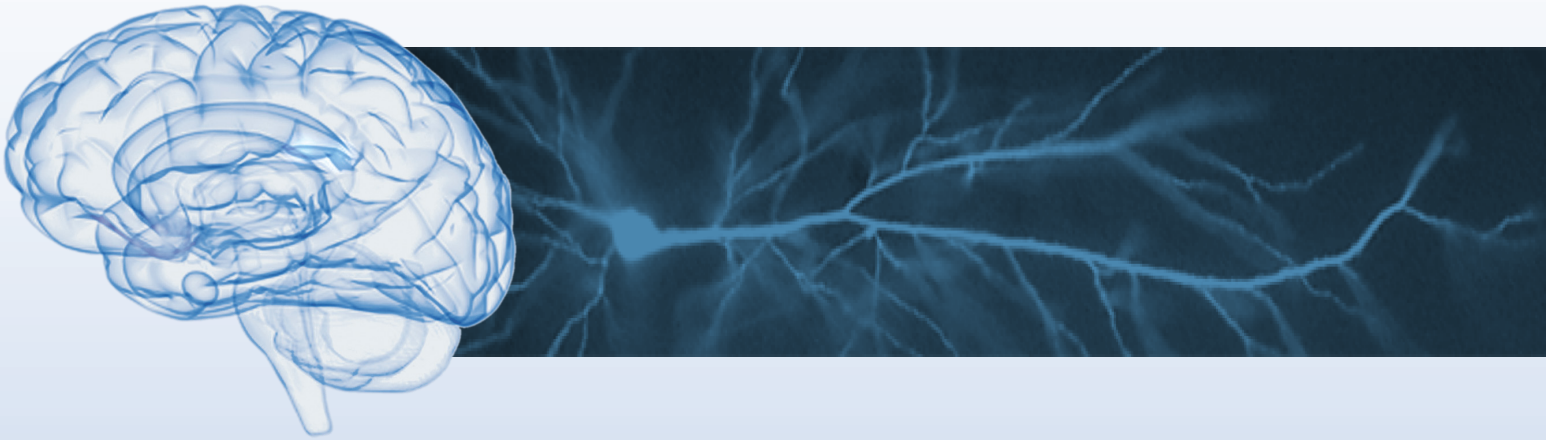

UT Austin Conference on Learning & Memory

Hosted by The Center for Learning and Memory
The University of Texas at Austin

April 12-14, 2013

Keynote Speakers

Edvard and May-Britt Moser,
Kavli Institute for Systems Neuroscience
Norwegian University of Science and Technology

Session Speakers

Morgan Barense
Gary Bassell
Sarah Bottjer
Neal Cohen
Michael Ehlers
Dan Feldman
Rick Huganir
Jim Knierim
Eve Marder
Kelsey Martin
Kimberly McAllister
Javier Medina
Coleen Murphy
Ken Norman
John O'Doherty
David Sweatt

Acknowledgements

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Conference Schedule

Friday April 12th
Keynote Presentations and Cocktail Reception
AT&T Conference Center, Amphitheater 204
Sponsored by NeuroTexas Institute at St. David's Health Care

2:00-3:00	Conference Registration, Amphitheater 204 lobby
3:00-5:30	Keynote Presentations Drs. May-Britt and Edvard Moser, Kavli Institute for Systems Neuroscience Norwegian University of Science and Technology
	Dr. May-Britt Moser *"The entorhinal-hippocampal space map"*
	Dr. Edvard Moser *"Functional organization of the grid-cell system"*
5:30-6:15	Cocktail reception, AT&T Conference Center Interior Courtyard
7:00-9:30	Lake Austin Dinner Cruise

Saturday April 13th
Speaker sessions will be held in the Welch Convocation Center (WEL 2.112)
Poster sessions and dining will be held in the NHB atrium and 24th street patio
Sponsored by a grant from the National Institute of Neurological Disorders and Strokes.
Additional support from Zeiss, Neuralynx, Oak Ridge Associated Universities and The Society for Neuroscience

8:00-8:30:	Breakfast, NHB 24th street patio
8:30-8:45	Opening Remarks, Welch Convocation Center Dan Johnston, Director, Center for Learning & Memory

Speaker session 1
Molecular approaches to the study of learning & memory

Moderators:	Kim Raab-Graham, UT Austin Center for Learning & Memory Gary Bassell, Emory University, Departments of Cell Biology and Neurology
8:45-9:15	David Sweatt, University of Alabama School of Medicine Department of Neurobiology, McKnight Brain Institute *"Epigenetic mechanisms in memory formation"*
9:15-9:45	Gary Bassell, Emory University Departments of Cell Biology and Neurology *"Dysregulation of PI3K regulated protein synthesis in fragile x syndrome"*
9:45-10:15	Coleen Murphy, Princeton University Department of Genomics & Molecular Biology *"C. elegans learning, memory, and longevity pathways"*

10:15-10:45 Rick Huganir, Johns Hopkins University
Department of Neuroscience
"Regulation of glutamate receptor function and learning & memory in the brain"

10:45-12:00: Poster session 1 and coffee, NHB atrium
Even numbered posters present

12:00-1:00: Lunch, NHB 24th street patio

Speaker session 2
Learning & memory in humans
Moderators: Alison Preston, UT Austin Center for Learning & Memory
Elizabeth Phelps, NYU, Department of Psychology

1:00-1:30 Morgan Barense, University of Toronto
Department of Psychology
"The interface of memory and perception: Where parts become whole"

1:30-2:00 Neal Cohen, University of Illinois
Department of Psychology
"Converging cognitive neuroscience studies of the hippocampus and relational memory"

2:00-2:30 Ken Norman, Princeton University
Department of Psychology
"Tracking memory retrieval dynamics with multivariate pattern analysis"

2:30-3:00 John O'Doherty, California Institute of Technology
Department of Psychology
"Neural mechanisms of goal-directed and habitual control"

3:00-4:15 Poster session 2 and snacks, NHB atrium
Odd numbered posters present

Speaker Session 3
Synaptic approaches to the study of learning & memory
Moderators: Kristen Harris, UT Austin Center for Learning & Memory
Michael Ehlers, Pfizer, Neuroscience Research Unit

4:15-4:45 Kimberly McAllister, University of California, Davis
Department of Neurology
"Molecular mechanisms of synapse formation and stability"

4:45-5:15 Kelsey Martin, University of California, Los Angeles
Department of Biological Chemistry
"Spatial regulation of gene expression during synapse formation and synaptic plasticity"

5:15-5:45 Michael Ehlers, Pfizer
Neuroscience Research Unit
"*Regulation of organelle ion homeostasis and surface sialylation by the angelman syndrome ubiquitin ligase Ube3a"*

5:45-6:15 Dan Feldman, University of California, Berkeley
Department of Molecular and Cell Biology
"Rapid homeostatic plasticity in inhibitory circuits during whisker map plasticity"

6:15-8:00 Cocktails and dinner, NHB 24th street patio

Sunday April 14th
Speaker sessions will be held in Welch Convocation Center (WEL 2.112)
Dining will be held on NHB 24th street patio

8:15-9:00 Breakfast, NHB 24th street patio

Poster competition winner speakers

9:00-9:15 Keegan Hines, UT Austin, Graduate Student
Center for Learning & Memory
"Introducing conditional binding using coupled energy transfer" [18]

9:15-9:30 Adina R Buxbaum, Albert Einstein College of Medicine, Graduate Student
Department of Anatomy and Structural Biology
"Stimulus induced release of β-actin mRNA from Neuronal RNA granules in dendrites regulates local translation" [13]

9:30-9:45 Break

Speaker Session 4
Systems approaches to the study of learning & memory
Moderators: Mike Mauk, UT Austin Center for Learning & Memory
Eve Marder, Brandeis University

9:45-10:15 Javier Medina, University of Pennsylvania
Department of Psychology
"Calcium-based representation of a behaviorally-relevant teaching signal in Purkinje cell dendrites"

10:15-10:45 Sarah Bottjer, University of Southern California
Department of Neurobiology
"Neural Representations of Current and Goal Behaviors During Sensorimotor Learning "

10:45-11:15 Jim Knierim, Johns Hopkins University
Department of Neuroscience
"Nonspatial and spatial processing in the hippocampal formation"

11:15-11:45 Eve Marder, Brandeis University
Department of Biology
"Homeostasis, Degeneracy and Robustness in Circuit Performance"

11:45 Rick Aldrich, UT Austin Center for Learning & Memory,
Poster committee chair - Announcement of poster competition winners

Dan Johnston, Director, UT Austin Center for Learning & Memory
Wrap-up and recess until 2015

Poster Abstracts

[1] Are aperiodic 1D grid-cell responses consistent with low-dimensional continuous attractor dynamics?

KiJung Yoon[1], Amina Kinkhabwala[2], David Tank[2], Ila Fiete[1]
[1]Center for Learning and Memory, The University of Texas at Austin
[2]Princeton Neuroscience Institute, Princeton University

Since the discovery of the striking activity of grid cells, the question of mechanism has received intense attention. One of two dominant models is based on 2D continuous attractor dynamics in recurrent networks. This model is fully consistent with the rate dynamics of grid cells in 2D-enclosures and has made many successful predictions. However, the response of cells along 1D-tracks remains a confounding and possible challenge. In 1D, grid cells fire at multiple locations, but the pattern is not periodic. Here we examine whether the 1D-response patterns are consistent with continuous attractor dynamics, by analyzing multiple simultaneously recorded grid cells, with responses elicited in both 2D- and 1D-environments. First, we show that aperiodic responses are not inconsistent with attractor dynamics: while attractor dynamics force cells to maintain fixed response relationships to each other, they do not dictate how network states are mapped to the external represented variable. This mapping may be continually varied or reset, e.g. by external landmarks. Second, we examine the stability of cell-cell relationships in 1D, even as individual cells exhibit drifts in the locations of fields over traversals of a track, showing that cell-cell response relationships are better preserved than the responses of individual cells. Third, we examine whether the 1D-response is quasi-periodic, generated as a slice though a periodic 2D-pattern. Our results suggest that, independent of the spatial mapping between 1D and 2D, and despite the disparity in 1D- and 2D-responses, the same low-dimensional dynamics observed in grid cells in 2D may underlie their 1D-responses.

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

Yongseok Yoo and Ila Fiete
Center for Learning and Memory, The University of Texas at Austin

Motivated by the unusual response properties of grid cells, we here analyze the mutual information between a stimulus and a neural population code consisting of periodic responses with different periods. Our aim is to derive the estimation error for the encoded variable, as a function of the widths of neural tuning curves in multi-period, periodic population codes. For circular variables represented by classical population codes (CPCs), narrow tuning curves are always better (in 1 and 2-dimensions). This is true for ideal decoders and for biologically plausible simple population decoders. Here we show that for ideal decoders, the optimal tuning curve width for the grid code (GC) is narrow, as in CPCs. However, for biologically plausible decoders, we show that it is better for the tuning curves to have finite width, regardless of dimension. Our results predict that the optimal tuning curve width should be similar in size to the expected errors that accumulate in the network between successive readouts.

[3] Spike train correlations among grid cells and the implications for the network model of grid formation

Sean Trettel, Ila Fiete, Laura Lee Colgin
Center for Learning and Memory, The University of Texas at Austin

The discovery of grid cells in the medial entorhinal cortex (MEC) has led to intense attention to the question of mechanism. There are several distinct models for the generation of grid cell-like spatial responses and for the conversion of velocity inputs to location estimates, a function grid cells are believed to perform. Numerous correlational, intracellular, and lesion studies have attempted to differentiate between the models, and have lent varying degrees of support to one or the other model. However, the connectivity between grid cells, a defining feature of network models, has remained relatively poorly characterized. Here, we assess functional network connectivity among grid cells through studies of spike correlations between neural pairs, in the awake animal during active exploration and during rest. We show that the spike correlations predicted by the class of continuous attractor models -- between grid cells, and between grid cells and putative inhibitory interneurons -- are present even during rest, when movement related inputs are restricted.

[4] Slow and fast gamma oscillations support distinct spatial coding modes in hippocampal place cells

Kevin Bieri, Katelyn Bobbitt and Laura Lee Colgin
Center for Learning and Memory, The University of Texas at Austin

In the hippocampus, two distinct variants of gamma oscillations, fast and slow gamma, differentially couple hippocampal subfield CA1 to two of its main inputs (Colgin et al., Nature 462, 2009). Fast gamma (~65 – 140 Hz) synchronizes CA1 with inputs from medial entorhinal cortex (MEC), a region that conveys information about an animal's current location. Slow gamma (~25 – 55 Hz) couples CA1 to neighboring subfield CA3, a circuit implicated in memory retrieval. These findings raise the possibility that fast gamma promotes encoding of ongoing experiences and slow gamma supports retrieval of stored memory representations. Hippocampal place cells are thought to represent the "where" component of memory by firing in distinct spatial locations. If fast gamma promotes memory encoding, then place cells firing during fast gamma episodes would be expected to encode recent locations ("retrospective coding"). If slow gamma supports memory retrieval, then place cells firing during slow gamma periods would be expected to predict upcoming locations ("prospective coding"). To test these hypotheses, we investigated CA1 place cell firing patterns in freely behaving rats during periods of fast and slow gamma. We found that fast gamma power and phase-locking of spike times were heightened during retrospective coding, whereas slow gamma power and phase-locking were enhanced during prospective coding. These findings suggest that fast gamma coordinates place cells during encoding of recently visited locations, while slow gamma coordinates place cells during retrieval of stored representations.

[5] Constructing a minimal molecular model of long-term memory

Sajiya Jalil*, Harel Shouval
Department of Neurobiology and Anatomy
The University of Texas Medical School at Houston
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*Sajiya.j.jalil@uth.tmc.edu

Memories are stored via changes in concentrations or states of specific molecules in synapses. A central question in learning and memory is how memories can be stored for time periods that are much longer than the lifetime of these molecules in the synapse. There is significant evidence that the formation of long term memory is correlated with persistent increase of a specific kinase, PKMζ, and that inactivating this molecule can reverse previously established synaptic plasticity and memory. We construct several models explaining how PKMζ can be persistent and active for periods of time larger than the protein's lifetime. We base these models on experimental observations, and add complexities only when necessary to account for the data. Doing this we construct a model that can sufficiently and qualitatively account for most experimental data, yet is simple, tractable and can be fully mathematically analyzed. Thus we identify key characteristics of a protein necessary for maintaining the life of a memory, advancing our current understanding of how memories last.

[6] Continuous Attractor Model for Place Cells Representing a Large Region

Kathryn Hedrick and Kechen Zhang
Dept. of Biomedical Engineering, Johns Hopkins University, Baltimore, MD
Contact: khedrick@jhu.edu, kechen@bme.jhu.edu

Several continuous attractor models have been proposed for the CA3 subregion of the hippocampus due to the prevalence of recurrent collaterals among its place cells. In their standard form, the models assume that each place cell has a single place field in a given environment. However, recent experiments conducted in large regions indicate that multiple fields is a fundamental characteristic of place cells. This characteristic may be crucial, as models with one field per cell are limited by the size of the enclosure, and there is no natural way to extend the attractor when the rat moves beyond the artificial boundaries of the map. We propose that place cells form a *megamap*, or a single continuous attractor in which each cell has multiple, irregularly shaped place fields within a large environment. Relatively weak external input drives the system to an attractor state in which a localized activity bump is centered at the simulated rat's location. Unlike previous models, the attractor has no artificial boundaries and can be extended naturally to include contiguous regions using a supervised learning rule. We compare the emergent properties of the megamap to those of a standard continuous attractor model, including the propensity for partial remapping.

[7] Deletion of PTEN in Cerebellar Granule Cells Results in Motor Learning deficits and hyperactivity

Andy Holley[1], Gregory Smith[2], Erin Arbuckle[2] and Joaquin N. Lugo[1,2]
[1]Institute of Biomedical Studies, [2]Department of Psychology and Neuroscience
Baylor University, Waco, TX

The neuron subset-specific (NS-Pten) conditional knockout mice have deletion of PTEN in the hippocampus, cortex, and cerebellum. There have been several reports that have evaluated the result of Pten deletion in the hippocampus and cortex, but there has been less examination into the influence of deletion of Pten in the cerebellum. We examined the NS-Pten wildtype, heterozygous, and knockout (KO) mice in the open field test to examine motor activity and used the rotarod test to examine motor learning. Mice were given two trials per day for four days with a 60-min rest interval after each trial on an accelerating rotarod (5-40 rpm over a 5-min period). The NS-Pten KO mice displayed hyperactivity in the open field test compared to controls, $p < 0.001$; and spent significantly less time in the center of the open field, $p < 0.05$. The NS-Pten KO mice had a significant impairment of their ability to learn the rotarod test across 2 trials per day for 4 days compared to wildtype and heterozygous mice, $p < 0.001$. The wildtype and heterozygous mice were not significantly different from one another. These findings demonstrate that NS-Pten KO mice have alterations in motor learning and hyperactivity.

[8] Hyperactivation of mTOR results in hippocampal-dependent learning and memory deficits

Erin Arbuckle[1], Gregory Smith[1], Jessica Morrison[2], Jessika White[2], and Joaquin Lugo[1,2]
[1]Institute of Biomedical Studies, [2]Department of Psychology and Neuroscience
Baylor University, Waco, TX

Rationale: Recent studies have shown that genetic deletion of genes that modulate the mTOR signaling pathway result in spatial learning deficits. Here, we evaluated the effects of mTOR hyperactivation on learning and memory by examining neuron subset-specific (NS-*Pten*) conditional knockouts in conditioned fear tests and novel object recognition. Methods: Multiple cohorts of NS-*Pten* knockouts (KO), heterozygous, and wildtype mice were examined in a battery of behavioral tests. Learning and memory was examined through a delayed fear conditioning protocol that measures amygdala-dependent and hippocampal-dependent types of memories. We examined a second cohort in a trace conditioning test. We then tested novel-object recognition to evaluate short-term memory in these mice Results: We found that the NS-*Pten* KO mice had deficits in contextual memory in the delayed fear conditioning test and deficits in trace conditioned fear, $p < 0.05$. The NS-*Pten* KO mice did not show deficits in the delayed conditioning task for tone conditioning. However, NS-*Pten* HT and KO mice had deficits in the novel-object recognition test for short-term memory. Conclusions: These findings demonstrate that hyperactivation of mTOR due to genetic deletion of *Pten* results in hippocampus-dependent learning and memory deficits. However, they do not appear to have deficits in associative tone conditioning.

[9] Early Postnatal Seizures Result in Spatial Learning Deficits and Increases Anxiety in Adult Mice

Gregory Smith[1], Erin Arbuckle[1], Nowrin Ahmed[2], and Joaquin N. Lugo[1,2]
[1]Institute of Biomedical Studies, [2]Department of Psychology and Neuroscience
Baylor University, Waco, TX

One of the most devastating aspects of developmental epilepsy is the long-term impact on behavior. To examine whether early-life seizures result in alterations in learning and memory and anxiety we administered the chemoconvulsant kainic acid to induce seizures in postnatal day ten C57BL/6 male mice. The subjects were then tested in a battery of behavioral tests in adulthood: open field activity, elevated-plus maze, light-dark test, conditioned fear, novel object recognition, and Morris water maze. The mice with early-life seizures showed a consistent increase in anxiety in all three behavioral tests that measure changes in anxiety. They spent less time in the center of an open field test ($p < 0.05$); less time in the open arms of the plus-maze test ($p < 0.05$); and showed fewer transitions between the light to dark areas compared to the controls ($p < 0.05$). The mice showed no differences in tone fear conditioning and had no deficits in short-term memory in the novel-object recognition test. However, the mice with early-life seizures had a deficit in spatial learning. They had a longer latency to reach the hidden platform across the 8 trials of testing ($p < 0.01$), and spent less time in the quadrant that originally housed the hidden platform during the probe trail ($p < 0.05$). These results demonstrate that mice with one insult of status epilepticus on postnatal day 10 have a long-lasting increase in spatial learning and anxiety.

[10] Frontoparietal control regions implicated in food preference changes

Akram Bakkour, Tom Schonberg, Ashleigh M. Hover, Jeanette A. Mumford and Russell A. Poldrack
The University of Texas at Austin Imaging Research Center and Center for Learning and Memory

One must be able to make better choices in order to overcome unhealthy behavior. Changing food preferences is an important strategy in addressing the obesity epidemic. Few paradigms have effectively changed food preferences and few studies have investigated the neural systems that support such changes. We developed a novel training paradigm where participants chose one item from pairs of palatable junk food items made up of one higher and one lower valued item. Participants only received points later converted to a cash bonus for choosing the lower valued item. In a later probe phase, participants chose from the same pairs for real consumption. Participants chose the lower valued item significantly more often for trained compared to untrained pairs during probe. We replicated the behavioral results in an independent sample of participants while they were scanned with fMRI. We found that as training progressed there was decreased recruitment of regions that have been previously associated with cognitive control; specifically left dorsolateral prefrontal cortex (dlPFC) and bilateral parietal cortices. These findings suggest that it is possible to change food preferences through training, and that this training is associated with a decreasing need for top down prefrontal control. Extensive training paradigms may be a promising basis for interventions aimed at changing real world food preferences.

Grants/Other support: NIA 1R01AG041653

[11] Perceptual bias reflects knowledge about task structure encoded in the fronto-striatal system

Mei-Yen Chen[1], Koji Jimura, Ph.D.[1,2], Corey N. White, Ph.D.[1], W. Todd Maddox, Ph.D.[1], Russell A. Poldrack, Ph.D.[1]
[1]Department of Psychology, The University of Texas at Austin, Texas; [2]Precision and Intelligence Laboratory, Tokyo Institute of Technology, Tokyo, Japan.

Perceptual decisions can be biased by choice outcomes such as rewards, but the mechanisms by which such biases are acquired remains unclear. We examined to what extent reinforcement learning approaches from the study of economic decision making provide insights into the mechanisms of developing bias. We found that bias in adot-motion discrimination task can be driven by task structure, such that when human participants experienced two different reward contexts signaled by state cues, their decisions were gradually biased toward the motion direction associated with greater reward in each context. This bias persists when trial-wise reward feedback was removed. The experienced task structure continued modulating individuals' performance in a novel context such that their perceptual bias reflected the weighted sum of the base-rates and reward magnitude contingent on each context. State-based and state-free reinforcement learning models were applied to the data and were used to generate regressors for fMRI analysis. Activity in lateral prefrontal and parietal cortex correlated with reward prediction errors from the state-based model, whereas activity in ventral striatum, ventromedial prefrontal, and posterior cingulate cortex correlated with a prediction error signal that was common to both state-based and state-free learning models. These findings confirm previous dissociations between model-based and model-free prediction error signals, and highlight the utility of bridging approaches between studies of perceptual and economic decision making.

[12] A topological model for hippocampal spatial map formation yields insights into spatial learning

M. Arai and Y. Dabaghian
Jan and Dan Duncan Neurological Research Institute, Baylor College of Medicine and Texas Children's Hospital, Houston, TX and Department of Computational and Applied Mathematics, Rice University, Houston, TX

Our ability to navigate our environments relies on our ability to form an internal representation of the spaces we're in. Since the discovery that certain hippocampal neurons fire in a location-specific way, we have known that these "place cells" serve a central role in forming this internal spatial map, but how they represent spatial information, and even what kind of information they encode, remains mysterious. (Perhaps the cells form something akin to a street map, with distances and angles, but they could also form something more akin to a subway map, with a focus on connectivity.) We reasoned that, because downstream brain regions must rely on place cell firing patterns alone (they have no direct access to the environment), the temporal pattern of neuronal firing must be key. Furthermore, because co-firing of two or more place cells implies spatial overlap of their respective place fields, a map encoded by co-firing should be based on connectivity and adjacency rather than distances and angles, i.e., it will be a topological map. Based on these considerations, we modeled hippocampal activity with a computational algorithm we designed using methods derived from Persistent Homology theory and algebraic topology. We found not only that an ensemble of place cells can, in fact, "learn" the environment (form a topologically accurate map), but that it does so within parameters of place cell number, firing rate, and place field size that are uncannily close to the values observed in biological experiments—beyond these parameters, this "learning region," spatial map formation fails. Moreover, we find that the learning region enlarges as we make the computational model more realistic, e.g., by adding the parameter of theta precession. The structure and dynamics of learning region formation provide a coherent theoretical lens through which to view both normal spatial learning and conditions that impair it.

**[13] Stimulus induced release of β-actin mRNA from Neuronal RNA granules in dendrites regulates local translation

Adina R Buxbaum, Robert H Singer
Department of Anatomy and Structural Biology
Albert Einstein College of Medicine, Bronx NY

Local translation and actin remodeling at dendritic spines are two mechanisms neurons employ to alter the strength of their synaptic connections in an activity dependent manner. The abundance of β-actin mRNA in dendrites suggests that local β-actin translation is necessary for the expression of plasticity, motivating us to investigate this further. Here we study local β-actin translational regulation by large (~0.5μm) ribosome dense organelles, or neuronal RNA granules, which maintain translational dormancy of dendritic mRNAs. Activity induced granule disassembly allows active translation, thus restricting synthesis of nascent proteins to stimulated synapses. We identified neuronal specific RNA granules through high resolution single molecule imaging in culture. Following chemical LTP, we observe a decrease of single β-actin mRNAs occupying RNA granules which was correlated with an increase in local translation of β-actin. The release of mRNA from granules was transient, reversible and was inhibited by blocking NMDA receptor signaling, suggesting that this process might be bidirectionally regulated by synaptic activity. Finally, we were able to visualize granule disassembly following cLTP in live neurons. By measuring activity induced single mRNA and granule dynamics, we have identified and characterized a mechanism whereby the translation of β-actin mRNA can be precisely regulated in response to synaptic activity with temporal and spatial precision.

****This poster has been selected for a Best Abstract Award and the content will be presented as a 10 min talk in speaker session 4****

[14] Sexually dimorphic parcellation of lateralized experience-dependent gene expression in the zebra finch auditory forebrain

F. Pirlepesov, M. Deshpande, T. Lints
Department of Biology, Texas A&M University

Brain lateralization is a phylogenetically widespread feature of vertebrate nervous system design. Nevertheless, the functional benefits of brain lateralization *per se* are largely obscure. Besides our population-level bias in handedness, humans are also markedly left lateralized in the neural substrates of language perception and production. Speech and language are critically dependent on imitative vocal learning, and this fundamental sensorimotor integration process also underlies the song learning process in birds. Moreover, aspects of song production and perception are lateralized in songbirds, although this area still lags far behind research on human language laterality. In order to determine whether left, right or mixed dominance in the songbird brain confers any benefit to processing complex socially-transmitted information, we have to develop ways to measure, localize and visualize brain lateralization properly. To develop and characterize such measures, we have combined whole brain 3D reconstruction of immediate early gene (IEG) expression with statistical parametric mapping (SPM), and applied these techniques to the question of whether auditory regions engaged by song perception are differentially lateralized in adult male and female birds. Here we report evidence for sexually dimorphic aspects of auditory lateralization in the zebra finch brain. In females, IEG expression reveals a consistent lateralization across medial auditory regions. In males, however, song-driven ZENK (but not ARC) IEG expression is much more laterally parcellated in these same auditory regions, which display adjacent domains of opposing lateralization. This data identifies neuroanatomical targets for investigating lateralized neuronal responses involved in the processing of learned vocal communication signals.

[15] A Novel Mouse Transgenic System for Rapid, Reversible, and Specific Arrest of Adult Neurogenesis

Dong-oh Seo and Michael Drew
Behavioral Neuroscience Program, Department of Psychology
Center for Learning and Memory, Section of Neurobiology
The University of Texas at Austin

New neurons are continuously generated in the adult mammalian brain, but the function of adult-born neurons is not fully understood. Although many studies have shown functional effects of ablating adult neurogenesis, many of these studies are difficult to interpret because the ablation methods targeted both neuronal and non-neuronal cell lineages. In addition, many studies are limited by the use of irreversible ablation methods, which make it difficult to address the role of neurogenesis in time-limited cognitive and emotional processes. To more precisely assess the role of adult neurogenesis in behavioral processes, we developed a transgenic a new mouse model that expresses a drug-activated suicide gene exclusively in neural progenitor cells. DCX-TK transgenic mice expresses herpes simplex virus thymidine kinase (HSV-TK) under control of the doublecortin (Dcx) gene promoter. HSV-TK activates the prodrug Ganciclovir (GCV), which terminates DNA synthesis, leading to the death of dividing cells. Here we demonstrate that DCX-TK system can be used to effect a rapid, reversible, and specific arrest of adult neurogenesis. We further assess the utility of these mice for studies of the contribution of adult neurogenesis to time-limited behavioral processes, such as memory acquisition and retrieval, and we describe preliminary data evaluating the effects of temporary neurogenesis arrest on behavior.

[16] Context familiarity inoculates against immediate extinction

Anthony Lacagnina, Brian Bernier, Michael Drew
Center for Learning and Memory, The University of Texas at Austin, Austin, TX

Contextual fear learning is a hippocampus-dependent form of Pavlovian conditioning in which an animal learns to associate a specific context with an aversive stimulus such as a footshock. Previous research has shown that contextual fear learning requires experience with the context preceding shock presentation, such that a shock delivered immediately after placing the animal within a novel context produces little conditioning. This phenomenon is known as the immediate shock deficit and has been thought to result from an inability of the animal to form a mental representation of the context in the limited time prior to shock delivery. Our research challenges this interpretation. We found that both immediate and delayed shock presentation produce equivalent fear conditioning when the post-shock context exposure is short (30 sec). However, when the post-shock interval was extended to 3.5 minutes both immediate and delayed shock animals exhibited little contextual fear when tested 24 hours later, suggesting that an immediate extinction of the fear memory takes place during the post-shock period. Interestingly, pre-exposure to the context on the day before conditioning, but not on the same day, prevented immediate extinction. Our findings suggest that contextual fear conditioning involves both learning and immediate extinction processes and that it is the timing and not the absolute amount of context exposure that regulates the durability of these fear memories.

[17] Relapse of extinguished fear after exposure to a dangerous context in rats

Travis Goode and Steve Maren
Texas A&M University; Department of Psychology & Institute for Neuroscience

Stress is thought to be a major factor in the relapse of fear following interventions for anxiety disorders. It has been shown that fear (i.e., freezing) to an extinguished conditioned stimulus (CS) relapses when rats are exposed to a dangerous context. We sought to replicate this finding as a prelude to studies exploring brain mechanisms of relapse. Male Long-Evans rats were conditioned (5 tone-shock trials) and then extinguished (45 tone alone trials per day for 3 days). Thirty minutes before a retention test in the extinction context, rats were exposed to either the conditioning context ('dangerous') or extinction context ('safe'). Although rats exposed to the conditioning context expressed high fear in that context, relapse did not occur when the CS was presented in the extinction context. In a second experiment, the conditioning, extinction, and retention testing trials all occurred in the same context. Another "dangerous" context was established before conditioning by exposing rats to a single unsignaled shock in a second context. Exposure to this dangerous context caused a relapse of fear to the CS during the retention test. These results indicate that the history of the context in which an extinguished CS is encountered influences the relapse of fear to that CS.

**[18] Introducing conditional binding using coupled energy transfer

Keegan Hines, Tom Middendorf, Jenni Greeson-Bernier, Rick Aldrich
The University of Texas Institute for Neuroscience, Center for Learning and Memory,
The University of Texas at Austin

Calmodulin is a ubiquitous calcium binding protein that plays vital roles in many important biological processes including muscle contraction, cellular motility, ion channel modulation, and synaptic plasticity. Calmodulin has four metal binding sites and the binding of calcium to calmodulin has been studied extensively. In order to understand calcium binding at the molecular level, it is important to establish the affinity for calcium of each of calmodulin's four binding sites as well as the cooperative interactions between sites. Despite tremendous experimental and modeling effort, there remains little agreement between different experimental groups in estimates of these biophysical parameters. In previous work, we have shown analytically that the impediment to understanding this system is of a fundamentally statistical nature: there is not enough information in typical calcium binding experiments (which measure total calcium binding) to uniquely constrain typical calmodulin models. It was demonstrated that improved experimental methods, such as site-specific binding and site-conditional binding measurements, are required to accurately measure the parameters of interest. Site-specific binding entails the measurement of binding occupancy in each individual binding site. Site-conditional binding entails the measurement of binding occupancy of each site, conditional on the occupancy of all other sites. We recently reported the experimental realization of site-specific binding in calmodulin using luminescent lanthanide ions sensitized by site-specific tryptophan excitation. Here we report an experimental realization of conditional binding which builds on the fluorescence system used previously. Individual binding sites in calmodulin are labeled with a tryptophan residue which is used to sensitize the absorbance of Terbium (Tb) ions bound at the associated binding site. Tb luminescence then provides an optical signal of ion binding only at the labeled site of interest. This scheme is taken further by including Neodymium (Nd) ions, whose absorbance spectrum overlaps favorably with the emission spectrum of Tb. The presence of Nd in the adjacent binding site results in a marked decrease in the lifetime of Tb luminescence due to energy transfer to Nd. Since we have a simultaneous measurement of relative occupancies of each binding site, we can parse out the distribution of all possible binding states within each lobe of calmodulin. Here we present preliminary data demonstrating that this coupled energy transfer does happen and that changes in Tb luminescence are easily detectable. Further, we show direct measurements of cooperative interactions between binding sites in calmodulin's N-lobe. A quantitative and detailed understanding of calcium-calmodulin interaction can be generalized when studying larger protein complexes such as interactions between calmodulin and CaMKII.

****This poster has been selected for a Best Abstract Award and the content will also be presented as a 10 min talk in speaker session 4****

[19] The Nav1.2 channel is regulated by GSK3

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Dysregulation of glycogen synthase kinase 3β (GSK3β) has been associated to several disorders, including Alzheimer's disease, addiction, and mood disorders and may be fundamentally linked to disorders of excitability in brain circuits. We hypothesize that a critical link between GSK3β and brain disorders may arise from regulation of voltage-gated sodium (Na_v) channels that are critical molecular determinants of neuronal excitability. To test this hypothesis, we used patch clamp electrophysiology to record sodium currents from $Na_v1.2$ channels stably expressed in human embryonic kidney (HEK) cells. We found that pharmacological inhibition of GSK3 with GSK3 inhibitor XIII potentiated peak current density of $Na_v1.2$ from -56.91 ± 10.60 pA/pF (0.05% DMSO) to -115.44 ± 17.51 pA/pF (10 μM GSK3 inhibitor XIII) at -10 mV ($p=0.01$) and shifted $V_{1/2}$ of the voltage dependence of steady-state inactivation from -63.79 ± 2.05 mV to -54.14 ± 0.67 mV ($p=0.001$), without affecting the voltage dependence of activation. To explore the notion that GSK3 may modulate the expression level of these channels, we used confocal microscopy to analyze $Na_v1.2$ protein expression within the cell. Our results indicate that exposure to GSK3 inhibitor XIII induced a significant increase in $Na_v1.2$ channel expression compared to DMSO treatment ($n>80$ cells, $p<0.0001$). Taken together, these findings indicate that GSK3β modulates pathways affecting Na_v channel expression and function, broadening the repertoire of possible targets for future therapeutic interventions against its associated disorders.

[20] Relative contributions of plasticity sites in cerebellum to a conditioned response

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One of the most commonly used behavioral paradigms to study the cerebellum is eyeblink conditioning. A commonly observed property in experiments using this paradigm is a decrease of animal's performance with an increase of inter stimulus interval (ISI). We have studied the possible reasons underlying this fact by constructing a mathematical model of cerebellar-olivary system. Two sites of plasticity were included into the model: at the granule cell to Purkinje cell (Gc->Pc) synapses and at the mossy fibers to deep cerebellar nucleus (Mf->Dn) synapses. One of the model's results was that at long ISIs plasticity in Mf->Dn synapses is induced less efficiently. To check this prediction we conducted behavioral experiments, using mossy fiber stimulation as a conditioned stimulus to make sure that all learning is constrained only to the cerebellum. We trained three groups of animals. Two groups were trained at ISIs 500ms and 1500ms respectively, and were switched to ISI 2500ms after reaching a learning asymptote. Control group was trained at ISI 2500ms from naïve state. Two groups with previous training at shorter ISIs showed robust well-timed conditioned responses at ISI 2500ms, while control group showed significantly lower performance. Together, our results suggest that cerebellar cortex is able to learn even at long ISI, making plasticity at Mf->Dn synapses a limiting factor determining the animal's performance.

[21] Responses of medial prefrontal cortex during acquisition of trace eyelid conditioning

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During trace eyelid conditioning the medial prefrontal cortex (mPFC) is thought to provide the cerebellum with an input initiated by the conditioned stimulus (CS), which persists into the stimulus free trace interval. The cerebellum uses input from the CS (tone) and persistent activity from mPFC to acquire trace eyelid conditioned responses over a few hundred paired trials. Persistent activity has been described in well-trained animals, however, very little is known about changes in persistent activity from a naïve state to a learned state. Trace eyelid conditioning provides an opportunity to investigate learning-related changes in mPFC persistent activity. Before training an 18 tetrode hyperdrive array was implanted dorsal to the contralateral prefrontal cortex. Neuronal activity was recorded during training with a 500 ms tone CS, 500 ms trace interval, and 50 ms periorbital stimulation unconditioned stimulus (US). Rabbits were either given 10 paired sessions or 10 unpaired sessions followed by paired training. Neurons were isolated with an interactive cluster-cutting program (WinClust). Paired and unpaired training revealed persistent activity in mPFC initialed by the CS on the first session of training. Following individual neurons for multiple sessions revealed changes in persistent activity that corresponded with the state of learning.

[22] Understanding perceptual decision-making in area LIP with latent variable models

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The activity of neurons in macaque lateral intraparietal cortex (LIP) exhibits coupling to both visual stimulus and motor response. Previous work has suggested that LIP plays an important role in perceptual decision-making by acting as a bridge between perception and action (Shadlen & Newsome, 2001). The averaged activity of LIP neurons, recorded during a motion direction discrimination task, stereotypically show spike rates that ramp up or down in relation to the strength of the visual motion stimulus. LIP neurons also show increased firing rates correlated with the monkey's decision to saccade to a target placed within the neuron's visual response field. This apparent spike-rate ramping has been postulated as evidence of integration of motion evidence and the formation of a decision of motion direction in LIP. Previous studies have proposed how LIP neurons' firing rates relate to the monkey's choices in terms of a behavioral, decision-making framework. However, statistical inference methods for analyzing and comparing models of LIP responses have not been applied to single-trial, spike-train data. Instead, model comparison has been performed on summary statistics of spike rates taken over many trials and even multiple neurons (Churchland et al., 2011). Examining only the spike-rate mean and variance over hundreds of trials could obscure how neural representations evolve during single trials. As a result, there is a lack of appropriate, well-defined statistical tools for comparing observed spike-train data to hypotheses of LIP's involvement in decision-making. We describe inference methods for two simple models of LIP spiking responses during a decision-making period using a latent variable model framework: a diffusion-to-bound model and a discrete-switch decision model. We applied fully Bayesian inference methods for model comparison using Markov chain Monte Carlo techniques. These methods demonstrate that the single-trial activity of a neuron can exhibit a discrete switch in firing rate while the activity averaged over many trials appears to implicate a ramping process.

[23] The RNA-binding protein Sam68 is required to maintain synaptic number and long-term plasticity in the hippocampus

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Proper synaptic function requires the spatial and temporal compartmentalization of RNA metabolism via transacting RNA-binding proteins (RBPs). Loss of RBP activity leads to abnormal posttranscriptional regulation and results in diverse neurological disorders with underlying deficits in synaptic transmission and plasticity. In particular, loss of the 68-kDa RBP Src associated in mitosis (Sam68) is associated with the pathogenesis of the neurological disorder Fragile X Tremor/Ataxia Syndrome (FXTAS); a disease characterized by ataxia and decline in cognitive function. Sam68 binds to many dendritically expressed mRNAs, including the mRNA of β-actin (actb), an integral cytoskeletal component of dendritic spines. We find that loss of Sam68 results in a decrease in the amount of actb mRNA and protein at synapses. Disruption of the binding between Sam68 and its actb mRNA cargo *in vitro* or acute knockdown of Sam68 *in vivo* results in a reduction in the number of functional synapses in the hippocampus. We propose that Sam68 regulates synapse number in a cell-autonomous manner through control of postsynaptic actb mRNA metabolism. Furthermore, we have begun to examine the role of Sam68 in long-term synaptic plasticity. Interestingly, we have discovered that the magnitude of translation-dependent long-term depression mediated by mGluRs (mGluR-LTD) is diminished in CA1 *stratum radiatum*. This finding suggests that Sam68 may be involved in the local translation of plasticity related proteins required for the expression of mGluR-LTD. In conclusion, our research identifies a role for Sam68 in the regulation of local dendritic translation and may provide insight into the pathophysiology of FXTAS.

[24] mGluR activation leads to an mTOR-dependent increase in alpha2/delta-2 calcium channel subunit levels

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A fundamental property of neurons thought to underlie learning and memory is the ability to alter synaptic connections through changes in neuronal activity. Protein synthesis is necessary for different types of synaptic plasticity and mTOR (mammalian target of rapamycin) activity represents an important regulator of translation initiation. While the role of mTOR signaling in synaptic plasticity has been well established, very few mTOR targets have been identified. mRNA for two voltage-gated calcium channel subunits (Cacna1c and Cacna2d2) have been found to localize to hippocampal synapses and we therefore characterized these subunits as possible new mTOR targets. Since mTOR activity has been reported to increase following induction of long term depression in the hippocampus by chemical activation of mGluR's we investigated whether this increase leads to changes in two voltage-gated calcium channel subunits. mGluR activation did not affect Cacna1c protein expression but did increase Cacna2d2 protein expression without altering mRNA levels. Furthermore, Cacna2d2 protein levels increase in the dendrites and colocalize with PSD95 to a greater degree after mGluR activation. Finally, we prevented the increase in Cacna2d2 protein expression by blocking mTOR activity with rapamycin. Characterizing the translational regulation of these mRNAs by mTOR activity will advance the current understanding of how local protein synthesis underlies changes in neuronal excitability and ultimately learning and memory processes.

[25] Functional Shift in GABABR required to activate mTOR dependent rapid antidepressants

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Activation of N-methyl-D-aspartate receptors (NMDAR) triggers site-specific protein synthesis in dendrites through the mammalian Target of Rapamycin Complex 1 (mTORC1) kinase. Administration of NMDAR antagonists initiates a rapid anti-depressant response also through mTORC1 kinase; however the molecular mechanism is unknown. Using a combination of in vitro and in vivo manipulations, we have discovered that upon NMDAR blockade, dendritic γ-amino-butyric acid B receptors ($GABA_BR$) facilitate dendritic calcium entry. The $GABA_BR$ mediated increase in calcium signal requires the availability of dendritic L-type calcium channels. Moreover, $GABA_BR$ can activate mTOR and increase mTOR dependent expression of BDNF under the same NMDAR blocked conditions. *In vivo,* blocking $GABA_BR$ prevents the fast-acting, anti-depressant effect of the NR2B antagonist, Ro-25-6891, decreases active mTORC1 kinase, and reduces expression of BDNF and the AMPA receptor subunit GluA1. These findings propose a novel role for $GABA_BRs$ in the anti-depressant action of NR2B antagonists and as an initiator/regulator of mTORC1-mediated translation.

[26] miR-129 Regulation of Kv1.1 in Temporal Lobe Epilepsy

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Little is known about how a neuron undergoes site-specific changes in intrinsic excitability in normal and diseased conditions. We provide evidence for a novel mechanism for the mammalian Target of Rapamycin Complex 1 (mTOR) kinase dependent translational regulation of the voltage-gated potassium channel Kv1.1 mRNA. We have observed previously that miR-129 binds to and represses the local translation of Kv1.1 when mTOR is active. We have also shown that HuD binds to and increases dendritic Kv1.1 when mTOR is inhibited. To determine if this mechanism for repression of Kv1.1 expression is conserved in a disease model where mTOR activity is overactive, we assessed the expression levels of active mTOR, Kv1.1, and miR-129 in a rat model of temporal lobe epilepsy (TLE). Unlike acute changes in mTOR activity, we found that miR-129 levels increase 30 days post status epilepticus (SE), consistent with overactive mTOR activity, reduced expression of Kv1.1, and reduced threshold for action potential initiation in CA1 pyramidal hippocampal neurons. FMRP, another target of miR-129, is also reduced in TLE which may result in relieving FMRP repression of CaMKIIα. This may allow HuD binding to CaMKIIα and result in sequestering HuD from binding Kv1.1 adding another layer of Kv1.1 suppression.

[27] APP overexpression, not Aβ overproduction, underlies epileptiform activity in a mouse model of Alzheimer's disease

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Alzheimer's disease patients show an elevated risk for seizures compared to the general population. Aberrant network activity may contribute to cognitive dysfunction, a critical part of AD progression. Consistent with this observation, many AD mouse models exhibit abnormal cortical discharges and seizures. We used tet-off amyloid precursor protein (APP) overexpressing mice that display abnormal electrical discharge events to understand how neuronal excitability is regulated by APP and amyloid beta (Aβ). APP suppression progressively decreases epileptiform activity to levels not significantly different from control mice after four weeks of treatment. Past studies have suggested that Aβ accumulation contributes to neuronal excitability and disruption of normal negative feedback. However, we found that treating tet-off APP mice with a γ-secretase inhibitor to selectively decrease Aβ levels while maintaining APP overexpression had no effect on sharp wave discharge frequency. To better understand the effect of APP overexpression on cortical network excitability, we tested the effect of APP suppression during the critical time period of post-natal development. Delaying APP overexpression until mice have matured delays onset of epileptiform activity, which suggests an interaction between APP and cortical development. We are currently working to understand the relationship of APP overexpression to disruption of the neuronal network excitatory: inhibitory balance at synapses.

[28] Viral transduction of the neonatal brain delivers controllable genetic mosaicism for visualizing and manipulating neuronal circuits in vivo

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We describe a rapid and simple method for creating brain-specific transgenic mice at any desired level of mosaicism. The technique is based on freehand injection of recombinant adeno-associated virus (AAV) into the lateral ventricles of neonatal mice. Viral transgenesis is fast, easy, and allows transduction brain regions such as cerebellum and brain stem that have been difficult to target with electroporation. We show that viral serotype can be used to broaden or restrict the distribution of transduced cells, and the timing of injection can be used to control whether neurons or astrocytes are primarily transduced. We demonstrate that expression of virally-encoded proteins is active much sooner than previously believed, allowing genetic perturbation during critical periods of neuronal plasticity, but is also long-lasting and stable, allowing chronic studies of aging. We also show that viral co-expression of fluorescent protein with Cre-recombinase or Tet-transactivator provides a vital label of genetically manipulated cells in vivo. Here we use this this technique to generate a inducible mosaic mouse model for Alzheimer's disease in which transgenic expression of disease-associated amyloid precursor protein was maintained for more than a year to produce animals with a substantial amyloid burden. This model will be used to distinguish the cell-intrinsic vs. -extrinsic effects of APP/Aβ on hippocampal neurophysiology and neuronal morphology with the goal of clarifying the mechanism by which these disease-associated proteins contribute to pathogenesis.

[29] Inferring Functional Human Language Pathways

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This ongoing research is providing insight about fundamental networks involved in human language processes by applying a statistical method to time series data recorded from intracranial electrodes implanted in human subjects. Language processes involve networks of neurons sending and receiving information through convoluted systems of fiber pathways distributed throughout the cortex, and due to the unavailability of temporally and spatially precise clinical data, understanding these functional pathways has proven to be a fundamental problem in medical and biological research. This work applied a well-developed, adaptable statistical tool, Granger Causality, to hundreds of time series recordings taken directly from the cortex (electrocorticography or ECoG) of human subjects while they participated in a verb completion task. Granger Causality was used to analyze the precise ECoG data by delivering intelligible results illustrating the direction and relative magnitude of interactions that occurred between time series over periods of time and at specific frequency values. These results are interpreted as indicating how and when the brain regions located underneath the electrodes interact during precise stages of language processes, and thus far, they have been consistent with modern language theory.

[30] Synaptogenesis during LTP promotes structural changes in smooth endoplasmic reticulum along developing hippocampal dendrites

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Smooth endoplasmic reticulum (SER) is an intracellular organelle important for local calcium regulation and protein trafficking. In the hippocampus, SER forms a tubular network throughout the dendritic arbor and occasionally enters dendritic spines. SER varies in complexity along the dendritic shaft, from regions of simple tubules to more complex zones with cisternal distensions and bridging elements between tubules of SER. Local zones of SER complexity confine newly synthesized transmembrane proteins, such as glutamatergic receptors, to vicinities with more dendritic spines. In mature rats (postnatal day (P) 55-65), SER is sequestered to enlarged spines and dendritic SER becomes more tubular at 2 hours after the induction of long-term potentiation (LTP) by theta-burst stimulation (TBS). Here we tested whether changes in SER structure accompany LTP induced by TBS in developing (P15) hippocampal dendrites, an age when synapses are naturally proliferating in vivo. SER was reconstructed through serial section electron microscopy in P15 CA1 dendrites at 2 hours after TBS induced LTP, and compared to dendrites in the same slice that received control stimulation. In contrast to adult hippocampus, P15 dendritic spine density increased while average synapse size decreased by 2 hr after TBS. Like adult hippocampus, SER was more complex in spiny vs nonspiny regions of a dendrite, the dendritic SER surface area, volume, and number of spines containing SER remained stable across conditions, and the dendritic shaft SER became more tubular by 2 hours after TBS. Thus, the SER network is modulated by LTP in developing dendrites, becoming more tubular and therefore possibly allowing glutamatergic receptors and other membranous proteins to be targeted to areas of new spine formation.

[31] Enduring LTP enhances spine number at the expense of synapse size along developing hippocampal CA1 dendrites

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Long-term potentiation is a robust model system to evaluate the structural synaptic plasticity. LTP can be induced by theta-burst stimulation (TBS), a naturalistic pattern of stimulation. Control stimulation or TBS was delivered to independent sites in hippocampal slices from P15 rats. We made 3D reconstructions of these differentially stimulated dendrites using serial section transmission electron microscopy. At 2 hr after TBS, the density of small spines (head diameter (hd) < .6 μm) doubled. There was no increase in the density of large spines (hd > .6 μm). Both spine types had smaller synapses on average. However, unlike adult dendrites, the total synaptic area was increased during LTP by 30 min. Local protein synthesis was evidenced by an elevation of polyribosomes throughout the dendritic shafts and spines at 5 min after TBS. Polyribosomes remained elevated in the base of spines for 30 min after TBS, but were reduced in the heads of spines by 2 hr. This result, in contrast to our previous results with tetanus, suggests that LTP induced with TBS might use newly synthesized proteins to support new spine formation. Our findings indicate that developing dendrites are primed to establish new synaptic contacts, while mature dendrites refine synaptic strength.

[32] Inducing long-term potentiation with light in acute hippocampal slices

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We have designed a viral construct to co-express Channelrhodopsin-2 (H134R) with membrane-targeted horseradish peroxidase (mHRP) and introduced it into area CA3 of the adult rat hippocampus through an intracranial injection, rendering the Schaffer collateral fibers sensitive to activation by light. A subset of the cells in CA3 become infected, providing a mixed population of axons within CA1 where some express the introduced proteins while others do not. The co-expression of mHRP allows the production an electron-dense precipitate after exposure to diaminobenzidine, enabling visualization of the infected cells by electron microscopy. By shining pulses of blue light onto acute hippocampal slices from these animals, we are able to induce post-synaptic potentials. We found these potentials to track closely the time-course and shape of potentials produced by standard electrical stimulation with a bipolar electrode. By incubating the slices with the AMPA receptor antagonist DNQX and the NMDA receptor antagonist AP-V we were able to eliminate these potentials. Further, we found that trains of light pulses at 50Hz could induce LTP for greater than two hours. By showing light-activated EPSPs and inducing potentiation, we have laid the groundwork for future studies to compare individual potentiated and non-potentiated synapses using the mHRP component of the construct for 3D-EM analysis.

[33] Structural synaptic scaling across the dendritic tree of dentate granule cells during LTP and concurrent LTD in freely moving rats

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Electrophysiological studies have established that when long-term potentiation (LTP) is produced in the middle molecular layer (MML) of the dentate gyrus, concurrent long-term depression (cLTD) occurs in the inner (IML) and outer (OML) molecular layers. Here, we have investigated whether these changes in granule cell physiology are associated with corresponding changes in synaptic ultrastructure. Two adult male Long-Evans rats were chronically implanted with monopolar stainless steel electrodes. Stimulating electrodes were positioned to activate independent medial and lateral projections to the MML and OML of the left hemisphere, and the medial projection to the MML of the right hemisphere. Recording electrodes were implanted in the hilus of both hemispheres. After a two week recovery period, 400 Hz delta burst stimulation (DBS) was applied to the MML of the left hemisphere and produced robust LTP and cLTD. The MML of the right hemisphere received baseline stimulation, and served as a control. Evoked waveforms were monitored for 30 minutes post-DBS before animals were perfused with mixed aldehydes and prepared for serial section transmission electron microscopy. Matched dendritic segments from IML, MML and OML were then traced, reconstructed and compared between left and right hemispheres. Results revealed that LTP produced significant increases in postsynaptic density (PSD) area within the MML, and concurrent decreases within the IML and OML. These data suggest LTP and cLTD are associated with equal but opposite changes in PSD area, and supports the hypothesis that structural synaptic scaling occurs across layers of the dentate granule cell dendritic tree.

[34] Evidence for necessity of dendritic spines to express L-LTP in the developing hippocampus

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Dendritic spines host >90% of excitatory synapses and they are lost or have abnormal structure in many developmental disorders that disrupt central nervous system function. Long-term potentiation (LTP) is a synaptic model of learning and memory well-suited to investigate the role of spine and synapse structure in the normal development of learning and memory. Spines are thought to be important because they sequester core structures and molecules needed for the protein synthesis-dependent or "late" phase of LTP (L-LTP) lasting >3hr. Recent work from our laboratory has established an abrupt onset at postnatal day (P)12 of L-LTP induced by a single bout of theta-burst stimulation (TBS, 8 trains, at 30 sec, of 10 bursts at 5Hz of 4 pulses each at 100 Hz). At P8 and P10, L-LTP is not produced by this first bout of TBS; however, multiple bouts of TBS at P10, but not at P8, produce L-LTP. Here we provide new serial section data from rat hippocampus at P8, P10, and P12. Dendritic spines with mature features first appear *in vivo* at P12. Furthermore, preliminary evidence suggests that even multiple bouts of TBS do not produce dendritic spines at P8. Our findings support the hypothesis that dendritic spines are necessary for the expression of L-LTP in the developing hippocampus

[35] Synaptogenesis overwhelms structural synaptic scaling during LTP in the young hippocampus

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Dendritic spines host most of the excitatory synapses in the brain, and they are lost or have abnormal structure in disorders that disrupt central nervous system function. Long-term potentiation (LTP) is a synaptic model of learning and memory well-suited to investigate the role of spine and synapse structure in the normal development and maturation of learning and memory. Spines are likely important because they sequester core structures and molecules needed for LTP. We have demonstrated using three-dimensional reconstruction from serial section electron microscopy that robust structural synaptic plasticity is accompanied by comparable structural synaptic scaling in the mature rat hippocampus (days 51-65). At 2 hr after induction of LTP by theta-burst stimulation significant numbers of small dendritic spines are lost and the remaining spine synapses are enlarged. Summed across dendrite length this loss and enlargement is perfectly balanced such that the total synapse area supported by the dendrites (and presumably the whole neuron) remains constant across time and condition. In contrast, during development, the same TBS induction paradigm results in more dendritic spines without concomitant structural synaptic scaling. Thus, in the young hippocampus (day 15), synaptogenesis overwhelms structural synaptic scaling during LTP. (This work was supported by National Institutes of Health grants NS021184, NS033574, and EB002170 to K. Harris and The Texas Emerging Technology Fund.)

[36] Extinction, reacquisition, and rapid forgetting of eyeblink conditioning in developing rats

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Eyeblink conditioning is a well-established model for studying the developmental neurobiology of associative learning and memory. However, widely-studied phenomena such as extinction and subsequent reacquisition during development have yet to be studied using this model. The present study examined extinction and reacquisition of the classically conditioned eyeblink response in developing rats. In Experiment 1, postnatal day (P) 17 and 24 rats were trained to a criterion of 80% conditioned responses (CRs) using electrical stimulation of the middle cerebellar peduncle as a conditioned stimulus (CS). Stimulation-alone extinction training commenced 20-24 hours later, followed by reacquisition training 20-24 hours after the 4th extinction session. Contrary to expected results, rats that were trained starting on P17 showed significantly fewer CRs to stimulation CS-alone presentations relative to P24s, including fewer CRs as early as the first block of extinction session 1. Furthermore, the P17 group was slower to reacquire at reacquisition. Experiment 2 was run to determine the extent to which the low CR percentage observed in P17s early in extinction reflected rapid forgetting versus rapid extinction. Twenty four hours after reaching criterion, subjects were trained in a session split into 50 stimulation-unconditioned stimulus paired trials followed immediately by 50 stimulation-alone trials. With this "immediate" extinction protocol, CR percentages were equivalent between P17 and 24 rats during early blocks of stimulation-alone presentations. The present findings suggest that some forgetting is observed in P17 relative to P24 rats in as little as 24 hours following acquisition. To our knowledge, this is the first demonstration of the infantile amnesia phenomenon in an animal model of eyeblink conditioning.

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[37] Anterior cingulate cortex is necessary for ignoring irrelevant stimuli during visual discriminations in rats

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The role of the anterior cingulate cortex (ACC) in attention has been studied in humans and primates. These studies suggest that the ACC governs task switching and ignoring irrelevant stimulus dimensions. However, few studies have investigated the role of ACC in rodents due to the technical difficulties. Here, we examined the effects of inactivating the ACC on as rodent touch-screen discrimination task. In every trial, two cue-stimuli were presented; one was task-relevant and the other was task-irrelevant. Rats were supposed to attend to the task-relevant stimulus over the task-irrelevant one to figure out which side of the touch-screen should be touched to obtain a reward. By placing the task-relevant stimulus in either the same (congruent) or opposite (incongruent) side to the correct response for the reward, congruency effects were also examined. After the rats were fully trained, a set of cannulae targeting ACC was bilaterally implanted. Alternative injections of saline and muscimol showed that accuracy was impaired when the ACC was inactivated. Also, latency was slowed down in incongruent condition during muscimol periods. Analyses on touches on the cue-stimuli showed that rats developed anticipatory touches toward the correct side for the reward. Rats touched the stimulus proximal to the correct side more, even when the stimulus was task-irrelevant. Those anticipatory touches toward the correct response were significantly weakened during muscimol inactivation. Analysis on the pre-surgery training data suggested that rats developed the anticipatory touches across training. Touches were equivalent on both cue-stimuli at the initial phase of training but touches became biased toward the correct response at the end of pre-training. A control experiment in which there were no irrelevant stimuli showed no effects of ACC inactivation on task performance or anticipatory touches. The current study showed that ACC plays the critical role in ignoring irrelevant stimuli and spatial congruency.

[38] The nature of learning by Long-Evans rats receiving limited instrumental training under different reinforcement schedules is influenced by ethanol exposure

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We previously found that, after limited instrumental training of male, Long-Evans rats, lever pressing that had been reinforced under a variable interval (VI) schedule by oral self-administration of a 10% sucrose/10% ethanol (10S10E) solution was relatively insensitive to devaluation of 10S10E, compared to that reinforced by 10S10E under a variable ratio (VR) schedule or 10% sucrose (10S) under a VI schedule. In recent experiments, we assessed if changing the instrumental contingency also differentially affected lever press performance. Rats received 9 sessions of operant training, in which lever presses were reinforced by access to 10S10E or 10S, under VI or VR schedules. Behavior then was probed over 4 test sessions in which access to the drinking solution was granted every 120 seconds unless the lever was pressed, which reset the timer. We observed a decrease in lever pressing across sessions in both 10S10E groups, but the reduction was greater in VR than VI rats. There was no such interaction with reinforcement schedule for rats that had received only 10S reinforcement during training. The differential sensitivity of the 10S10E VI group to instrumental contingency change is consistent with our previous findings, and taken together, these studies strongly suggest that the nature of learning and, concomitantly, the mechanisms governing instrumental performance, are qualitatively different for rats receiving 10S10E reinforcement under a VI schedule

[39] Age-related Changes in the Somato-dendritic Expression of Store Depletion Induced h Plasticity in CA1 Hippocampal Neurons of the Dorsal and Ventral Hippocampus

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Plasticity of h channels in CA1 pyramidal neurons of the hippocampus has been implicated in learning and memory, disease, and adaptation to cellular stress. Here, we report that the somato-dendritic expression of one form of adaptive intrinsic plasticity, store-depletion induced (SDI) h plasticity, is highly dependent on age and dorso-ventral region of the hippocampus. Whole-cell current clamp recordings were made from neurons in the dorsal and ventral hippocampus of young and aged animals. We observed a peri-somatic expression of plasticity in young dorsal and ventral neurons. In aged animals, however, we observed a dendritic expression of plasticity for dorsal and ventral neurons, with a curious loss of plasticity at the somata of dorsal neurons. Upon further investigation, we found that the expression of SDI h plasticity in aged animals is highly dependent on membrane voltage and activation of L-type Ca^{2+} channels. Our findings demonstrate that SDI h plasticity expression is dynamic and may assume varying somato-dendritic configurations depending on age and hippocampal region. We suggest that this may be accommodative for altered needs to adapt to the Ca^{2+} dysregulation that occurs during the aging of neurons in the hippocampus.

[40] Ih and a barium-sensitive conductance interact to regulate the intrinsic excitability of CA1 pyramidal neurons from the dorsal and ventral hippocampus

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The hyperpolarization activated, cyclic nucleotide gated channel, which underlies the h current *(I_h)* is active across a range of subthreshold membrane potentials; it directly depolarizes resting membrane potential and lowers input resistance. Given the opposing nature of these two influences, it is not clear whether I_h contributes to a decrease or increase in intrinsic excitability of CA1 pyramidal neurons. To address this question, whole-cell current-clamp recordings were performed with CA1 pyramidal neurons in dorsal and ventral slices from 11-13 weeks-old rats. Blockade of I_h by ZD7288 (2 μM) in ventral neurons showed a decrease in firing, however, we observed no significant change in firing with ZD7288 in dorsal pyramidal neurons. Given the hyperpolarized resting membrane potential and lower input resistance in dorsal hippocampal CA1 neurons, we performed Ba^{2+} wash-in experiments. Blockade of Ba^{2+} sensitive K^+ channels showed large changes in the intrinsic membrane properties of dorsal neurons and minor changes in ventral neurons. Finally, blockade of Ba^{2+} sensitive K^+ channels and I_h produced different effects on resting membrane potential – depolarized in dorsal and hyperpolarized in ventral. Furthermore, changes in intrinsic excitability were different – a large increase in dorsal and minor increase in ventral. These results suggest that I_h interacting with Ba^{2+} sensitive current differentially influence intrinsic excitability in dorsal and ventral CA1 pyramidal neurons.

[41] Dendritic contributions to metabotropic glutamate receptor-mediated short- and long-term changes in intrinsic properties of layer 5 neurons

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Many prefrontal cortex (PFC)-dependent tasks require the ability of individual neurons to fire persistently in response to brief stimuli. Persistent activity is proposed to require changes in intrinsic properties that increase a neuron's sensitivity to inputs. This hypothesis may be particularly relevant to the dendrite where the bulk of synaptic inputs arrive. We tested the effects of group 1 metabotropic glutamate receptor (mGluR) activation on persistent activity-related properties in two classes of L5 neurons with distinct membrane properties; pons projecting (CPn) and commissural projecting (COM) neurons. mGluR activation produced long-term changes in the subthreshold properties of CPn, but not COM neurons. These changes involved a decrease in hyperpolarization-activated cation non-selective current (I_h) at both the soma and dendrite. mGluR activation also transiently increased the amplitude of the post-burst slow afterdepolarization potential (sADP) along the extent of the apical dendrite in both neuron types. Simultaneous somatic/dendritic recordings revealed that the dendritic sADP does not result solely from passive propagation of the somatic sADP. Focal mGluR activation in L5, near the soma or at the border of L1/2, near the tuft, generates a local sADP. This sustained dendritic depolarization may act synergistically with synaptic inputs to affect mnemonic activity in PFC.

[42] Dendritic A-type potassium channel function is altered in a mouse model of Fragile X Syndrome

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Patients with Fragile X Syndrome, the most common form of inherited mental impairment, display deficits in both working and episodic memory. Additionally, up to 90% of male Fragile X patients exhibit at least one feature of autism and 15-30% meet all the criteria. Investigations into the potential causes of Fragile X Syndrome, suggest that many deficits occur at the level of individual neurons. Despite their critical importance for neuron function almost nothing is known about how voltage-gated ion channels are altered in Fragile X Syndrome. Two recent biochemical investigations of $K_V4.2$, the putative protein subunit of the A-type potassium channel, in the *fmr1* knockout mouse model of Fragile X Syndrome came to opposite and conflicting conclusions. Using cell-attached patch clamp recordings, we directly measured the density and biophysical properties of somatic and dendritic A-type K^+ channels in hippocampal CA1 pyramidal neurons from wildtype and *fmr1-/-* mice. We found that there was significantly less A-type K^+ current (I_{KA}) in the dendrites of CA1 pyramidal neurons from *fmr1-/-* mice compared to wildtype. Measurements of the recovery from inactivation revealed that the remaining I_{KA} present in *fmr1-/-* dendrites was mediated by $K_V4.2$ containing channels. Interestingly, the activation curve for both somatic and dendritic A-type K^+ channels was hyperpolarized in *fmr1-/-* compared to wildtype. The effect these differences in I_{KA} had on dendritic function was determined by a combination of dendritic Ca^{2+} imaging and dendritic current clamp measurements. In addition to the pore-forming subunit $K_V4.2$, there are a large number of molecular substrates that control the expression and function of A-type K^+ channels. These molecules represent potential new targets for the development of therapeutic agents that could alleviate some of the debilitating effects of FXS.

[43] **Stimulus-associated dendritic calcium events during trace eyeblink conditioning**

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A central question in neuroscience is how external stimuli are transformed by the brain to produce learned behavior. To this end, we have developed a head-fixed preparation that allows for 2-photon *in vivo* imaging of dendritic calcium transients in awake behaving mice as they are trained in an associative memory task. The medial prefrontal cortex (mPFC), an area believed to be involved in this task, was injected with viral constructs to co-express the genetically encoded calcium reporter GCaMP5 and tdTomato red fluorescent protein as a structural indicator. To allow for subsequent imaging during behavior the dorsal aspect of the brain was covered by a glass coverslip and secured with dental cement. Following a 2-week recovery period, robust expression of tdTomato and GCaMP was observed in the tuft dendrites of pyramidal neurons originating in the M2 region of the mPFC. The same dendrites could be imaged over multiple days. Each training trial began with the presentation of a conditioning stimulus (150 ms blue light) followed by a 200 ms stimulus-free trace interval and ending with an unconditioned stimulus (10 ms corneal airpuff). Every other trial represented a control in which training stimuli were not presented. For several regions of dendrite, the likelihood of observing a calcium event was significantly enhanced during the presentation of the conditioning stimulus compared to the stimulus-free control trials. These results suggest that the same dendrites can be imaged across multiple training days in order to determine if there are changes in the calcium events associated with learning, and subsequent alterations to the conditioning paradigm, such as during extinction training

[44] **Advances in trace eyeblink conditioning in mice**

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Due to recent advances in genetic tools, mice provide a unique opportunity for progress in the field of trace eyelid conditioning. Previous work has shown two components to a conditioned eyelid response (CR) in the mouse—in addition to the well-established cerebellar component, there is also a short latency amygdala-dependent response (Boele, et al. 2010 Front Cell Neurosci 3: 1-13). A recent delay conditioning study utilized a head-fixed preparation in which mice were able to freely run on a wheel during conditioning. This relative lack of restraint combined with the use of a light as the conditioned stimulus paired with a corneal airpuff resulted in CRs that appeared devoid of the amygdala-dependent component (Chettih, et al. 2011 Front Integr Neurosci 5: 1-11). We extended this training paradigm by using a trace eyelid conditioning protocol and tested whether mice can also develop a CR without a short latency response in a trace paradigm. Groups of mice were trained at one of three different trace intervals (150, 200, or 300 ms between light offset and airpuff onset). More than 90% of the mice were able to learn, exhibiting CRs during 60-85% of trials during a given session. The onsets of CRs were similar for the different trace intervals, occurring 100-200 ms after light onset. However, the latency to peak response was well-timed to the onset of the airpuff for the different trace intervals. The results suggest that the amygdala is not necessary for this form of associative learning and that trace eyelid conditioning similar to that observed in rabbits can also be obtained in mice.

[45] Activity-dependent intrinsic plasticity of principal cells of the medial superior olive near the onset of hearing

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Within days after hearing onset, principal neurons of the medial superior olive (MSO) transform from slow, electrically compact neurons into fast, leaky neurons capable of detecting sub-millisecond differences in the timing of binaural inputs that are used for encoding the location of sounds along the horizontal plane. While the maturation of intrinsic properties has been characterized previously, little is known about how this transformation occurs developmentally or what mechanisms are involved. To address these questions, we delivered repetitive synchronous activation of excitatory inputs to MSO neurons in brainstem slices from Mongolian gerbils just prior to hearing onset (P9-P11). Subthreshold synaptic stimulation (trains of 10 monolateral stimuli at 100 Hz, repeated 20 times once every 5 s) produced an average decrease in input resistance (R_N) of 44±11% (n=8), the equivalent of ~2 days of development after hearing onset. The resting potential (V_m) also hyperpolarized by ~17 mV (from -54±1 mV to -71±3 mV, n=8). These changes typically occurred 5-10 minutes after stimulation and persisted for the duration of recordings (>30 min. post-stimulus). When subthreshold synaptic stimuli (4-10 mV amplitude) were paired with action potentials triggered at the peak of each EPSP by depolarizing current pulses, a similar decrease in R_N was observed (54±9%) along with a 10±4 mV hyperpolarization of the resting membrane potential (n=5). Activity-dependent changes in R_N were attenuated by blocking NMDA receptor-mediated calcium influx with 50 µM AP-5 (17±11% decrease in R_N, 8±2 mV hyperpolarization of V_m, n=4) and completely blocked by depleting intracellular calcium stores with 100 µM cyclopiazonic acid (2±7% decrease in R_N, 0±2 mV change in V_m, n=7). In addition to synaptic stimulation, application of metabotropic glutamate receptor agonists from each group, produced an average decrease in the input resistance of (DHPG 100 µM, 33±10%; LY379268 100nM, 40±10%; L-AP4 100 µM, 52±5%). The similarity between the effects of the mGluR agonists to those induced by synaptic stimulation suggest that these receptors may play an important role in the maturation of intrinsic electrical properties. The target of the calcium influx and intracellular release was examined and found to be a class of two-pore-domain potassium channels better known as leak channels. Measurement of the slope of the leak current in cell-attached recordings increased 52% after the application of the Group I mGluR agonist. Experiments using synaptic stimulation and intracellular peptides that block the phosphorylation of the TRESK leak channel by calcineurin effectively reduced the decrease in input resistance to an average of only 4%. Based on our results, we propose a model for the development of temporal precision in MSO principal cells in which the increase in temporal correlations across excitatory inputs during early auditory experience activate mGluRs and NMDARs, which then cooperatively trigger calcium-induced calcium release and subsequent changes in intrinsic ion channels, improving the speed and precision of binaural cue processing.

[46] Oscillatory synchrony of theta and gamma inputs in CA1 pyramidal neurons

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Timing is a crucial aspect of synaptic integration. For cortical pyramidal neurons, which integrate thousands of synaptic inputs spread across hundreds of microns, it is thus a challenge to maintain the timing of incoming inputs at the axo-somatic integration site. Here we show, that these neurons use a gradient of inductance in the form of HCN channels as an active mechanism to counteract location-dependent temporal differences of dendritic inputs at the soma. Using simultaneous multisite whole cell recordings complemented by computational modeling, we find that this intrinsic biophysical mechanism produces temporal synchrony of rhythmic inputs in the theta and gamma frequency ranges across wide regions of the dendritic tree. While these oscillations are thought to play important roles in synchronizing activity across space in active neuronal networks, our results identify a novel mechanism by which this synchronization extends to activity within single pyramidal neurons with extended morphologies.

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