The Fifth International Neural Microcircuitry Conference
JST Session
Microcircuitry of Cortex

Program

Miraikan, MIRAICAN Hall, Tokyo, Japan
June 29th-30th, 2010

Organizing committee:
Yoshivuki Kubota (NIPS, Japan)
Mutsuo Nuriya (Keio Univ, Japan)
Dear participants,

The fifth International Neural Microcircuitry Conference "Microcircuitry of Cortex", will be held in Miraikan, Tokyo, Japan, on June 29th - 30th, 2010.

This meeting is of significant importance for the field of cortical microcircuitry in neuroscience. The meeting will present cutting edge data obtained from studies in cortex, hippocampus, and the basal ganglia using neurophysiological approaches, molecular manipulation, electron microscopy and theoretical analysis. We are proud to have many distinguished speakers who are in the forefront of their fields from the U.S.A., U.K., Germany, Australia, China and Japan.

We hope you can join us and share this special opportunity.

Organizing Committees
Yoshiyuki Kubota, Ph.D.
Mutsuo Nuriya, Ph.D.
### Program

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- **Mirai Can Hall**
- **Conference room 3**
Program

Tuesday, June 29th

9:00 - 9:05  Opening remarks  Mutsumo Nuriya

Session 1  Chaired by Greg Stuart

9:05 - 10:00  IS1  Peter Jonas  (University of Freiburg, Germany)
  Mechanisms Underlying the Fast Synaptic Output of GABAergic Interneurons

10:00 - 10:55  IS2  Nelson Spruston  (Northwestern University, U.S.A.)
  Persistent Firing from the Axon of a Molecularly Identified Population of Inhibitory Interneurons in the Hippocampus

10:55 - 11:15  coffee break at “Conference room 3”  Chaired by Peter Jonas

11:15 - 12:10  IS3  Greg Stuart  (Australian National University, Australia)
  Somatic and Dendritic Inhibition in Cortical Pyramidal Neurons

12:10 –12:20  photo shoot

12:20 –13:35  lunch at “Conference room 3”

Session 2  Chaired by Allan Gulledge

13:35 - 14:30  IS4  Fumino Fujiyama  (Kyoto University, Japan)
  Morphological Re-evaluation of the Network in Basal Ganglia

14:30 - 15:25  IS5  Yoko Yazaki-Sugiyama  (RIKEN/Brain Science Institute, Japan)
  Bidirectional Plasticity in a Specific Cortical Inhibitory Circuit by Visual Experience

15:25 – 16:20  IS6  Gina Turrigiano  (Brandeis University, U.S.A.)
  Visual Deprivation During a Critical Period Selectively Suppresses L5 Pyramidal Neuron Excitability by Modulating the Induction of Intrinsic Plasticity

16:20 - 16:40  coffee break at “Conference room 3”

Session 3  Chaired by Gina Turrigiano

16:40 - 17:35  IS7  Yoshikazu Isomura  (Tamagawa University, Japan)
  Microcircuitry Mechanism Underlying Self-Initiation of Voluntary Movements

17:35 - 18:30  IS8  Masanori Murayama  (RIKEN/Brain Science Institute, Japan)
  Dendritic Activity In Awake Animals

Banquet

18:45 – 21:00  banquet at “Conference room 3”
Wednesday, June 30th

Session 4  
Chaired by Sacha Nelson

8:30 – 9:25  IS9  Mutsuo Nuriya (Keio University, Japan)  
Biochemical and Optical Analyses of Membrane Potential Dynamics in Neurons

9:25 – 10:20  IS10  Bartlett Mel (University of South California, U.S.A.)  
“Dark Computation” in the Neocortex: How the Computing Functions of Pyramidal Neuron Dendrites may Depend on 'Invisible' Parameters

10:20 - 10:40  coffee break at “Conference room 3”

Session 5  
Chaired by Yousheng Shu

10:40 – 11:35  IS11  Mazahir T Hasan (Max Planck Institute, Germany)  
Towards Studying the Brain with Light

11:35 – 12:30  IS12  Sacha Nelson (Brandeis University, U.S.A.)  
Physiological Genomics of Rett Syndrome

12:30 –14:30  lunch at “Conference room 3”

Session 6  
Chaired by Mazahir Hasan

14:30 - 15:25  IS13  Yousheng Shu (Shanghai Institutes for Biological Sciences)  
Membrane Potential-Dependent Modulation of Recurrent Inhibition in Neocortex

15:25 – 16:20  IS14  Masanori Matsuzaki (University of Tokyo, Japan)  
Optical Methods for Revealing the Synaptic Function and Structure in the Local Circuit

16:20 - 16:40  coffee break at “Conference room 3”

Session 7  
Chaired by Bartlett Mel

16:40 - 17:35  IS15  Allan Gulledge (Dartmouth Medical School, U.S.A.)  
Why do Neurons have Spines?

17:35 - 18:30  IS16  Yoshiyuki Kubota (National Institute for Physiological Sciences, Japan)  
Dendritic Dimensions and Signal Conduction Properties of Cortical Nonpyramidal Cells

18:30 – 18:40  Concluding Remarks  
Yoshiyuki Kubota
Abstract
Mechanisms Underlying the Fast Synaptic Output of GABAergic Interneurons

Peter Jonas

Institute of Physiology, Freiburg, Germany; Institute of Science and Technology (IST) Austria, Klosterneuburg, Austria

Fast-spiking, parvalbumin-expressing GABAergic interneurons play a key role in the function of neuronal networks. They mediate fast feedforward and feedback inhibition and are involved in the generation of oscillatory activity in the brain. For all of these functions, the rapid transmitter release at the outputs synapses of these interneurons is critically important. However, the mechanisms underlying rapid transmission are insufficiently understood. We addressed these questions at the basket cell – granule cell synapse in the dentate gyrus.

To examine whether tight coupling between Ca$^{2+}$ channels and exocytotic Ca$^{2+}$ sensors contributes to rapid transmission, we mapped the distance by introducing exogenous Ca$^{2+}$ chelators, combining paired recording and patch pipette perfusion. GABA release at basket cell-granule cell synapses was sensitive to millimolar concentrations of the fast Ca$^{2+}$ chelator BAPTA, but insensitive to the slow Ca$^{2+}$ chelator EGTA. Quantitative modeling indicates that Ca$^{2+}$ source and Ca$^{2+}$ sensor are tightly coupled at this synapse, with distances in the range of 10 – 20 nm.

The tight coupling between Ca$^{2+}$ channels and Ca$^{2+}$ sensors places constraints on the number of Ca$^{2+}$ channels involved in synaptic transmission. To determine the number of open Ca$^{2+}$ channels necessary for transmitter release at basket cell output synapses, we combined presynaptic Ca$^{2+}$ imaging and paired recording. Our results suggest that the opening of three or fewer Ca$^{2+}$ channels triggers transmitter release. Furthermore, a small number of Ca$^{2+}$ channels can evoke release with high temporal precision, despite stochastic Ca$^{2+}$ channel opening.

In conclusion, several factors contribute to rapid exocytosis at the output synapses of fast-spiking, parvalbumin-expressing GABAergic interneurons. These factors contribute to fast feedforward and feedback inhibition in hippocampal microcircuits.
References:


Persistent Firing from the Axon of a Molecularly Identified Population of Inhibitory Interneurons in the Hippocampus

Mark Sheffield¹, Tyler Best¹, William L. Kath² and Nelson Spruston¹

¹ Dept. of Neurobiology & Physiology; ² Dept. of Engineering Sciences and Applied Mathematics; Northwestern University, Evanston, Illinois, USA

Inhibitory interneurons are famously diverse, consisting of many subtypes with different morphologies, molecular identities and neurophysiological fingerprints. One study estimated the number of subtypes at sixteen in the CA1 region of the hippocampus alone [1]. In order to study a molecularly identified population of hippocampal interneurons, we obtained a BAC transgenic mouse expressing EGFP under the control of the gene for the 5-HT 5B receptor (Htr5b) [2]. A population of EGFP-positive interneurons with diverse anatomical properties but unique physiological properties was identified in the CA1 region of these mice. Labeled interneurons were present in all CA1 subfields, but we focused our study on those with cell bodies near the border of stratum radiatum and stratum lacunosum-moleculare.

In whole-cell recording from hippocampal slices, labeled interneurons exhibited a remarkable pattern of persistent firing following the delivery of multiple depolarizing current steps in the soma. Persistent firing lasted an average of about one minute, but continued for several minutes in many cells (max. 13 minutes). The number of action potentials required to evoke persistent firing was variable, and depended on the duration of each current injection and the time between current injections. Higher frequencies of firing were generally more effective, and repeated firing was more effective than epochs of firing interrupted by seconds-long periods with no stimulation. Firing patterns recorded from hippocampal interneurons in vivo evoked persistent firing very effectively. During persistent firing, the action potentials arose rapidly from the holding potential, even when the somatic recording was hyperpolarized below the usual resting potential of about -66 mV. The persistent action potentials resembled antidromic spikes in this regard. Hyperpolarization of the soma sometimes resulted in the appearance of spikelets, which were also observed during somatic hyperpolarization and antidromic stimulation of the
axon. Computational modeling suggested that the spikelets observed under these conditions are likely to be axonal action potentials that fail to actively propagate to the soma. Furthermore, the model indicated that variability in spikelet amplitude between cells is likely due to failure of antidromic action potentials at different electrotonic distances from the soma.

Persistent firing could be evoked by repetitive antidromic stimulation of the axon, even when the soma was hyperpolarized to prevent full-sized action potentials from propagating to the soma. In paired recordings from EGFP-positive interneurons, current injection into one neuron sometimes (3/19 pairs) evoked persistent firing in the second neuron, despite the absence of direct electrotonic coupling of subthreshold membrane potential.

Together, these observations suggest that action potential firing leads to a slow and cumulative process that triggers spontaneous persistent firing in the axon of some inhibitory interneurons in the hippocampus. The resulting action potentials appear to be generated in the axon, far enough from the soma that their initiation is resistant to hyperpolarization of the soma. Our results suggest that a network of inhibitory interneurons, coupled via as of yet unidentified axo-axonal interactions, can fire persistently in their axons, independent of any depolarization of the soma or dendrites.

References:
Somatic and Dendritic Inhibition in Cortical Pyramidal Neurons

Greg Stuart

John Curtin School of Medical Research, Australian National University,
Canberra, Australia

I will discuss how somatic and dendritic inhibition can impact on information processing in cortical layer 5 pyramidal neurons. The primary inhibitory neurotransmitter in the brain is GABA, which acts at ionotropic GABA-A and metabotropic GABA-B receptors. GABA-A receptors directly activate a chloride conductance, whereas GABA-B receptors either activate a potassium conductance or down-regulate voltage-activated calcium channels. In the first half of my talk I will focus on the interaction of action potentials (APs) with somatic and dendritic GABA-A mediated inhibition. This work indicates that somatic GABA-A inhibitory postsynaptic potentials (IPSPs) can be substantially reduced by appropriately timed APs due to “shunting” via the large conductance changes that occur in the axon during AP generation. In contrast, dendritic IPSPs could be boosted by APs due to an increase in driving force for inhibitory current flow during the backpropagating AP. In the second half of my talk I will focus on somatic and dendritic GABA-B mediated inhibition. Somatic GABA-B receptor activation led to a hyperpolarization of the resting membrane potential and a decrease in input resistance via a barium-sensitive potassium conductance. In contrast, dendritic GABA-B receptor activation had no effect on dendritic membrane properties, but could block dendritic calcium electrogenesis evoked by high-frequency action potential trains. This effect was mediated by a down-regulation of dendritic calcium channels. Together, these findings indicate that GABA-A and GABA-B receptor-mediated inhibition acts to modulate excitability of layer 5 pyramidal neurons via different, location-dependent mechanisms.
Morphological Re-evaluation of the Network in Basal Ganglia

Fumino Fujiyama¹², Jaerin Sohn¹, Takashi Nakano³, Takeshi Kaneko¹

¹Department of Morphological Brain Science, Graduate School of Medicine, Kyoto University, Kyoto 606-8501, JAPAN
²Japan Science and Technology Agency, CREST, Sanbancho, Chiyoda-ku, Tokyo, 102-0075, JAPAN

The axonal arborizations of single striosome projection neurons in rat neostriatum were visualized in their entirety using a viral vector expressing membrane-targeted green fluorescent protein, and compared with that of matrix projection neurons. Not only matrix but also striosome compartments were revealed to give rise to the dual striatofugal systems, i.e. direct and indirect pathways. Furthermore, only striatonigral neurons in the striosome compartment projected directly to the substantia nigra pars compacta (SNc), although they sent a substantial numbers of axon collaterals to the globus pallidus and/or substantia nigra pars reticulata. These results suggest that striosome neurons but not matrix neurons play an important role in the formation of reward-related signals of SNc dopaminergic neurons. Finally, we showed mathematically that these direct and indirect striosome-SNc pathways together with nigrostriatal dopaminergic neurons might help striosome neurons to acquire the state-value function in the reinforcement learning theory.

In addition to the two segregated striatofugal neurons, direct and indirect neurons, the neostriatum contains four kinds of interneurons. However, striatopetal innervation on the striatal interneurons has not been understood completely. To clarify the relationship between striatal parvalbumin (PV)-producing interneurons and striatopetal glutamatergic afferents, we examined the distribution of corticostriatal and thalamostriatal afferents and cholinergic striatal interneurons on the PV-producing neurons, using the transgenic mice expressing dendritic membrane-targeted GFP (green fluorescent protein) in PV-producing neurons and immunohistochemical detection of three kinds of vesicular glutamate transporters, VGLUT1, VGLUT2 and VGLUT3.
With these experiments, we are getting the hint how differently the striatal local circuit processes two lines of striatopetal excitatory information.

References:
Bidirectional Plasticity in a Specific Cortical Inhibitory Circuit by Visual Experience

Yoko Yazaki-Sugiyama1,2, Siu Kang3, Hideyuki Câteau3, Tomoki Fukai3 and Takao K. Hensch1,2

1 CREST, JST, Osaka, Japan
2 Laboratory for Neuronal Circuit Development, RIKEN Brain Science Institute, Saitama, Japan
3 Laboratory for Neural Circuit Theory, RIKEN Brain Science Institute, Saitama, Japan

Neuronal circuits in the brain can be intensively shaped during developmental critical periods. Biased visual response to one eye over the other (ocular dominance) has been a premier model of cortical circuit formation and refinement. Ocular dominance plasticity in response to altered visual experience, reflects balanced cortical circuit excitation and inhibition. Notably, mature inhibitory circuit function is required for ocular dominance plasticity to begin. Among a large variety of cortical inhibitory neuron sub-types, increasing evidence implicates a specific GABA cell-type, the parvalbumin-positive, fast-spiking cells, to be important. However, whether there is plasticity in the inhibitory circuit itself has remained largely unknown, due to the technical challenge of recording from this small, sparse cell population with extracellular methods.

Here, we have applied intracellular recording techniques in vivo to the mouse visual cortex, which allows both physiological and anatomical identification, as well as slow pharmacological access from within the same cell. Fast-spiking interneurons were identified by their characteristic thin spike shape and post mortem basket-type morphology. Surprisingly, we found that these cells exhibit an unexpected bidirectional ocular dominance plasticity, first in favor of the deprived eye then toward the open eye. This is in striking contrast to the classic monotonic ocular dominance bias shift in favor of the open eye by the major pyramidal neurons. Pharmacological blockade of GABA currents within single pyramidal neurons confirmed a dynamically modified inhibition during ocular dominance plasticity. We further tested whether a spike-timing dependent plasticity rule, unique to the fast-spiking interneuron, is sufficient for explaining this
bidirectional plasticity.

Taken together, our results suggest that dynamic ocular dominance plasticity within a specific inhibitory circuit may regulate cortical response plasticity by visual experience.
Visual Deprivation During A Critical Period Selectively Suppresses L5 Pyramidal Neuron Excitability By Modulating The Induction Of Intrinsic Plasticity

Kiran Nataraj, Sandrine LeFort, Marc Nahmani, and Gina Turrigiano

Dept of biology MS 08, Brandeis University, Waltham, MA 02454

Sensory cortex is highly sensitive to disruption by sensory deprivation during an early critical period (CP). In visual cortex monocular deprivation (MD) reduces the ability of the deprived eye to activate visual cortex, but the underlying cellular plasticity mechanisms are incompletely understood. Here we show that MD selectively reduces the intrinsic excitability of layer 5 (L5) pyramidal neurons, a major output pathway of cortex. Deprived neurons were less excitable, and when driven to fire at high frequencies had enhanced long-term potentiation of intrinsic excitability (LTP-IE). These excitability changes occurred through endocytosis-dependent changes in a persistent $K_v$ current, were tightly correlated with the classical visual system CP, and (like the functional effects of MD) could be rapidly reversed when vision was restored. These data suggest that LTP-IE plays an important role in the activity-dependent refinement of visual cortical circuits, by regulating the excitability of a major output pathway of cortex.
Neurons in the motor cortex are activated at a variety of timing during self-initiated voluntary movement. However, how excitatory (glutamatergic) and inhibitory (GABAergic) neurons in distinct cortical layers of motor cortex participate in organizing the voluntary movement has been poorly understood. Here, we performed juxtacellular recordings and multiunit recordings from the motor cortex of actively behaving rats to demonstrate temporally and functionally distinct activations of excitatory pyramidal cells and inhibitory fast-spiking (FS) interneurons. Across the cortical layers, pyramidal cells were activated diversely for sequential motor phases (e.g., preparation, initiation, execution). In contrast, FS interneurons, including parvalbumin-positive basket cells, were recruited predominantly for motor execution with pyramidal cells producing a command-like activity. The FS interneurons exhibited less direction specificity of execution-related activity than the pyramidal cells. Thus, FS interneurons may underlie command-shaping by balanced inhibition or recurrent inhibition, rather than command-gating by temporally alternating excitation and inhibition. Furthermore, our cross-correlation analysis of multiunit activity suggested that initiation-associated pyramidal cells discharged synchronously with similar and different functional classes of neurons through direct (or indirect) synaptic connections. It implies that these cells do not just initiate voluntary movement but also coordinate sequential motor information.

References:
Dendritic Activity In Awake Animals

Masanori Murayama¹,²

¹Behavioral Neurophysiology Lab, Brain Science Institute, Riken, Saitama, Japan

Very little is known about dendritic activity in living animals and even less about sensory processing and its relationship to behavior. Here, we measured dendritic calcium activity in layer 5 (L5) pyramidal neuron in the sensorimotor cortex of awake and anesthetized rats following sensory stimulation by using a fiberoptic imaging method (Murayama et al., *J Neurophysiol.*, 2007; Murayama & Larkum, *Nat. Protoc.*, 2009). Dendrites of L5 pyramidal cells in somatosensory area were bolus-loaded with Ca²⁺-sensitive dye. Hind limb stimulation evoked bi-phasic (fast and slow) dendritic responses. The strength of sensory stimulation was encoded in the fast dendritic calcium response of a local population of L5 pyramidal cells in a graded manner. Using various forms of pharmacological interventions we could show that the slope of the stimulus–response function was under the control of a particular subset of inhibitory neurons (Martinotti cell) activated by synaptic inputs predominantly in L5. Recordings from single apical tuft dendrites *in vitro* showed that activity in L5 pyramidal neurons disynaptically coupled via interneurons directly blocks the initiation of dendritic calcium spikes in neighbouring pyramidal neurons. A model of the results revealed that the microcircuit is organized so that local populations of apical dendrites can adaptively encode bottom-up sensory stimuli linearly across their full dynamic range. (Murayama et al., *Nature*, 2009).

In the awake state, there was a prominent slow, delayed response whose integral was ~14 fold larger than in the anesthetized state. These changes were confined to layer 5 pyramidal dendrites and were not reflected in the activity of layer 2/3 neurons in general. Inactivating a higher cortical, supplementary motor area (SMA) with tetrodotoxin suppressed dendritic activity as did transecting the region between the two cortical areas. Conversely, stimulation of the supplementary motor area resulted in increases in dendritic activity. Anterogradely labeling of L5 neurons with a neural tracer in the SMA showed corticocortical projections to primary sensory area. These
physiological and anatomical findings demonstrate the SMA drives the large dendritic activity in sensory area. We conclude that during the awake state, top-down connections control the duration of dendritic activity which is functionally related to behavior (Murayama & Larkum, PNAS, 2009).
Biochemical and Optical Analyses of Membrane Potential Dynamics in Neurons

Mutsuo Nuriya¹, Takashi Ito¹², Takeshi Arimitsu¹ and Masato Yasui¹

¹ Department of Pharmacology, Keio University School of Medicine, Tokyo, Japan; ² Department of Pediatrics, Kitasato University Graduate School of Medicine, Kanagawa, Japan

Voltage gated ion channels modulate intrinsic excitability of neurons and thereby transduction of voltage information through the cable. While plasticity of intrinsic excitability of neurons has been well documented by electrophysiological studies, little is known about the underlying cellular and molecular mechanisms. To better understand these mechanisms, we utilized in vivo and in vitro models and investigated the nature of biochemical changes of voltage gated ion channel in neurons.

When neuronal activity was suppressed by Tetrodotoxin, we found that hyperpolarization-activated cation channel 1 (HCN1) protein expression level is down-regulated in a reversible manner. Furthermore, we found that this modulation is accompanied by reduction in surface trafficking in neurons, which coordinately lead to decrease in functional HCN1 channel on the dendritic plasma membrane. Next, we tested these changes under pathological conditions. For this goal, we established a clinically-relevant mouse model of anoxia and following recovery. Using this model, we found that Kv2.1 channel expressed at the soma undergoes rapid and reversible changes. Detailed analyses revealed that these changes are the result of rapid dephosphorylation of Kv2.1 after over-activation of NMDA receptors. These lines of evidence suggest that voltage gated ion channels expressed in neurons are regulated in a very dynamic manner in a protein level and contribute to the plasticity of intrinsic excitability of neurons.

To further characterize these changes in voltage gated ion channels and thereby intrinsic excitability of plasma membrane, we have developed an optical method to quantitatively measure membrane potential dynamics in neurons. To this goal, a 2-photon phenomenon of the second harmonic generation imaging was employed. By applying this method to low-density hippocampal cultured neurons, membrane potential dynamics in both
dendrite and axons could be measured in a quantitative manner. Therefore, combination of biochemical and optical approaches should lead to better understanding of the membrane potential dynamics in neurons.

References:
“Dark Computation” in the Neocortex: How the Computing Functions of Pyramidal Neuron Dendrites may Depend on 'Invisible' Parameters

Bartlett W. Mel

University of Southern California, Los Angeles, CA, U.S.A.

Both experimental data and modeling studies over the past 25 years support the view that dendrites contribute substantially to the computing functions of CNS neurons. A guiding concept in the realm of dendritic computation has been that of a computational "subunit" which combines two ideas proposed by Christof Koch in the 1980's, that (1) dendrites tend to compartmentalize voltage signals within separate dendritic subregions, thus defining groups of synapses that interact with each other "as a unit", and (2) the idea that nonlinear membrane mechanisms can effect logical, algebraic, and/or temporal computations that occur in parallel with computations ongoing in other subunits. In the past few years, we have begun to explore within-subunit effects in the thin dendrites of pyramidal neurons both in computer models and brain slice experiments in collaboration with Jackie Schiller's lab, and have found that differences in the absolute and relative locations of excitatory and inhibitory synapses within a dendrite, and in the relative amounts of AMPA vs. NMDA conductance expressed by different groups of synapses, can lead to profoundly different subunit computations. In this talk, the biophysical basis of a variety of within-subunit computations will be discussed, including those that may underlie nonlinear contextual and attentional modulation effects, divisive vs. subtractive normalization, and temporal order sensitivity.
Towards Studying the Brain with Light

Mazahir T. Hasan

Department of Molecular Neurobiology
Max Planck Institute for Medical Research
Heidelberg, Germany

To understand how information is encoded in neuronal circuits and modified by experience it is necessary to identify neural correlates of various aspects of animal behavior, from sensory processing to decision-making and motor output. We are developing optogenetic methods to 1) identify candidate neural correlates by \textit{in vivo} two-photon imaging of neuronal activity with genetically-encoded fluorescent calcium indicator proteins (FCIPs) and 2) target the identified cell populations for activity manipulations. An initial critical challenge has been to develop methods that allow measurement of population recordings of neuronal activity with single-cell, single-spike resolution. Population recording of neuronal activity, repeatedly and over long time periods, preferably in freely moving subjects, is therefore a key requirement for studying the dynamic spatio-temporal relationship between neuronal activity, experience-dependent plasticity and behavior. To identify and permanently tag neurons which are activated by sensory experience, even neuronal circuits involved in associative learning and memory, we have developed a genetic approach based on immediate-early genes called genetic, activity-induced tagging (GAIT) of cells. These optogenetic approaches should enable the mapping of neuronal circuits that integrate multimodal sensory experience and behavior.

References:


Physiological Genomics of Rett Syndrome

Sacha Nelson

Dept of biology MS 08, Brandeis University, Waltham, MA 02454, U.S.A.

Rett syndrome is a devastating developmental disorder characterized by a period of normal development followed, after six to eighteen months, by a period of regression. During this period of regression patients typically lose many of the linguistic, motor and cognitive abilities they have developed before stabilizing. Patients can grow to adulthood but are often severely mentally retarded, unable to converse and have limited use of their hands and legs. Rett Syndrome is an Autism-spectrum disorder, but unlike Autism, it is due in most cases to a single, X-linked gene. The gene, Mecp2 (Methyl CpG binding protein 2) is a DNA binding protein that recognizes methylated DNA. Although how this produces the disorder is not well understood.

We have been studying a mouse model of Rett Syndrome in which the Mecp2 gene has been deleted. Our work has revealed that loss of Mecp2 function produces a shift in the balance between cortical excitation and inhibition in favor of inhibition. This is due to a loss of recurrent excitatory connections between pyramidal neurons. The loss of excitation reduces cortical activity and makes it more difficult to induce synaptic plasticity.

At a molecular level, we have found that loss of Mecp2 leads to changes in gene expression which are widespread, but which are different in different cell types. One category of genes, cell adhesion molecules, is overrepresented in each of the cell types tested. Cell adhesion genes are known to be important for establishing and maintaining appropriate synaptic connections within the nervous system. Therefore, it is tempting to speculate that Mecp2 normally orchestrates a cell-type specific transcriptional program of cell adhesion molecules that fine-tunes synaptic strength during the later phases of activity-dependent development.
Membrane Potential-Dependent Modulation of Recurrent Inhibition in Neocortex

Jie Zhu, Man Jiang, Mingpo Yang and Yousheng Shu

Institute of Neuroscience, State Key Laboratory of Neuroscience, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, Shanghai, China

A dynamic balance of excitation and inhibition is crucial for network stability and cortical processing, but it is unclear how this balance is achieved at different membrane potential ($V_m$) states, e.g., during persistent activity or slow $V_m$ oscillation. It has been shown that cortical excitatory neurons communicate not only through the generation of all-or-none action potentials (digital mode) but also through a presynaptic $V_m$-dependent modulation of transmitter release (analog mode)$^{1,2}$. Considering that interneurons within cortical microcircuits are driven by excitatory neurons, leading to recurrent inhibition$^{3,4}$, we hypothesized that the amount of recurrent inhibition might be subjected to modulation in a manner that depends on the state of depolarization of the excitatory neuron. Whole-cell recording from paired layer-5 pyramidal cells (PCs) in rat somatosensory cortical slices revealed that the amplitude of disynaptic IPSPs mediated by low-threshold spiking and fast spiking interneurons were increased in a manner directly proportional to the level of depolarization of the presynaptic PC. Further PC-interneuron pair recording showed that this modulation was attributed to PC depolarization-induced increase of EPSP amplitudes (analog communication) that elevated interneuronal firing and inhibition of neighboring PCs. Thus, an immediate $V_m$ state-dependent modulation of recurrent inhibition dynamically maintains excitation-inhibition balance of local circuits and thereby contributes to cortical information processing.

References:


Optical Methods for Revealing the Synaptic Function and Structure in the Local Circuit

Masanori Matsuzaki\textsuperscript{1,2}, Graham C.R. Ellis-Davies\textsuperscript{3}, Srinivas Kantevari\textsuperscript{3}, Yuya Kanemoto\textsuperscript{1}, Tatsuya Hayama\textsuperscript{1}, and Haruo Kasai\textsuperscript{1}

\textsuperscript{1}\ Graduate School of Medicine, University of Tokyo, Tokyo, Japan; \\
\textsuperscript{2}\ PREST and CREST, Japan Science and Technology Agency, Saitama, Japan; \\
\textsuperscript{3}\ Department of Pharmacology and Physiology, Drexel University College of Medicine, Philadelphia, USA

Two-photon (2P) excitation is a method that has revolutionized many areas of biological science as it enables three-dimensionally defined excitation of chromophores in biological tissue. We have developed 2P uncaging methods to reveal the microarchitecture of synaptic connections at a level of single synapses. Recently, we synthesized two novel caged-GABA compounds. 2P excitation of the first caged GABA produced rapid activation of GABAergic currents in neurons in brain slices with an axial resolution of approximately 2 µm and enabled high-resolution functional mapping of GABA-A receptors. The other caged GABA, when combined with an appropriate caged glutamate, allowed bimodal control of neuronal membrane potential with subcellular resolution using optically independent 2P uncaging of each neurotransmitter. We used two-color, 2P uncaging to fire and block action potentials from rat hippocampal CA1 neurons in brain slices with 720-nm and 830-nm light, respectively. In addition, we have combined 2P uncaging of glutamate over a broad area with 2P calcium imaging in a narrow region. The former was used for systematic activation of layer 2/3 pyramidal cells in the rat motor cortex, while the latter was used to detect the dendritic spines of layer 5 pyramidal cells that were innervated by some of the photoactivated cells. This technique allowed identification of various sizes of innervating spine located <140 µm laterally from the postsynaptic soma. Our new methods will be powerful tools for clarifying the microarchitecture of synaptic connections, including the positional and structural characteristics of excitatory and inhibitory synapses.
References:
Why do Neurons have Spines?

Greg J. Stuart¹, and Allan T. Gulledge²

¹ John Curtin School of Medical Research, Canberra, Australia
² Dartmouth Medical School, Hanover, NH, USA

Most excitatory cortical neurons receive glutamatergic excitatory input onto specialized neuronal processes called dendritic spines. Dendritic spines are complex structures, and malformation of spines is characteristic of many disease states associated with decreased cognition. What advantage do spines provide spiny neurons? And why are spines exclusively associated with excitatory glutamatergic synaptic transmission? In the absence of spines, the amplitude and kinetics of excitatory postsynaptic potentials (EPSPs) at the site of synaptic input are highly variable and dependent on the local dendritic geometry. Here we demonstrate a fundamental biophysical attribute of spines that limits location-dependent variability in EPSP properties at the site of synaptic input. In simplified and reconstructed neuronal morphologies, simulated excitatory synaptic conductances onto spines generate local (within spine-head) EPSPs with limited location-dependent variability in amplitude, peak latency, and half-width. The same synaptic conductances onto dendritic shafts generate local (within shaft) EPSPs whose amplitude and shape are highly location-dependent. The impact of spines on local EPSP properties is independent of synaptic conductance, but is negatively correlated with spine neck resistance. We propose that one function of spines is to standardize the amplitude and kinetics of local EPSPs, making them less dependent on synapse location within the dendritic tree. A consequence of spine-dependent EPSP standardization is that local voltage-dependent processes will be more uniformly activated at all synaptic locations. Indeed, we found that spines limited location-dependent variability in NMDA receptor activation and standardized AMPA/NMDA ratios. Because NMDA receptors and other voltage-sensitive process underly many forms of synaptic plasticity, the ability of spines to standardize local EPSP properties may allow neurons to utilize similar post-synaptic molecular mechanisms at all synaptic locations. These advantages may explain why spines occur almost exclusively at glutamatergic synapses showing dynamic, Hebbian-like plasticity.
Dendritic dimensions and signal conduction properties of cortical nonpyramidal cells

Yoshiyuki Kubota\textsuperscript{1,2,3}, Fuyuki Karube\textsuperscript{1,3}, Masaki Nomura\textsuperscript{3,4}, Allan Gulledge\textsuperscript{5}, Atsushi Mochizuki\textsuperscript{6} and Yasuo Kawaguchi\textsuperscript{1,2,3}

\textsuperscript{1} National Institute for Physiological Sciences, Okazaki, Japan;
\textsuperscript{2} The Graduate University for Advanced Studies (SOKENDAI), Okazaki, Japan;
\textsuperscript{3}JST, CREST, Tokyo, Japan;
\textsuperscript{4} Department of Applied Analysis and Complex Dynamical Systems, Kyoto University, Kyoto, Japan
\textsuperscript{5} Department of Physiology and Neurobiology, Dartmouth Medical School, Lebanon, NH, 03755 U.S.A.;
\textsuperscript{6} Theoretical Biology Laboratory, RIKEN Advanced Science Institute, Wako, Japan

Neurons receive thousands of synaptic inputs onto their dendrites and soma, and spatially and temporally integrate these inputs to produce appropriate output in the form of action potentials generated in axons. The morphology of dendrites can influence the integration of synaptic input, as well as effect the pattern of action potentials generated by suprathreshold stimuli. Using three-dimensional reconstructions from light and electron microscopic observations, we quantified the morphologies of the dendritic trees of four cortical interneuron subtypes present in the rat frontal cortex: Martinotti cells, fast spiking basket cells, double bouquet neurons, and large-basket neurons. Our ultrastructural data reveal four conserved principles governing the dendritic dimensions of these neurons. First, the cross-sectional area at any given point within a dendrite is proportional to the summed length of distally located dendrites beyond it, including all subsequent dendritic branches. Second, the total cross-sectional area is conserved at dendritic bifurcation points. Third, dendritic cross-sections are typically irregular ellipsoids rather than circles. Finally, in all neurons we found branch diameters consistent with Rall’s conductance matching assumption for dendritic bifurcations. These conserved features may facilitate even distribution of cellular components, as well as
somatic depolarization, into all compartments of the dendritic tree, and may also limit the effects of dendritic topology on action potential generation.
Information

1) Outline
   June 29th (Tue) ~ 30th (Wed)
   Conference room: Mirai CAN Hall, Miraikan 7F, Tokyo
   Reception starts at 8:40 am on 29th
   Place: Foyer in front of the Mirai CAN Hall

2) Banquet
   Place: “Conference room 3” on 7th floor
   Date & Time: at 18:45 - 21:00 on June 29th
   Fee: general fee 5,500 yen, student fee 4,000 yen (on-site)

3) Dining
   American style sandwich with drink is served at “Conference room 3”
   for 1,000 JPY upon your online registration.
   You can take lunch at restaurant (7F) or cafe (5F) in Miraikan.
   You can have your own lunch at the conference room 1 on 7th floor.

4) Excursion
   Enjoy the Miraikan exhibition (National Museum of Emerging Science and Innovation), especially robot performance show by Honda ASIMO at 14:00 – 14:10 during the long lunch break on 30th.

5) Coffee break
   Coffee and drink are served in “Conference room 3”.
   Please understand that eating and drinking is prohibited in “Mirai CAN Hall”.

Oral Presentation Instruction

Please bring your own note PC and check the connection with the projector in advance during the coffee break or before the session. Someone should wait for you to help checking the connectivity between your note PC and the projector during the coffee break or at least 15 - 30 minutes before the session.
ご案内

1）国際研究集会概要
日程：2010年6月29日（火）〜30日（水）
場所：東京お台場 日本科学未来館 7階
  みらいCANホール
受付：29日午前8時40分〜
受付場所：7階 みらいCANホール前 ホワイエ

2）懇親会
開催場所：会議室3 7階
開催時間：29日18:45〜21:00
会費：一般5,500円 学生4,000円（当日申込可）

3）食事
7階の会議室3において、バイキング形式でアメリカンサンドイッチランチ
（飲物付）を1,000円で提供します。
7階のレストラン、5階のカフェもご利用ください。
また、周辺には、他施設のレストランやコンビニが徒歩5分程度の所にあります。
日本科学未来館7階の会議室1を、お弁当をご持参された方の為の昼食会場として開放します。

4）日本科学未来館団体入場割引券
日本科学未来館団体入場割引券を販売します。事前にオンライン申込にて受付けます。また、入場日の朝9時半までに、会場受付においても受付けます。

5）コーヒーブレイク
コーヒーブレイクは、7階会議室3に準備します。なお、みらいCANホールは、
一切飲食禁止です。ペットボトルやコーヒー等の飲み物他の持ち込みはご遠慮下さい。

招待講演者の方へ

ご講演に際しては、ご自身のノートPCをご持参の上、コーヒーブレイクで
セッションの前にプロジェクターとの接続を各自でご確認下さい。必要な場合は、
担当者がお手伝いしますので、声をおかけ下さい。
ACCESS(MAP)

You can use various modes of transportation to visit Miraikan, such as the Tokyo Waterfront New Transit YURIKAMOME, the Tokyo Waterfront Area Rapid Transit RINKAI LINE, the Bay Shuttle (free bus service), Buses, and automobile.

Tokyo Waterfront New Transit YURIKAMOME
5 minutes walk from "Fune-no Kagakukan station"
4 minutes walk from "Telemic Center station"

Tokyo Waterfront Area Rapid Transit RINKAI LINE
15 minutes walk from "Tokyo Teleport station"

Bay Shuttle (free bus service)
Buses are available every 15-25 minutes, from 11:00 to 20:00

Miraikan Exhibition is closed on June 29th.
日本科学未来館は、6月29日は定休日です。
ASIMO Demonstration

The science communicator of Miraikan, "ASIMO" will make its appearance. Let's together think about the future where we live with robots.

Time: 11:00 - 11:10 2. 14:00 - 14:10
Venue: 3F Robot World

Geo-Cosmos Demonstration

Using the world's first spherical display, "Geo-Cosmos," the science communicator will introduce the condition of the earth as seen from outer space etc. Let's think together about "Our planet - earth."

Time: 1. 12:00 - 12:15 (Only on Sat., Sun. and Holidays) 2. 15:00 - 15:15
Venue: 3F "Innovation and the Future"

Special Exhibition scheduled in the future

Special Exhibition "DORAEMON's Scientific Future"

Term: June 12(Sat.) - September 27 (Mon.). 2010
Venue: 1F Exhibition Space
Admission Fees: 1,300 yen, 18 years old and under: 600 yen (Permanent Exhibition can be viewed.)

The MANGA "DORAEMON" has attracted people of all ages and nationalities. One key to its fame, no doubt, are the magical gadgets featured in the story. See how far those dreamlike secret items are actualized with the current science and technology. Let's experience and enjoy this exhibition with the entire family!

Dome Theater GAIA - Program Schedule

Reservations are required for the Dome Theater GAIA. Pick up a numbered ticket on the 1F. (Tickets will be available from the opening time of 10:00 am, in the order of arrival, valid only for the day of issue. 1 reservation ticket will be issued for each admission ticket. In addition to this, each person can make reservations for only one show on Saturdays, Sundays and Holidays.)

<table>
<thead>
<tr>
<th>Time</th>
<th>Program</th>
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<tbody>
<tr>
<td>11:00</td>
<td>Birthday (Live)</td>
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<td>12:00</td>
<td>Tender is the Night (Only on Sat., Sun. and Holidays)</td>
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<td>15:00</td>
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<td>16:00</td>
<td>Tender is the Night (Only on Sat., Sun. and Holidays)</td>
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3D Image Program "BIRTHDAY - What Links the Universe and Me"

Birthday

This program is the introduction of Atmos, presented to all of those who wonder about "the beginning."

We will portray a realistic image of space using the 3D images of "Atmos" and the 5 million head stars of the "MEGASTAR-III cosmos."

(Run Time: Approx. 25 min.)

Planetarium Presentation "Tender is the Night"

The starmy sky as seen from various districts on Earth, the sounds that can be heard within those regions, along with words of poetry that describe the night in these various areas will be presented through the planetarium program which makes visitors aware of their existence on this vast Earth.

(Run Time: Approx. 25 min.)
日立卓上顕微鏡
TM3000

全世界で1000台以上の出荷実績を持つ
TM-1000の後継機として待望の次世代機登場

特長
卓上サイズでコンパクト設計
従来機*1と比べ設置面積を約20%削減しました。

オート機能でシンプル操作
オートスタート、オートフォーカス、オート輝度などの機能を搭載しました。

高倍率で焦点深度の深い*2形態観察
観察倍率15倍〜30,000倍の設定が可能です。

*1 当社製品機TM-1000比
*2 一部の光学系機種を除く

TM3000操作画面（モニターに表示されている写真の試料は太陽電池です）

最先端を、最前線へ。
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Easy Environment for Live Cells

BioStation CT

多量のサンプルを安定した環境で培養しながら自動観察！

- 安定環境のインキュベータ内で、培養サンプルを自動で顕微鏡撮影します。
- いつでもどこでも、同じクオリティで大量サンプルの複数倍率のタイムラブースデータを簡単に取得できます。
- 培養容器全体を再解像して撮影するフルスキャン機能により、樹立効率の低いIPS-ES細胞も確実にイメージングします。
- 各種プラスコ、ディッシュ、ウェルプレートに対応できます。

生細胞タイムラブースイメージング装置

Bio Station IMq

培養から高感度タイムラブース画像取得・解析まで、これ一台で簡単！

- 培養、画像取得、解析の3つの機能を一体化。顕微鏡やカメラの操作に慣れていない方でも簡単で観察・撮影が可能です。
- 長時間観察で大きな問題となるフォーカスリフトを、温度変化、振動の両面からも解消しました。
- タイムラブース撮影しながら培地交換可能なオプションユニットと、コントロール実験可能な4分割ディッシュをご用意。
ハヤシはモノづくりの全工程をお手伝いします。

協賛企業：

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