryn E. Ondricek¹, Suzzane Horani¹, Ui P. Lee¹, Pierre-Jean Corringer³, Erik Lindahl², James R. Trudell⁴, R. Adron Harris¹

¹The University of Texas at Austin, USA; ²KTH Royal Institute of Technology, Sweden; ³Institute Pasteur, France; ⁴Stanford University School of Medicine, USA

Despite its long history of use and abuse in human culture, the molecular basis for alcohol action in the brain is poorly understood. The recent determination of the atomic-scale structure of GLIC, a prokaryotic member of the pentameric ligand-gated ion channel (pLGIC) family, provides a novel opportunity to characterize the structural basis for modulation of these channels, many of which are alcohol targets in brain. We found that GLIC recapitulates bimodal modulation by *n*-alcohols, similar to some eukaryotic pLGICs: methanol and ethanol weakly potentiated proton-activated currents in GLIC, whereas *n*-alcohols larger than ethanol potently inhibited them. Mapping of putative alcohol binding sites from ionotropic receptors for glycine, γ -aminobutyric acid, and acetylcholine onto GLIC revealed their proximity to intrasubunit and intersubunit transmembrane cavities that may accommodate one or more alcohol molecules. We used site-directed mutations in the pore-lining M2 helix to identify four residues that influence alcohol potentiation, with the direction of their effects reflecting α -helical periodicity. At one of these sites, decreased side chain volume converted GLIC into a highly ethanol-sensitive channel, comparable to its eukaryotic relatives. Covalent labeling of M2 sites with a methanethiosulfonate reagent further implicated residues at the extracellular end of the helix in alcohol binding. Molecular dynamics simulations elucidated structural changes associated with enhanced potentiation, and suggested a structural mechanism for alcohol potentiation via specific transmembrane cavities. These results provide a novel structural model for independent potentiating and inhibitory interactions of *n*-alcohols with a pLGIC.

Human Skin-Derived Precursor Cells Generate Dermal Neurofibromas in Neurofibromatosis Type I [48]

Rebecca M. Brown, PhD; Chiachi Liu, BS; Zhiguo Chen, PhD; Lu Q. Le, PhD

*Department of Developmental Biology, Department of Dermatology, and Simmons Comprehensive Cancer Center
The University of Texas Southwestern Medical Center*

Neurofibromatosis type I (NF1) is a heritable tumor-predisposition syndrome characterized by the hyperproliferation of neural crest-derived cells. One of its herald features is the progressive and sometimes prolific eruption of benign peripheral nerve sheath tumors called neurofibromas. Neurofibromas are associated with paraesthesias, impairment of nerve conduction through local compression, and malignant conversion; however, neither pharmacotherapy nor surgery provides reliable palliation. Mature Schwann cells, endothelial cells, neurons, fibroblasts, and inflammatory mast cells contribute to the complex architecture of each tumor, making it difficult to pinpoint the founder cell identity in order to develop targeted molecular therapies. Skin-Derived Precursors (SKPs) are an adult multipotent cell population that resides in the dermis and can differentiate into neurons, Schwann cells, smooth muscle cells, and adipocytes. Recently our lab demonstrated that murine SKPs are capable of initiating dermal neurofibromas. In the current study, we investigated whether human SKPs can be induced to form neurofibromas. SKPs were isolated from healthy control skin and from NF1 patient neurofibromas, propagated in culture, and exposed to siRNA knock down of NF1 expression. We then transplanted the NF1 -/- SKPs into the tissue adjacent to the nude mouse sciatic nerve and confirmed neurofibroma growth. These preliminary results suggest that human SKPs could serve as a source of neurofibromas in NF1 patients.

γ -Amino butyric acid receptor B activates local protein synthesis [47]

Emily Workman and Kimberly Raab-Graham

*¹Center for Learning and Memory, Section of Neurobiology,
University of Texas at Austin, Austin, TX 78712, USA*

Mammalian target of rapamycin (mTOR) is a serine/threonine kinase required for local protein synthesis. While it is well established that local protein synthesis is necessary for the long-term stabilization of changes to synapse structure and composition arising from excitatory activity, how inhibitory signals alter synapse structure and composition (Turrigiano et al. 1998, Chen et al. 2011) is unknown. One major inhibitory receptor, γ -Amino butyric acid receptor B (GABA_B), regulates synaptic inhibition through trimeric G proteins in two distinct ways: 1) by closing presynaptic calcium channels and 2) by opening postsynaptic potassium channels. Consistent with its inhibitory role, in control cultures, GABA_B receptors decrease dendritic calcium signals. In contrast, we have discovered that GABA_B receptor activation increases local, dendritic calcium signals when NMDA receptors are blocked. Further, upon GABA_B receptor activation, hot spots of local mTOR activity appear specifically in the dendrites. These hotspots appear to increase the local translation of activity dependent proteins such as Ca²⁺/calmodulin-dependent protein kinase II α (CaMKII α). We propose that GABA_B receptors underlie the plastic changes seen at the synapse during periods of decreased excitatory input.

Notes:

Notes:

