

This Week in The Journal

● Cellular/Molecular

Spines Rich in PSD-95 Can Retract

Georgia F. Woods, Won Chan Oh, Lauren C. Boudewyn, Sarah K. Mikula, and Karen Zito

(see pages 12129–12138)

The postsynaptic density protein PSD-95 creates a scaffold for organizing receptors, ion channels, cytoskeletal proteins, adhesion molecules, and signaling molecules at glutamatergic synapses. As such, PSD-95 plays a central role in determining postsynaptic density size and helps regulate synaptic strength. PSD-95 is thought to be an important component of synaptic plasticity, because its overexpression increases synaptic glutamate receptor levels, EPSC amplitude, and spine density. Given these roles, Woods et al. hypothesized that reduction of PSD-95 would be necessary during destabilization and elimination of dendritic spines. Consistent with this hypothesis, time-lapse two-photon microscopy revealed that most dendritic spines that retracted within a 1 h recording session in rat hippocampal slice cultures had relatively low levels of PSD-95. Nonetheless, some spines that retracted had relatively high levels of PSD-95, and levels remained high during retraction. Thus, high PSD-95 expression does not guarantee spine retention, and loss of PSD-95 is not a prerequisite for spine elimination.

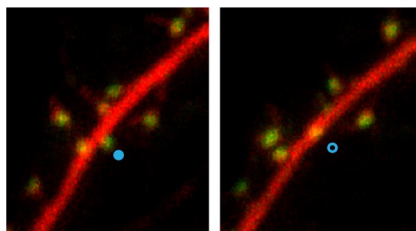
▲ Development/Plasticity/Repair

p38 Triggers Cholinergic Switch in Sympathetic Neurons

Bernhard Loy, Galina Apostolova, Roland Dorn, Victoria A. McGuire, J. Simon C. Arthur, et al.

(see pages 12059–12067)

Sympathetic neurons are noradrenergic when they first differentiate. Some of these neurons, specifically those that innervate sweat glands, subsequently transdifferentiate into cholinergic neurons in response to target-derived cytokines. These cytokines act on gp130/LIFR β heterodimeric recep-



Spines that have relatively high levels of PSD-95 (blue circle, left) can retract (right). See the article by Woods et al. for details.

tors, leading via poorly defined signaling cascades to activation of the nuclear matrix protein Satb2, which drives expression of cholinergic genes. Loy et al. discovered that p38 mitogen-activated protein kinase—a kinase normally associated with cell stress pathways and apoptosis—is required for this cholinergic switch. Treatment of cultured rodent noradrenergic sympathetic neurons with ciliary neurotrophic factor (CNTF) or leukemia inhibitory factor (LIF), both of which cause transdifferentiation, led to rapid and sustained activation of p38. Overexpression of p38 caused upregulation of cholinergic markers, whereas p38 inhibitors prevented CNTF- and LIF-induced upregulation of Satb2 and cholinergic markers. In addition, mice lacking p38 β had fewer cholinergic neurons than control mice in the ganglion that innervates sweat glands.

■ Behavioral/Systems/Cognitive

Subiculum Generates Fast and Slow Gamma Rhythms

Jesse Jackson, Romain Goutagny, and Sylvain Williams

(see pages 12104–12117)

Local field potentials (LFPs) within many brain areas oscillate at multiple frequencies. Oscillations at gamma frequencies (~ 30 – 140 Hz) depend on local inhibitory connections and are thought to be important for synchronizing ensembles of principal neurons to facilitate and temporally organize information transfer. Two distinct gamma frequency bands are present within the hippocampal formation: slow (25–50 Hz), which originates in CA3, and

fast (80–140 Hz), which originates in medial entorhinal cortex (MEC). CA3 and MEC transmit gamma oscillations to distinct subsets of CA1 neurons at different times, depending on whether information is being encoded or retrieved. Because CA1 and MEC project to the subiculum, Jackson et al. expected to find both slow and fast oscillations in this structure. Indeed, both frequencies were present in rat subiculum *in vitro*, but unexpectedly, these oscillations were generated within the subiculum itself. Unlike in CA1, both frequencies sometimes occurred simultaneously in subiculum, and neurons could phase-lock to either frequency.

◆ Neurobiology of Disease

Sympathetic Outflow Is Not Resistant to Leptin in Obese Mice

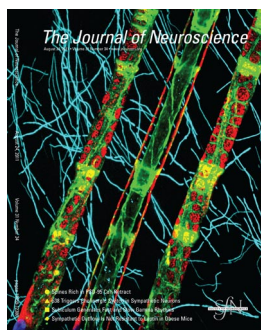
Pablo J. Enriori, Puspha Sinnayah, Stephanie E. Simonds, Cecilia Garcia Rudaz, and Michael A. Cowley

(see pages 12189–12197)

Unlike the more familiar white fat tissue, brown adipose tissue (BAT) does not function in lipid storage, but rather in thermogenesis. Sympathetic stimulation of brown adipocytes leads to activation of uncoupling protein 1, which allows the electrochemical gradient across inner mitochondrial membranes to dissipate without producing ATP; instead, heat is produced. This process allows small mammals to survive in cold climates, and it helps to maintain energy balance by boosting energy consumption when caloric intake is high. Hypothalamic nuclei involved in energy balance respond to leptin, a hormone present in blood at levels proportional to body fat. Increased leptin levels decrease appetite and increase sympathetic outflow to BAT, stimulating thermogenesis. If consumption of high-calorie foods continues, however, rodents become resistant to leptin, which no longer reduces appetite. Nonetheless, Enriori et al. found that leptin retained its ability to induce BAT thermogenesis in these mice. Thermogenesis raised body temperature, but did not consume sufficient energy to prevent obesity.

The Journal of Neuroscience

August 24, 2011 • Volume 31 Number 34 • www.jneurosci.org



Cover legend: An isolated sciatic nerve fiber, partially projected to show each half and the middle of the fiber. The fiber is stained with fluorescent phalloidin (green), dystrophin-related protein 2 antibodies (red), and nuclear DAPI (dark blue) to show compartments present outside myelin, which is stained with antibodies against myelin basic protein (light blue). For more information, see the article by Court et al. in this issue (pages 12208–12217).

i This Week in The Journal

Brief Communications

- 12159 **Age-dependent Homeostatic Plasticity of GABAergic Signaling in Developing Retinal Networks**
Matthias H. Hennig, John Grady, James van Coppenhagen, and Evelyne Sernagor

Articles

CELLULAR/MOLECULAR

- 12083 **Synaptic Autoregulation by Metalloproteases and γ -Secretase**
Sophie Restituito, Latika Khatri, Ipe Ninan, Paul M. Mathews, Xin Liu, Richard J. Weinberg, and Edward B. Ziff
- 12094 **Maintenance of Dendritic Spine Morphology by Partitioning-Defective 1b through Regulation of Microtubule Growth**
Kenji Hayashi, Atsushi Suzuki, Syu-ichi Hirai, Yasuyuki Kurihara, Casper C. Hoogenraad, and Shigeo Ohno
- 12118 **Cyclin B1 Expression Regulated by Cytoplasmic Polyadenylation Element Binding Protein in Astrocytes**
Ki Chan Kim, Won Jung Oh, Kwang Ho Ko, Chan Young Shin, and David G. Wells
- 12129 **Loss of PSD-95 Enrichment Is Not a Prerequisite for Spine Retraction**
Georgia F. Woods, Won Chan Oh, Lauren C. Boudewyn, Sarah K. Mikula, and Karen Zito
- 12180 **Counting Ion and Water Molecules in a Streaming File through the Open-Filter Structure of the K Channel**
Masayuki Iwamoto and Shigetoshi Oiki
- 12208 **MMP2-9 Cleavage of Dystroglycan Alters the Size and Molecular Composition of Schwann Cell Domains**
Felipe A. Court, Desirée Zambroni, Ernesto Pavoni, Cristina Colombelli, Chiara Baragli, Gianluca Figlia, Lydia Sorokin, William Ching, James L. Salzer, Lawrence Wrabetz, and M. Laura Feltri
- 12241 **Polycystin-1 Is Required for Stereocilia Structure But Not for Mechanotransduction in Inner Ear Hair Cells**
Katherine A. Steigelman, Andrea Lelli, Xudong Wu, Jiangang Gao, Susan Lin, Klaus Piontek, Claas Wodarczyk, Alessandra Boletta, Hyunkho Kim, Feng Qian, Gregory Germino, Gwenaëlle S. G. Géléoc, Jeffrey R. Holt, and Jian Zuo

12251 **Acute Cocaine Exposure Weakens GABA_B Receptor-Dependent G-Protein-Gated Inwardly Rectifying K⁺ Signaling in Dopamine Neurons of the Ventral Tegmental Area**
Devinder Arora, Matthew Hearing, Desirae M. Haluk, Kelsey Mirkovic, Ana Fajardo-Serrano, Martin W. Wessendorf, Masahiko Watanabe, Rafael Luján, and Kevin Wickman

12371 **Two Amino Acid Residues Contribute to a Cation- π Binding Interaction in the Binding Site of an Insect GABA Receptor**
Sarah C. R. Lummis, Ian McGonigle, Jamie A. Ashby, and Dennis A. Dougherty

DEVELOPMENT/PLASTICITY/REPAIR

12059 **p38 α and p38 β Mitogen-Activated Protein Kinases Determine Cholinergic Transdifferentiation of Sympathetic Neurons**
Bernhard Loy, Galina Apostolova, Roland Dorn, Victoria A. McGuire, J. Simon C. Arthur, and Georg Dechant

12068 **Bone Morphogenetic Protein Inhibition Promotes Neurological Recovery after Intraventricular Hemorrhage**
Krishna Dummula, Govindaiah Vinukonda, Philip Chu, Yiping Xing, Furong Hu, Sabrina Mailk, Anna Csiszar, Caroline Chua, Peter Mouton, Robert J. Kayton, Joshua C. Brumberg, Rashmi Bansal, and Praveen Ballabh

12139 **Effects of Training of Processing Speed on Neural Systems**
Hikaru Takeuchi, Yasuyuki Taki, Hiroshi Hashizume, Yuko Sassa, Tomomi Nagase, Rui Nouchi, and Ryuta Kawashima

BEHAVIORAL/SYSTEMS/COGNITIVE

12104 **Fast and Slow Gamma Rhythms Are Intrinsically and Independently Generated in the Subiculum**
Jesse Jackson, Romain Goutagny, and Sylvain Williams

12149 **Complementary Sensory and Associative Microcircuitry in Primary Olfactory Cortex**
Hauke F. Wiegand, Prateep Beed, Michael H. K. Bendels, Christian Leibold, Dietmar Schmitz, and Friedrich W. Jochenning

12165 **Frequency-Dependent Tuning of the Human Motor System Induced by Transcranial Oscillatory Potentials**
Matteo Feurra, Giovanni Bianco, Emiliano Santarnecchi, Massimiliano Del Testa, Alessandro Rossi, and Simone Rossi

12171 **Ultrafast Population Encoding by Cortical Neurons**
Tatjana Tchumatchenko, Aleksey Malyshev, Fred Wolf, and Maxim Volgushev

12198 **Adaptation Changes Stereoscopic Depth Selectivity in Visual Cortex**
Thang Duong, Bartlett D. Moore IV, and Ralph D. Freeman

12218 **Electrical Synaptic Input to Ganglion Cells Underlies Differences in the Output and Absolute Sensitivity of Parallel Retinal Circuits**
Gabe J. Murphy and Fred Rieke

12229 **Relationship between Functional Magnetic Resonance Imaging-Identified Regions and Neuronal Category Selectivity**
Andrew H. Bell, Nicholas J. Malecek, Elyse L. Morin, Fadila Hadj-Bouziane, Roger B. H. Tootell, and Leslie G. Ungerleider

12258 **Hippocampal Telomerase Is Involved in the Modulation of Depressive Behaviors**
Qi-Gang Zhou, Yao Hu, Dan-Lian Wu, Li-Juan Zhu, Chen Chen, Xing Jin, Chun-Xia Luo, Hai-Yin Wu, Jing Zhang, and Dong-Ya Zhu

12270 **Memory-Guided Learning: CA1 and CA3 Neuronal Ensembles Differentially Encode the Commonalities and Differences between Situations**
Amir S. Bahar, Prasad R. Shirvalkar, and Matthew L. Shapiro

- 12282 **A Model of Intracellular Theta Phase Precession Dependent on Intrinsic Subthreshold Membrane Currents**
L. Stan Leung
- 12297 **Single Synapse Information Coding in Intraburst Spike Patterns of Central Pattern Generator Motor Neurons**
Ludmila Brochini, Pedro V. Carelli, and Reynaldo D. Pinto
- 12307 **Functional Heterogeneity of Macaque Lateral Intraparietal Neurons**
Elsie Premereur, Wim Vanduffel, and Peter Janssen
- 12318 **Endogenous Brain-Derived Neurotrophic Factor in the Nucleus Tractus Solitarius Tonically Regulates Synaptic and Autonomic Function**
Catharine G. Clark, Eileen M. Hasser, Diana L. Kunze, David M. Katz, and David D. Kline
- 12339 **Orientation Selectivity of Synaptic Input to Neurons in Mouse and Cat Primary Visual Cortex**
Andrew Y. Y. Tan (陈勇毅), Brandon D. Brown, Benjamin Scholl, Deepankar Mohanty, and Nicholas J. Priebe
- 12351 **Anatomical Evidence for the Involvement of the Macaque Ventrolateral Prefrontal Area 12r in Controlling Goal-Directed Actions**
Elena Borra, Marzio Gerbella, Stefano Rozzi, and Giuseppe Luppino
- 12364 **Sex Differences in the Use of Anticipatory Brain Activity to Encode Emotional Events**
Giulia Galli, Noham Wolpe, and Leun J. Otten
- 12377 **The Representation of Visual and Motor Aspects of Reaching Movements in the Human Motor Cortex**
Michal Eisenberg, Lior Shmuelof, Eilon Vaadia, and Ehud Zohary

NEUROBIOLOGY OF DISEASE

- 12189 **Leptin Action in the Dorsomedial Hypothalamus Increases Sympathetic Tone to Brown Adipose Tissue in Spite of Systemic Leptin Resistance**
Pablo J. Enriori, Puspha Sinnayah, Stephanie E. Simonds, Cecilia Garcia Rudaz, and Michael A. Cowley
- 12330 **Antipsychotic Drugs Rapidly Induce Dopamine Neuron Depolarization Block in a Developmental Rat Model of Schizophrenia**
Ornella Valenti, Pierangelo Cifelli, Kathryn M. Gill, and Anthony A. Grace
- 12385 **Correction:** The article "A Novel Transient Glutamatergic Population Migrating from the Pallial-Subpallial Boundary Contributes to Neocortical Development," by Anne Teissier, Amélie Griveau, Lisa Vigier, Tristan Piolot, Ugo Borello, and Alessandra Pierani, originally appeared on pages 10563–10574 of the August 4, 2010 issue. A correction for that article appears on page 12385.

Persons interested in becoming members of the Society for Neuroscience should contact the Membership Department, Society for Neuroscience, 1121 14th St., NW, Suite 1010, Washington, DC 20005, phone 202-962-4000.

Instructions for Authors are available at <http://www.jneurosci.org/misc/itoa.shtml>. Authors should refer to these Instructions online for recent changes that are made periodically.

Brief Communications Instructions for Authors are available via Internet (http://www.jneurosci.org/misc/ifa_bc.shtml).

Submissions should be submitted online using the following url: <http://jneurosci.msubmit.net>. Please contact the Central Office, via phone, fax, or e-mail with any questions. Our contact information is as follows: phone, 202-962-4000; fax, 202-962-4945; e-mail, jn@sfn.org.

Synaptic Autoregulation by Metalloproteases and γ -Secretase

Sophie Restituito,¹ Latika Khatri,¹ Ipe Ninan,² Paul M. Mathews,^{2,3} Xin Liu,⁴ Richard J. Weinberg,⁵ and Edward B. Ziff¹

Departments of ¹Biochemistry and ²Psychiatry, New York University Langone Medical Center, New York, New York 10016, ³Nathan Kline Institute for Psychiatric Research, Orangeburg, New York, 10962, ⁴Department of Molecular and Medical Pharmacology, University of California, Los Angeles, California 90095, and ⁵Department of Cell and Developmental Biology, Neuroscience Center, University of North Carolina, Chapel Hill, North Carolina 27599

The proteolytic machinery comprising metalloproteases and γ -secretase, an intramembrane aspartyl protease involved in Alzheimer's disease, cleaves several substrates in addition to the extensively studied amyloid precursor protein. Some of these substrates, such as N-cadherin, are synaptic proteins involved in synapse remodeling and maintenance. Here we show, in rats and mice, that metalloproteases and γ -secretase are physiologic regulators of synapses. Both proteases are synaptic, with γ -secretase tethered at the synapse by δ -catenin, a synaptic scaffolding protein that also binds to N-cadherin and, through scaffolds, to AMPA receptor and a metalloprotease. Activity-dependent proteolysis by metalloproteases and γ -secretase takes place at both sides of the synapse, with the metalloprotease cleavage being NMDA receptor-dependent. This proteolysis decreases levels of synaptic proteins and diminishes synaptic transmission. Our results suggest that activity-dependent substrate cleavage by synaptic metalloproteases and γ -secretase modifies synaptic transmission, providing a novel form of synaptic autoregulation.

The Journal of Neuroscience, August 24, 2011 • 31(34):12083–12093

Maintenance of Dendritic Spine Morphology by Partitioning-Defective 1b through Regulation of Microtubule Growth

Kenji Hayashi,¹ Atsushi Suzuki,¹ Syu-ichi Hirai,¹ Yasuyuki Kurihara,² Casper C. Hoogenraad,^{3,4} and Shigeo Ohno¹

¹Department of Molecular Biology, Yokohama City University Graduate School of Medical Science, Kanazawa-ku, Yokohama 236-0004, Japan, ²Laboratory of Molecular Biology, Faculty of Engineering, Yokohama National University, Hodogaya-ku, Yokohama 240-8501, Japan, ³Cell Biology, Faculty of Science, Utrecht University, 3584 CH, Utrecht, The Netherlands, and ⁴Department of Neuroscience, Erasmus Medical Center, 3013GE, 3000 CA, Rotterdam, The Netherlands

Dendritic spines are postsynaptic structures that receive excitatory synaptic input from presynaptic terminals. Actin and its regulatory proteins play a central role in morphogenesis of dendritic spines. In addition, recent studies have revealed that microtubules are indispensable for the maintenance of mature dendritic spine morphology by stochastically invading dendritic spines and regulating dendritic localization of p140Cap, which is required for actin reorganization. However, the regulatory mechanisms of microtubule dynamics remain poorly understood. Partitioning-defective 1b (PAR1b), a cell polarity-regulating serine/threonine protein kinase, is thought to regulate microtubule dynamics by inhibiting microtubule binding of microtubule-associated proteins. Results from the present study demonstrated that PAR1b participates in the maintenance of mature dendritic spine morphology in mouse hippocampal neurons. Immunofluorescent analysis revealed PAR1b localization in the dendrites, which was concentrated in dendritic spines of mature neurons. PAR1b knock-down cells exhibited decreased mushroom-like dendritic spines, as well as increased filopodia-like dendritic protrusions, with no effect on the number of protrusions. Live imaging of microtubule plus-end tracking proteins directly revealed decreases in distance and duration of microtubule growth following PAR1b knockdown in a neuroblastoma cell line and in dendrites of hippocampal neurons. In addition, reduced accumulation of GFP-p140Cap in dendritic protrusions was confirmed in PAR1b knock-down neurons. In conclusion, the present results suggested a novel function for PAR1b in the maintenance of mature dendritic spine morphology by regulating microtubule growth and the accumulation of p140Cap in dendritic spines.

The Journal of Neuroscience, August 24, 2011 • 31(34):12094–12103

Cyclin B1 Expression Regulated by Cytoplasmic Polyadenylation Element Binding Protein in Astrocytes

Ki Chan Kim,¹ Won Jung Oh,¹ Kwang Ho Ko,¹ Chan Young Shin,^{2,3} and David G. Wells³

¹Department of Pharmacology, College of Pharmacy, Seoul National University, Seoul 151-742, Korea, ²Department of Pharmacology, School of Medicine and Center for Geriatric Neuroscience Research, Institute of Biomedical Science and Technology, Konkuk University, Seoul 143-701, Korea, and ³Department of Molecular, Cellular, and Developmental Biology, Yale University, New Haven, Connecticut 06520-8103

Astrocytes are the most abundant cells in the brain, playing vital roles in neuronal survival, growth, and function. Understanding the mechanism(s) regulating astrocyte proliferation will have important implications in brain development, response to injury, and tumorigenesis. Cyclin B1 is well known to be a critical regulator of mitotic entry via its interaction with cyclin-dependent kinase 1. In rat astrocytes, we now show that the mRNA binding protein cytoplasmic polyadenylation element binding protein 1 (CPEB1) is associated with cyclin B1 mRNA and that this interaction is enriched at the centrosome. In addition, if growth-arrested astrocytes are stimulated to divide, CPEB1 is phosphorylated and cyclin B1 mRNA is polyadenylated, both hallmarks of CPEB1 activation, resulting in an increase in cyclin B1 protein. CPEB1 binding to mRNA initially inhibits translation; therefore, removing CPEB1 from mRNA should result in an increase in translation due to derepression. Indeed, when we either knocked down CPEB1 protein with siRNA or sequestered it from endogenous mRNA by expressing RNA containing multiple CPEB1 binding sites, cyclin B1 protein was increased and cell

proliferation was stimulated. Our data suggest a mechanism wherein CPEB1 is bound and represses cyclin B1 mRNA translation until a signal to proliferate phosphorylates CPEB1, resulting in an increase in cyclin B1 protein and progression into mitosis. Our results demonstrate for the first time a role for CPEB1 in regulating cell proliferation in the brain.

The Journal of Neuroscience, August 24, 2011 • 31(34):12118–12128

Loss of PSD-95 Enrichment Is Not a Prerequisite for Spine Retraction

Georgia F. Woods, Won Chan Oh, Lauren C. Boudewyn, Sarah K. Mikula, and Karen Zito

Center for Neuroscience, University of California, Davis, California 95618

Changes in neuronal structure are thought to underlie long-term behavioral modifications associated with learning and memory. In particular, considerable evidence implicates the destabilization and retraction of dendritic spines along with the loss of spine synapses as an important cellular mechanism for refining brain circuits, yet the molecular mechanisms regulating spine elimination remain ill-defined. The postsynaptic density protein, PSD-95, is highly enriched in dendritic spines and has been associated with spine stability. Because spines with low levels of PSD-95 are more dynamic, and the recruitment of PSD-95 to nascent spines has been associated with spine stabilization, we hypothesized that loss of PSD-95 enrichment would be a prerequisite for spine retraction. To test this hypothesis, we used dual-color time-lapse two-photon microscopy to monitor rat hippocampal pyramidal neurons cotransfected with PSD-95-GFP and DsRed-Express, and we analyzed the relationship between PSD-95-GFP enrichment and spine morphological changes. Consistent with our hypothesis, we found that the majority of spines that retracted were relatively unenriched for PSD-95-GFP. However, in the subset of PSD-95-GFP-enriched spines that retracted, spine shrinkage and loss of PSD-95-GFP were tightly coupled, suggesting that loss of PSD-95-GFP enrichment did not precede spine retraction. Moreover, we found that, in some instances, spine retraction resulted in a significant enrichment of PSD-95-GFP on the dendritic shaft. Our data support a model of spine retraction in which loss of PSD-95 enrichment is not required prior to the destabilization of spines.

The Journal of Neuroscience, August 24, 2011 • 31(34):12129–12138

Counting Ion and Water Molecules in a Streaming File through the Open-Filter Structure of the K Channel

Masayuki Iwamoto and Shigetoshi Oiki

Department of Molecular Physiology and Biophysics, University of Fukui Faculty of Medical Sciences, Eiheiji-cho, Yoshida-gun, Fukui 910-1193, Japan

The mechanisms underlying the selective permeation of ions through channel molecules are a fundamental issue related to understanding how neurons exert their functions. The “knock-on” mechanism, in which multiple ions in the selectivity filter are hit by an incoming ion, is one of the leading concepts. This mechanism has been supported by crystallographic studies that demonstrated ion distribution in the structure of the *Streptomyces lividans* (KcsA) potassium channel. These still pictures under equilibrium conditions, however, do not provide a snapshot of the actual, ongoing permeation processes. To understand the dynamics of permeation, we determined the ratio of the ion and water flow [the water-ion coupling ratio (CR_{w-i})] through the KcsA channel by measuring the streaming potential (V_{stream}) electrophysiologically. The V_{stream} value was converted to the CR_{w-i} value, which reveals how individual ion and water molecules are queued in the narrow and short filter during permeation. At high K^+ concentrations, the CR_{w-i} value was 1.0, indicating that turnover between the alternating ion and water arrays occurs in a single-file manner. At low K^+ , the CR_{w-i} value was increased to a point over 2.2, suggesting that the filter contained mostly one ion at a time. These average behaviors of permeation were kinetically analyzed for a more detailed understanding of the permeation process. Here, we envisioned the permeation as queues of ion and water molecules and sequential transitions between different patterns of arrays. Under physiological conditions, we predicted that the knock-on mechanism may not be predominant.

The Journal of Neuroscience, August 24, 2011 • 31(34):12180–12188

MMP2-9 Cleavage of Dystroglycan Alters the Size and Molecular Composition of Schwann Cell Domains

Felipe A. Court,¹ Desirée Zambroni,¹ Ernesto Pavoni,¹ Cristina Colombelli,¹ Chiara Baragli,¹ Gianluca Figlia,¹ Lydia Sorokin,² William Ching,³ James L. Salzer,³ Lawrence Wrabetz,¹ and M. Laura Feltri¹

¹Division of Genetics and Cell Biology, San Raffaele Scientific Institute, 20132 Milan, Italy, ²Institute of Physiological Chemistry and Pathobiochemistry, University of Muenster, 48149 Muenster, Germany, and ³Department of Cell Biology and Neurology, and the Smilow Neuroscience Program, New York University School of Medicine, New York, New York 10016

Myelinating glial cells exhibit a spectacular cytoarchitecture, because they polarize on multiple axes and domains. How this occurs is essentially unknown. The dystroglycan–dystrophin complex is required for the function of myelin-forming Schwann cells. Similar to other tissues, the dystroglycan complex in Schwann cells localizes with different dystrophin family members in specific domains, thus promoting polarization. We show here that cleavage of dystroglycan by matrix metalloproteinases 2 and 9, an event that is considered pathological in most tissues, is finely and dynamically regulated in normal nerves and modulates dystroglycan complex composition and the size of Schwann cell compartments. In contrast, in nerves of $Dy^{2j/2j}$ mice, a model of laminin 211 deficiency, metalloproteinases 2 and 9 are increased, causing excessive dystroglycan cleavage and abnormal compartments. Pharmacological inhibition of cleavage rescues the cytoplasmic defects of $Dy^{2j/2j}$ Schwann cells. Thus, regulated cleavage may be a general mechanism to regulate protein complex composition in physiological conditions, whereas unregulated processing is pathogenic and a target for treatment in disease.

The Journal of Neuroscience, August 24, 2011 • 31(34):12208–12217

Polycystin-1 Is Required for Stereocilia Structure But Not for Mechanotransduction in Inner Ear Hair Cells

Katherine A. Steigelman,^{1,2} Andrea Lelli,³ Xudong Wu,¹ Jiangang Gao,¹ Susan Lin,¹ Klaus Piontek,⁴ Claas Wodarczyk,⁵ Alessandra Boletta,⁵ Hyunho Kim,⁴ Feng Qian,⁴ Gregory Germino,^{4,6} Gwenaëlle S. G. Gélécoc,³ Jeffrey R. Holt,³ and Jian Zuo¹

¹Department of Developmental Neurobiology, St. Jude Children's Research Hospital, Memphis, Tennessee 38105, ²Department of Anatomy and Neurobiology, University of Tennessee Health Science Center, Memphis, Tennessee 38163, ³Department of Neuroscience, University of Virginia, Charlottesville, Virginia 22908, ⁴Division of Nephrology, Johns Hopkins University, Baltimore, Maryland 21205, ⁵Dulbecco Telethon Institute, DIBIT San Raffaele Scientific Institute, 20132 Milan, Italy, and ⁶National Institute of Diabetes and Digestive and Kidney Disease, National Institutes of Health, Bethesda, Maryland 20892

The *polycystic kidney disease-1* (*Pkd1*) gene encodes a large transmembrane protein (polycystin-1, or PC-1) that is reported to function as a fluid flow sensor in the kidney. As a member of the transient receptor potential family, PC-1 has also been hypothesized to play a role in the elusive mechanoelectrical transduction (MET) channel in inner ear hair cells. Here, we analyze two independent mouse models of PC-1, a knock-in (KI) mutant line and a hair cell-specific inducible Cre-mediated knock-out line. Both models exhibit normal MET channel function at neonatal ages despite hearing loss and ultrastructural abnormalities of stereocilia that remain properly polarized at adult ages. These findings demonstrate that PC-1 plays an essential role in stereocilia structure and maintenance but not directly in MET channel function or planar cell polarity. We also demonstrate that PC-1 is colocalized with F-actin in hair cell stereocilia *in vivo*, using a hemagglutinin-tagged PC-1 KI mouse model, and in renal epithelial cell microvilli *in vitro*. These results not only demonstrate a novel role for PC-1 in the cochlea, but also suggest insight into the development of polycystic kidney disease.

The Journal of Neuroscience, August 24, 2011 • 31(34):12241–12250

Acute Cocaine Exposure Weakens GABA_B Receptor-Dependent G-Protein-Gated Inwardly Rectifying K⁺ Signaling in Dopamine Neurons of the Ventral Tegmental Area

Devinder Arora,^{1*} Matthew Hearing,^{1*} Desirae M. Haluk,^{1*} Kelsey Mirkovic,¹ Ana Fajardo-Serrano,³ Martin W. Wessendorf,² Masahiko Watanabe,⁴ Rafael Luján,³ and Kevin Wickman¹

Departments of ¹Pharmacology and ²Neuroscience, University of Minnesota, Minneapolis, Minnesota 55455, ³Departamento de Ciencias Médicas, Universidad de Castilla–La Mancha, 02006 Albacete, Spain, and ⁴Department of Anatomy, Hokkaido University School of Medicine, Sapporo 060-8638, Japan

Enhanced glutamatergic neurotransmission in dopamine (DA) neurons of the ventral tegmental area (VTA), triggered by a single cocaine injection, represents an early adaptation linked to the more enduring effects of abused drugs that characterize addiction. Here, we examined the impact of *in vivo* cocaine exposure on metabotropic inhibitory signaling involving G-protein-gated inwardly rectifying K⁺ (Girk) channels in VTA DA neurons. Somatodendritic Girk currents evoked by the GABA_B receptor (GABA_BR) agonist baclofen were diminished in a dose-dependent manner in mice given a single cocaine injection. This adaptation persisted for 3–4 d, was specific for DA neurons of the VTA, and occurred in parallel with an increase in spontaneous glutamatergic neurotransmission. No additional suppression of GABA_BR–Girk signaling was observed following repeated cocaine administration. While total Girk2 and GABA_BR1 mRNA and protein levels were unaltered by cocaine exposure in VTA DA neurons, the cocaine-induced decrease in GABA_BR–Girk signaling correlated with a reduction in Girk2-containing channels at the plasma membrane in VTA DA neurons. Systemic pretreatment with sulpiride, but not SCH23390 (7-chloro-3-methyl-1-phenyl-1,2,4,5-tetrahydro-3-benzazepin-8-ol), prevented the cocaine-induced suppression of GABA_BR–Girk signaling, implicating D_{2/3} DA receptor activation in this adaptation. The acute cocaine-induced weakening of somatodendritic Girk signaling complements the previously demonstrated cocaine-induced strengthening of glutamatergic neurotransmission, likely contributing to enhanced output of VTA DA neurons during the early stages of addiction.

The Journal of Neuroscience, August 24, 2011 • 31(34):12251–12257

Two Amino Acid Residues Contribute to a Cation- π Binding Interaction in the Binding Site of an Insect GABA Receptor

Sarah C. R. Lummis,¹ Ian McGonigle,¹ Jamie A. Ashby,¹ and Dennis A. Dougherty²

¹Department of Biochemistry, University of Cambridge, Cambridge CB2 1QW, United Kingdom, and ²Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125

Cys-loop receptor binding sites characteristically possess an “aromatic box,” where several aromatic amino acid residues surround the bound ligand. A cation- π interaction between one of these residues and the natural agonist is common, although the residue type and location are not conserved. Even in the closely related vertebrate GABA_A and GABA_C receptors, residues in distinct locations perform this role: in GABA_A receptors, a Tyr residue in loop A forms a cation- π interaction with GABA, while in GABA_C receptors it is a loop B residue. GABA-activated Cys-loop receptors also exist in invertebrates, where they have distinct pharmacologies and are the target of a range of pesticides. Here we examine the location of GABA in an insect binding site by incorporating a series of fluorinated Phe derivatives into the receptor binding pocket using unnatural amino acid mutagenesis, and evaluating the resulting receptors when expressed in *Xenopus* oocytes. A homology model suggests that two aromatic residues (in loops B and C) are positioned such that they could contribute to a cation- π interaction with the primary ammonium of GABA, and the data reveal a clear

correlation between the GABA EC₅₀ and the cation- π binding ability both at Phe206 (loop B) and Tyr254 (loop C), demonstrating for the first time the contribution of two aromatic residues to a cation- π interaction in a Cys-loop receptor.

The Journal of Neuroscience, August 24, 2011 • 31(34):12371–12376

DEVELOPMENT/PLASTICITY/REPAIR

p38 α and p38 β Mitogen-Activated Protein Kinases Determine Cholinergic Transdifferentiation of Sympathetic Neurons

Bernhard Loy,¹ Galina Apostolova,¹ Roland Dorn,¹ Victoria A. McGuire,² J. Simon C. Arthur,² and Georg Dechant¹

¹Institute for Neuroscience, Innsbruck Medical University, MZA, 6020 Innsbruck, Austria, and ²MRC Protein Phosphorylation Unit, College of Life Sciences, University of Dundee, Dundee, Scotland DD1 5EH, United Kingdom

Although the p38 mitogen-activated protein kinases are active in many neuronal populations in the peripheral and central nervous systems, little is known about the physiological functions of p38 in postmitotic neurons. We report that p38 activity determines *in vitro* and *in vivo* the switch from noradrenergic to cholinergic neurotransmission that occurs in sympathetic neurons on exposure to the neurotrophic cytokines CNTF and LIF. This transdifferentiation serves as a model for the plastic mechanisms that enable mature neurons to change some of their central functions without passing through the cell cycle. We demonstrate that in postmitotic neurons, p38 and STAT pathways are concurrently activated by neurotrophic cytokine treatment for at least 12 h overlapping with changes in neurotransmitter marker gene expression. Inhibition of p38 blocks the upregulation of the nuclear matrix protein Satb2 and of cholinergic markers by CNTF without affecting STAT3 phosphorylation. Conversely, overexpression of p38 α or β in the absence of cytokines stimulates cholinergic marker expression. The neurotransmitter switch *in vitro* is impaired in neurons isolated from p38 β ^{−/−} mice. Consistent with these *in vitro* results, a substantial loss of cells expressing cholinergic properties is observed *in vivo* in the stellate ganglion of mature mice deficient in the p38 β isoform.

The Journal of Neuroscience, August 24, 2011 • 31(34):12059–12067

Bone Morphogenetic Protein Inhibition Promotes Neurological Recovery after Intraventricular Hemorrhage

Krishna Dummula,^{1,8} Govindaiah Vinukonda,^{1,2} Philip Chu,³ Yiping Xing,¹ Furong Hu,¹ Sabrina Mailk,¹ Anna Csiszar,⁴ Caroline Chua,¹ Peter Mouton,⁵ Robert J. Kayton,⁶ Joshua C. Brumberg,³ Rashmi Bansal,⁷ and Praveen Ballabh^{1,2}

Departments of ¹Pediatrics and ²Anatomy and Cell Biology, New York Medical College–Westchester Medical Center, Valhalla, New York 10595,

³Department of Psychology, Queens College, City University of New York, Flushing, New York 11367, ⁴Reynolds Oklahoma Center on Aging, Department of Geriatric Medicine, University of Oklahoma Health Science Center, Oklahoma City, Oklahoma 73104, ⁵Department of Pathology and Cell Biology, University of South Florida School of Medicine, Tampa, Florida 33612, ⁶Department of Physiology and Pharmacology, Oregon Health & Science University, Portland, Oregon 97239, ⁷Department of Neuroscience, University of Connecticut Medical School, Farmington, Connecticut 06030, and ⁸Department of Pediatrics, University of Kansas, School of Medicine, Kansas City, Kansas 66160

Intraventricular hemorrhage (IVH) results in neural cell death and white matter injury in premature infants. No therapeutic strategy is currently available against this disorder. Bone morphogenetic protein (BMP) signaling suppresses oligodendrocyte development through basic-helix-loop-helix (bHLH) transcription factors and promotes astrocytosis. Therefore, we hypothesized that IVH in premature newborns initiates degeneration and maturation arrest of oligodendrocyte lineage and that BMP inhibition alleviates hypomyelination, gliosis, and motor impairment in the survivors of IVH. To test the hypotheses, a rabbit model of IVH was used in which premature rabbit pups (E29) are treated with intraperitoneal glycerol at 2 h of age to induce IVH; and the pups with IVH exhibit hypomyelination and gliosis at 2 weeks of postnatal age. Maturation of oligodendrocyte lineage was evaluated by specific markers, and the expression of bHLH transcription factors was assessed. BMP levels were measured in both premature rabbit pups and autopsy materials from premature infants. Recombinant human noggin was used to suppress BMP action; and neurobehavioral performance, myelination and gliosis were assessed in noggin-treated pups compared with untreated controls. We found that IVH resulted in apoptosis and reduced proliferation of oligodendrocyte progenitors, as well as arrested maturation of preoligodendrocytes in rabbits. BMP4 levels were significantly elevated in both rabbit pups and human premature infants with IVH compared with controls. Importantly, BMP inhibition by recombinant human noggin restored the levels of phospho-Smad1/5/8, Olig2 transcription factor, oligodendrocyte maturation, myelination, astrocyte morphology, and motor function in premature pups with IVH. Hence, BMP inhibition might enhance neurological recovery in premature infants with IVH.

The Journal of Neuroscience, August 24, 2011 • 31(34):12068–12082

Effects of Training of Processing Speed on Neural Systems

Hikaru Takeuchi,¹ Yasuyuki Taki,² Hiroshi Hashizume,² Yuko Sassa,² Tomomi Nagase,³ Rui Nouchi,¹ and Ryuta Kawashima^{1,2,4}

¹Smart Ageing International Research Center, Institute of Development, Aging and Cancer, ²Division of Developmental Cognitive Neuroscience, Institute of Development, Aging and Cancer, ³Faculty of Medicine, and ⁴Department of Functional Brain Imaging, Institute of Development, Aging and Cancer, Tohoku University, Sendai 980-8575, Japan

Processing speed (PS) training improves performance on untrained PS tasks in the elderly. However, PS training's effects on the PS of young adults and on neural mechanisms are still unknown. In humans, we investigated this issue using psychological measures, voxel-based morphometry, the *n*-back task [a typical task for functional magnetic resonance imaging (fMRI) studies with conditions of 0-back (simple cognitive processes) and 2-back tasks (working memory; WM)], resting-state fMRI for the analysis of functional connectivity between brain regions during rest (resting-FC), and intensive adaptive training of PS. PS training was associated with (1) significant or substantial improvement in the performance of PS measures, (2) changes in the gray matter structures of the left superior temporal gyrus and the bilateral regions around the occipitotemporal junction, (3) changes in functional activity that are related to simple cognitive processes (but not those of WM) in the left perisylvian region, and (4) increased resting-FC between the left perisylvian area and the area that extends to the lingual gyrus and calcarine cortex. These results confirm the PS-training-induced plasticity in PS and the training-induced plasticity of functions and structures that are associated with speeded cognitive processes. The observed neural changes caused by PS training may give us new insights into how PS training, and possibly other cognitive training, can improve PS.

The Journal of Neuroscience, August 24, 2011 • 31(34):12139–12148

BEHAVIORAL/SYSTEMS/COGNITIVE

Fast and Slow Gamma Rhythms Are Intrinsically and Independently Generated in the Subiculum

Jesse Jackson, Romain Goutagny, and Sylvain Williams

Douglas Mental Health University Institute, McGill University, Department of Psychiatry, Montréal, Québec, Canada H4H 1R3

Gamma rhythms are essential for memory encoding and retrieval. Despite extensive study of these rhythms in the entorhinal cortex, dentate gyrus, CA3, and CA1, almost nothing is known regarding their generation and organization in the structure delivering the most prominent hippocampal output: the subiculum. Here we show using a complete rat hippocampal preparation *in vitro* that the subiculum intrinsically and independently generates spontaneous slow (25–50 Hz) and fast (100–150 Hz) gamma rhythms during the rising phase and peak of persistent subicular theta rhythms. These two gamma frequencies are phase modulated by theta rhythms without any form of afferent input from the entorhinal cortex or CA1. Subicular principal cells and interneurons phase lock to both fast and slow gamma, and single cells are independently phase modulated by each form of gamma rhythm, enabling selective participation in neural synchrony at both gamma frequencies at different times. Fast GABAergic inhibition is required for the generation of fast gamma, whereas slow gamma is generated by excitatory and inhibitory mechanisms. In addition, the transverse subicular axis exhibits gamma rhythm topography with faster gamma coupling arising in the distal subiculum region. The subiculum therefore possesses a unique intrinsic circuit organization that can autonomously regulate the timing and topography of hippocampal output synchronization. These results suggest the subiculum is a third spontaneous gamma generator in the hippocampal formation (in addition to CA3 and the entorhinal cortex), and these gamma rhythms likely play an active role in mediating the flow of information between the hippocampus and multiple cortical and subcortical brain regions.

The Journal of Neuroscience, August 24, 2011 • 31(34):12104–12117

Complementary Sensory and Associative Microcircuitry in Primary Olfactory Cortex

Hauke F. Wiegand,^{1,4} Prateep Beed,¹ Michael H. K. Bendels,² Christian Leibold,^{5,6} Dietmar Schmitz,^{1,3,7*} and Friedrich W. Jochenning^{1*}

¹Neuroscience Research Center, ²Neurophysics Group, Department of Neurology, ³Cluster of Excellence “NeuroCure,” and ⁴Department of Psychiatry, Charité-Universitätsmedizin Berlin, 10117 Berlin, Germany, ⁵Bernstein Center for Computational Neuroscience Munich, 82152 Planegg-Martinsried, Germany, ⁶Division of Neurobiology, Ludwig-Maximilians-Universität München, 82152 Planegg-Martinsried, Germany, and ⁷Bernstein Center for Computational Neuroscience Berlin, 10115 Berlin, Germany

The three-layered primary olfactory (piriform) cortex is the largest component of the olfactory cortex. Sensory and intracortical inputs converge on principal cells in the anterior piriform cortex (aPC). We characterize organization principles of the sensory and intracortical microcircuitry of layer II and III principal cells in acute slices of rat aPC using laser-scanning photostimulation and fast two-photon population Ca^{2+} imaging. Layer II and III principal cells are set up on a superficial-to-deep vertical axis. We found that the position on this axis correlates with input resistance and bursting behavior. These parameters scale with distinct patterns of incorporation into sensory and associative microcircuits, resulting in a converse gradient of sensory and intracortical inputs. In layer II, sensory circuits dominate superficial cells, whereas incorporation in intracortical circuits increases with depth. Layer III pyramidal cells receive more intracortical inputs than layer II pyramidal cells, but with an asymmetric dorsal offset. This microcircuit organization results in a diverse hybrid feedforward/recurrent network of neurons integrating varying ratios of intracortical and sensory input depending on a cell's position on the superficial-to-deep vertical axis. Since burstiness of spiking correlates with both the cell's location on this axis and its incorporation in intracortical microcircuitry, the neuronal output mode may encode a given cell's involvement in sensory versus associative processing.

The Journal of Neuroscience, August 24, 2011 • 31(34):12149–12158

Frequency-Dependent Tuning of the Human Motor System Induced by Transcranial Oscillatory Potentials

Matteo Feurra, Giovanni Bianco, Emiliano Santarnecchi, Massimiliano Del Testa, Alessandro Rossi, and Simone Rossi

Dipartimento di Neuroscienze, Sezione Neurologia e Neurofisiologia Clinica, Azienda Ospedaliera-Universitaria Senese, Policlinico Le Scotte, I-53100 Siena, Italy

Different corticothalamic brain modules intrinsically oscillate at a “natural frequency” in a topographically organized manner. In “quiescent” human sensorimotor regions, the main detectable oscillatory activity peaks at ~ 20 Hz, and partly contributes to determine the state of corticospinal excitability. Here, we showed that the transcranial application of an imperceptible, short-lasting (90 s) electric field oscillating at a physiological range increases corticospinal excitability online, with well defined frequency dependence and regional specificity. Indeed, the size of motor evoked potentials (MEPs) induced by navigated single-pulse TMS over the motor cortex significantly increased only during the local application of transcranial alternating current stimulation (tACS) at 20 Hz (β range). Other tACS frequencies (5, 10, and 40 Hz) applied on the motor cortex did not impact MEPs’ size. Moreover, tACS applied on a control site (parietal cortex) and on a peripheral site (ulnar nerve) also failed to modulate MEPs. These results help clarifying the functional significance of the 20 Hz idling β rhythm of sensorimotor regions and suggest potential clinical applications of this approach.

The Journal of Neuroscience, August 24, 2011 • 31(34):12165–12170

Ultrafast Population Encoding by Cortical Neurons

Tatjana Tchumatchenko,^{1,2} Aleksey Malyshev,^{3,4} Fred Wolf,¹ and Maxim Volgushev^{3,4,5}

¹Max Planck Institute for Dynamics and Self-Organization and Bernstein Center for Computational Neuroscience, D-37073 Goettingen, Germany,

²Collaborative Research Center 889 Cellular Mechanisms of Sensory Processing, D-37075 Goettingen, Germany, ³Institute of Higher Nervous Activity and Neurophysiology, Russian Academy of Sciences, Moscow 117485, Russia, ⁴Department of Psychology, University of Connecticut, Storrs, Connecticut 06269, and ⁵Department of Neurophysiology, Ruhr University Bochum, D-44801 Bochum, Germany

The processing speed of the brain depends on the ability of neurons to rapidly relay input changes. Previous theoretical and experimental studies of the timescale of population firing rate responses arrived at controversial conclusions, some advocating an ultrafast response scale but others arguing for an inherent disadvantage of mean encoded signals for rapid detection of the stimulus onset. Here we assessed the timescale of population firing rate responses of neocortical neurons in experiments performed in the time domain and the frequency domain *in vitro* and *in vivo*. We show that populations of neocortical neurons can alter their firing rate within 1 ms in response to somatically delivered weak current signals presented on a fluctuating background. Signals with amplitudes of miniature postsynaptic currents can be robustly and rapidly detected in the population firing. We further show that population firing rate of neurons of rat visual cortex *in vitro* and cat visual cortex *in vivo* can reliably encode weak signals varying at frequencies up to ~ 200 – 300 Hz, or ~ 50 times faster than the firing rate of individual neurons. These results provide coherent evidence for the ultrafast, millisecond timescale of cortical population responses. Notably, fast responses to weak stimuli are limited to the mean encoding. Rapid detection of current variance changes requires extraordinarily large signal amplitudes. Our study presents conclusive evidence showing that cortical neurons are capable of rapidly relaying subtle mean current signals. This provides a vital mechanism for the propagation of rate-coded information within and across brain areas.

The Journal of Neuroscience, August 24, 2011 • 31(34):12171–12179

Adaptation Changes Stereoscopic Depth Selectivity in Visual Cortex

Thang Duong, Bartlett D. Moore IV, and Ralph D. Freeman

Group in Vision Science, School of Optometry, Helen Wills Neuroscience Institute, University of California, Berkeley, Berkeley, California 94720-2020

Exposure to specific visual stimuli causes a reduction in sensitivity to similar subsequent stimulation. This adaptation effect is observed behaviorally and for neurons in the primary visual cortex. Here, we explore the effects of adaptation on neurons that encode binocular depth discrimination in the cat’s primary visual cortex. Our results show that neuronal preference for binocular depth is altered selectively with appropriate adaptation. At the preferred depth, adaptation causes substantial suppression of subsequent responses. Near the preferred depth, the same procedure causes a shift in depth preference. At the null depth, adaptation has little effect on binocular depth coding. These results demonstrate that prior exposure can change the depth selectivity of binocular neurons. The findings are relevant to the theoretical treatment of binocular depth processing. Specifically, the prevailing notion of binocular depth encoding based on the energy model requires modification.

The Journal of Neuroscience, August 24, 2011 • 31(34):12198–12207

Electrical Synaptic Input to Ganglion Cells Underlies Differences in the Output and Absolute Sensitivity of Parallel Retinal Circuits

Gabe J. Murphy^{1,2} and Fred Rieke¹

¹Howard Hughes Medical Institute and Department of Physiology & Biophysics, University of Washington, Seattle, Washington 98195-7290, and ²HHMI/Janelia Farm Research Campus, Ashburn, Virginia 20147

Parallel circuits throughout the CNS exhibit distinct sensitivities and responses to sensory stimuli. Ambiguities in the source and properties of signals elicited by physiological stimuli, however, frequently obscure the mechanisms underlying these distinctions. We found that differences in the degree to which activity in two classes

of Off retinal ganglion cell (RGC) encode information about light stimuli near detection threshold were not due to obvious differences in the cells' intrinsic properties or the chemical synaptic input the cells received; indeed, differences in the cells' light responses were largely insensitive to block of fast ionotropic glutamate receptors. Instead, the distinct responses of the two types of RGCs likely reflect differences in light-evoked electrical synaptic input. These results highlight a surprising strategy by which the retina differentially processes and routes visual information and provide new insight into the circuits that underlie responses to stimuli near detection threshold.

The Journal of Neuroscience, August 24, 2011 • 31(34):12218–12228

Relationship between Functional Magnetic Resonance Imaging-Identified Regions and Neuronal Category Selectivity

Andrew H. Bell,¹ Nicholas J. Malecek,¹ Elyse L. Morin,¹ Fadila Hadj-Bouziane,¹ Roger B. H. Tootell,^{1,2,3} and Leslie G. Ungerleider¹

¹Laboratory of Brain and Cognition, National Institute of Mental Health, National Institutes of Health, Bethesda, Maryland 20892, ²Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Charlestown, Massachusetts 02129, and ³Department of Radiology, Harvard Medical School, Boston, Massachusetts 02115

Functional magnetic resonance imaging (fMRI) has been used extensively to identify regions in the inferior temporal (IT) cortex that are selective for categories of visual stimuli. However, comparatively little is known about the neuronal responses relative to these fMRI-defined regions. Here, we compared in nonhuman primates the distribution and response properties of IT neurons recorded within versus outside fMRI regions selective for four different visual categories: faces, body parts, objects, and places. Although individual neurons that preferred each of the four categories were found throughout the sampled regions, they were most concentrated within the corresponding fMRI region, decreasing significantly within 1–4 mm from the edge of these regions. Furthermore, the correspondence between fMRI and neuronal distributions was specific to neurons that increased their firing rates in response to the visual stimuli but not to neurons suppressed by visual stimuli, suggesting that the processes associated with inhibiting neuronal activity did not contribute strongly to the fMRI signal in this experiment.

The Journal of Neuroscience, August 24, 2011 • 31(34):12229–12240

Hippocampal Telomerase Is Involved in the Modulation of Depressive Behaviors

Qi-Gang Zhou,^{1*} Yao Hu,^{1*} Dan-Lian Wu,¹ Li-Juan Zhu,¹ Chen Chen,¹ Xing Jin,¹ Chun-Xia Luo,^{1,2} Hai-Yin Wu,² Jing Zhang,¹ and Dong-Ya Zhu^{1,2}

¹Department of Pharmacology, School of Pharmacy, and ²Laboratory of Cerebrovascular Disease, Nanjing Medical University, Nanjing 210029, China

Telomere and telomerase alterations have been reported in mood disorders. However, the role of telomerase in depression remains unclear. Here we show that chronic mild stress (CMS) led to a significant decrease in telomerase reverse transcriptase (TERT) level and telomerase activity in the hippocampus. Treatment with antidepressant fluoxetine reversed the CMS-induced TERT and telomerase activity changes. Inhibiting telomerase by systemic administration (100 mg · kg⁻¹ · d⁻¹, i.p., for 14 d), intrahippocampal microinjection (0.7 μmol, 2 μl), or infusion (using an osmotic minipump, 0.134 μg/μl, 0.25 μl/h) of 3'-azido-deoxythymidine (AZT) resulted in depression-like behaviors and impaired hippocampal neurogenesis in mice. In contrast, overexpressing telomerase by intrahippocampal infusion of recombinant adenovirus vector expressing mouse TERT (Ad-mTERT-GFP) led to neurogenesis upregulation, produced antidepressant-like behaviors, and prevented the CMS-induced behavioral modifications. Disrupting neurogenesis in the dentate gyrus by X-irradiation (15 Gy) of a restricted region of mouse brain containing the hippocampus abolished the antidepressant-like effect of Ad-mTERT-GFP. Additionally, AZT had no effect on DNA polymerase activity and did not cause cell damage *in vitro* and *in vivo*. Microinjection of AZT into the subventricular zone of lateral ventricle (0.7 μmol, 2 μl) inhibited local neurogenesis but had no behavioral effect. These results suggest that hippocampal telomerase is involved in the modulation of depression-related behaviors, possibly by regulating adult neurogenesis.

The Journal of Neuroscience, August 24, 2011 • 31(34):12258–12269

Memory-Guided Learning: CA1 and CA3 Neuronal Ensembles Differentially Encode the Commonalities and Differences between Situations

Amir S. Bahar, Prasad R. Shirvalkar, and Matthew L. Shapiro

Fishberg Department of Neuroscience and Alfred B. and Gudrun J. Kastor Neurobiology of Aging Laboratories, Mount Sinai School of Medicine, New York, New York 10029-6574

Memory influences learning, but how neural signals support such transfer are unknown. To investigate these mechanisms, we trained rats to perform a standard spatial memory task in a plus maze and tested how training affected learning and neural coding in two new task variants. A switch task exchanged the start and goal locations in the same environment, whereas, an altered environment task contained unfamiliar local and distal cues. Learning was facilitated in both variants compared with the acquisition of the standard task. In the switch task, performance was largely maintained, and was accompanied by immediate and stable place-field remapping. Place-field maps in CA1 were anticorrelated in the standard and switch sessions, and the anticorrelation covaried with switch performance. Simultaneously, CA3 maps were uncorrelated overall in the standard and switch, though many CA3 cells had fields in shifted locations in the same maze arms. In the altered environment, performance was initially impaired, and place fields changed dynamically. CA1 fields were initially unstable, and their stabilization correlated with improving performance. Most CA3 cells, however, stopped firing on the maze in the altered environment, even as the same cells maintained prominent fields in standard sessions recorded before and after. CA1 and CA3 place fields thus revealed different coding dynamics that correlated with both learning and memory performance. Together, CA1 and CA3 ensembles represented the similarities and differences between new and familiar situations through concurrent rate and place remapping.

The Journal of Neuroscience, August 24, 2011 • 31(34):12270–12281

A Model of Intracellular Theta Phase Precession Dependent on Intrinsic Subthreshold Membrane Currents

L. Stan Leung

Department of Physiology and Pharmacology, University of Western Ontario, London, Ontario N6A5C1, Canada

A hippocampal place cell fires at an increasingly earlier phase in relation to the extracellular theta rhythm as a rodent moves through the place field. The present report presents a compartment model of a CA1 pyramidal cell that explains the increase in amplitude and the phase precession of intracellular theta oscillations, with the assumption that the cell receives an asymmetric ramp depolarization (<10 mV) in the place field and rhythmic inhibitory and/or excitatory synaptic driving. Intracellular subthreshold membrane potential oscillations (MPOs) increase in amplitude and frequency, and show phase precession within the place field. Theta phase precession and MPO power and frequency increase in the place field are caused by a shift in excitatory–inhibitory response, intrinsic theta-frequency resonance, and intrinsic oscillations that depend on voltage-dependent persistent Na^+ and slowly inactivating K^+ currents, but not on I_h . Phase precession is diminished when theta-frequency resonance is decreased. Simulated spikes fire near the peak of MPOs and precess similarly as the MPOs. The phase of the MPOs/spikes codes for distance in a one-dimensional place field, and phase precession is only weakly dependent on firing rate, running speed, or the duration needed to cross the place field. In addition, phase precession within the place field resumes quickly after disruption by maximal afferent pulse stimulation.

The Journal of Neuroscience, August 24, 2011 • 31(34):12282–12296

Single Synapse Information Coding in Intraburst Spike Patterns of Central Pattern Generator Motor Neurons

Ludmila Brochini,^{1,2} Pedro V. Carelli,^{2,3} and Reynaldo D. Pinto¹

¹Department of Physics and Informatics, Institute of Physics of São Carlos, University of São Paulo, São Carlos 13566-590, Brazil, ²Department of General Physics, Institute of Physics, University of São Paulo, São Paulo 05508-090, Brazil, and ³Department of Physics, Federal University of Pernambuco, Recife 50670-901, Brazil

Burst firing is ubiquitous in nervous systems and has been intensively studied in central pattern generators (CPGs). Previous works have described subtle intraburst spike patterns (IBSPs) that, despite being traditionally neglected for their lack of relation to CPG motor function, were shown to be cell-type specific and sensitive to CPG connectivity. Here we address this matter by investigating how a bursting motor neuron expresses information about other neurons in the network. We performed experiments on the crustacean stomatogastric pyloric CPG, both in control conditions and interacting in real-time with computer model neurons. The sensitivity of postsynaptic to presynaptic IBSPs was inferred by computing their average mutual information along each neuron burst. We found that details of input patterns are nonlinearly and inhomogeneously coded through a single synapse into the fine IBSPs structure of the postsynaptic neuron following burst. In this way, motor neurons are able to use different time scales to convey two types of information simultaneously: muscle contraction (related to bursting rhythm) and the behavior of other CPG neurons (at a much shorter timescale by using IBSPs as information carriers). Moreover, the analysis revealed that the coding mechanism described takes part in a previously unsuspected information pathway from a CPG motor neuron to a nerve that projects to sensory brain areas, thus providing evidence of the general physiological role of information coding through IBSPs in the regulation of neuronal firing patterns in remote circuits by the CNS.

The Journal of Neuroscience, August 24, 2011 • 31(34):12297–12306

Functional Heterogeneity of Macaque Lateral Intraparietal Neurons

Elsie Premereur,¹ Wim Vanduffel,^{1,2,3} and Peter Janssen¹

¹Laboratorium voor Neuro- en Psychofysiologie, Katholieke Universiteit Leuven, 3000 Leuven, Belgium, ²Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Charlestown, Massachusetts 02129, and ³Department of Radiology, Harvard Medical School, Boston, Massachusetts 02129

The macaque lateral intraparietal area (LIP) has been implicated in many cognitive processes, ranging from saccade planning and spatial attention to timing and categorization. Importantly, different research groups have used different criteria for including LIP neurons in their studies. While some research groups have selected LIP neurons based on the presence of memory-delay activity, other research groups have used other criteria such as visual, presaccadic, and/or memory activity. We recorded from LIP neurons that were selected based on spatially selective saccadic activity but regardless of memory-delay activity in macaque monkeys. To test anticipatory climbing activity, we used a delayed visually guided saccade task with a unimodal schedule of go-times, for which the conditional probability that the go-signal will occur rises monotonically as a function of time. A subpopulation of LIP neurons showed anticipatory activity that mimicked the subjective hazard rate of the go-signal when the animal was planning a saccade toward the receptive field. A large subgroup of LIP neurons, however, did not modulate their firing rates according to the subjective hazard function. These non-anticipatory neurons were strongly influenced by salient visual stimuli appearing in their receptive field, but less so by the direction of the impending saccade. Thus, LIP contains a heterogeneous population of neurons related to saccade planning or visual salience, and these neurons are spatially intermixed. Our results suggest that between-study differences in neuronal selection may have contributed significantly to the findings of different research groups with respect to the functional role of area LIP.

The Journal of Neuroscience, August 24, 2011 • 31(34):12307–12317

Endogenous Brain-Derived Neurotrophic Factor in the Nucleus Tractus Solitarius Tonically Regulates Synaptic and Autonomic Function

Catharine G. Clark,^{1,2} Eileen M. Hasser,^{1,2,3} Diana L. Kunze,^{4,5} David M. Katz,^{5*} and David D. Kline^{1,2*}

¹Dalton Cardiovascular Research Center, Departments of ²Biomedical Sciences, and ³Medical Pharmacology and Physiology, University of Missouri, Columbia, Missouri 65211, ⁴Rammelkamp Center, MetroHealth Systems, Cleveland, Ohio 44109, and ⁵Department of Neurosciences, Case Western Reserve University, Cleveland, Ohio 44106

Brain-derived neurotrophic factor (BDNF) and its receptor, TrkB, are highly expressed in the nucleus tractus solitarius (nTS), the principal target of cardiovascular primary afferent input to the brainstem. However, little is known about the role of BDNF signaling in nTS in cardiovascular homeostasis. We examined whether BDNF in nTS modulates cardiovascular function *in vivo* and regulates synaptic and/or neuronal activity in isolated brainstem slices. Microinjection of BDNF into the rat medial nTS (mnTS), a region critical for baroreflex control of sympathetic outflow, produced dose-dependent increases in mean arterial pressure (MAP), heart rate (HR), and lumbar sympathetic nerve activity (LSNA) that were blocked by the tyrosine kinase inhibitor K252a. In contrast, immunoneutralization of endogenous BDNF (anti-BDNF), or microinjection of K252a alone, decreased MAP, HR, and LSNA. The effects of anti-BDNF were abolished by blockade of ionotropic glutamate receptors, indicating a role for glutamate signaling in the response to BDNF. *In vitro*, BDNF reduced the amplitude of miniature EPSCs as well as solitary tract (TS) evoked EPSC amplitude and action potential discharge (APD) in second-order nTS neurons. BDNF effects on EPSCs were independent of GABAergic signaling and abolished by AMPA receptor blockade. In contrast, K252a increased spontaneous EPSC frequency and TS evoked EPSC amplitude. BDNF also attenuated APD evoked by injection of depolarizing current into second-order neurons, indicating reduced intrinsic neuronal excitability. Our data demonstrate that BDNF signaling in mnTS plays a tonic role in regulating cardiovascular function, likely via modulation of primary afferent glutamatergic excitatory transmission and neural activity.

The Journal of Neuroscience, August 24, 2011 • 31(34):12318–12329

Orientation Selectivity of Synaptic Input to Neurons in Mouse and Cat Primary Visual Cortex

Andrew Y. Y. Tan (陈勇毅), Brandon D. Brown, Benjamin Scholl, Deepankar Mohanty, and Nicholas J. Priebe

Center for Perceptual Systems, Section of Neurobiology, School of Biological Sciences, College of Natural Sciences, The University of Texas at Austin, Austin, Texas 78705

Primary visual cortex (V1) is the site at which orientation selectivity emerges in mammals: visual thalamus afferents to V1 respond equally to all stimulus orientations, whereas their target V1 neurons respond selectively to stimulus orientation. The emergence of orientation selectivity in V1 has long served as a model for investigating cortical computation. Recent evidence for orientation selectivity in mouse V1 opens cortical computation to dissection by genetic and imaging tools, but also raises two essential questions: (1) How does orientation selectivity in mouse V1 neurons compare with that in previously described species? (2) What is the synaptic basis for orientation selectivity in mouse V1? A comparison of orientation selectivity in mouse and in cat, where such measures have traditionally been made, reveals that orientation selectivity in mouse V1 is weaker than in cat V1, but that spike threshold plays a similar role in narrowing selectivity between membrane potential and spike rate. To uncover the synaptic basis for orientation selectivity, we made whole-cell recordings *in vivo* from mouse V1 neurons, comparing neuronal input selectivity—based on membrane potential, synaptic excitation, and synaptic inhibition—to output selectivity based on spiking. We found that a neuron's excitatory and inhibitory inputs are selective for the same stimulus orientations as is its membrane potential response, and that inhibitory selectivity is not broader than excitatory selectivity. Inhibition has different dynamics than excitation, adapting more rapidly. In neurons with temporally modulated responses, the timing of excitation and inhibition was different in mice and cats.

The Journal of Neuroscience, August 24, 2011 • 31(34):12339–12350

Anatomical Evidence for the Involvement of the Macaque Ventrolateral Prefrontal Area 12r in Controlling Goal-Directed Actions

Elena Borra, Marzio Gerbella, Stefano Rozzi, and Giuseppe Luppino

Department of Neuroscience, University of Parma and Brain Center of Motor and Social Cognition of Italian Institute of Technology, 43100 Parma, Italy

The macaque ventrolateral prefrontal (VLPF) area 12r is thought to be involved in higher-order nonspatial information processing. We found that this area is connectionally heterogeneous, and the intermediate part is fully integrated in a cortical network involved in selecting and controlling object-oriented hand and mouth actions. Specifically, intermediate area 12r displayed dense connections with the caudal half of area 46v and orbitofrontal areas and relatively strong extraprefrontal connections involving the following: (1) the hand- and mouth-related ventral premotor area F5 and the anterior intraparietal (AIP) area, jointly involved in visuomotor transformations for grasping; (2) the SII sector that is connected to AIP and F5; (3) a sector of the inferotemporal area TEa/m, primarily corresponding to the sector densely connected to AIP; and (4) the insular and opercular frontal sectors, which are connected to AIP and F5. This connectivity pattern differed markedly from those of the caudal and rostral parts of area 12r. Caudal area 12r displayed dense connections with the caudal part of the VLPF, including oculomotor areas 8/FEF and 45B, relatively weak orbitofrontal connections and extraprefrontal connections limited to the inferotemporal cortex. Rostral area 12r displayed connections mostly with rostral prefrontal and orbitofrontal areas and relatively weaker connections with the fundus and the upper bank of the superior temporal sulcus. The present data suggest that the intermediate part of area 12r is involved in nonspatial information processing related to object properties and identity, for selecting and controlling goal-directed hand and mouth actions.

The Journal of Neuroscience, August 24, 2011 • 31(34):12351–12363

Sex Differences in the Use of Anticipatory Brain Activity to Encode Emotional Events

Giulia Galli, Noham Wolpe, and Leun J. Otten

Institute of Cognitive Neuroscience, University College London, London, WC1N 3AR, United Kingdom

Women and men differ in the way they experience emotional events. Previous work has indicated that the impact of an emotional event depends on how it is anticipated. Separately, it has been shown that anticipation affects memory formation. Here, we assessed whether anticipatory brain activity influences the encoding of emotional events into long-term memory and, in addition, how biological sex affects the use of such activity. Electrical brain activity was recorded from the scalps of healthy men and women while they performed an incidental encoding task (indoor/outdoor judgments) on pleasant, unpleasant, and neutral pictures. Pictures were preceded by a cue that indicated the valence of the upcoming item. Memory was tested after a 20 min delay with a recognition task incorporating the remember/know procedure. Brain activity before picture onset predicted later memory of an event. Crucially, the role of anticipatory activity depended entirely on the valence of a picture and the sex of an individual. Right-lateralized anticipatory activity selectively influenced the encoding of unpleasant pictures in women, but not in men. These findings indicate that anticipatory processes influence the way in which women encode negative events into memory. The selective use of such activity may indicate that anticipatory activity is one mechanism by which individuals regulate their emotions.

The Journal of Neuroscience, August 24, 2011 • 31(34):12364–12370

The Representation of Visual and Motor Aspects of Reaching Movements in the Human Motor Cortex

Michal Eisenberg,^{1,2} Lior Shmuelof,^{1*} Eilon Vaadia,^{2,3,4} and Ehud Zohary^{1,2,4}

¹Neurobiology Department, Life Sciences Institute and the ²Interdisciplinary Center for Neural Computation, Hebrew University, Jerusalem 91904, Israel,

³Department of Medical Neurobiology, The Institute for Medical Research Israel–Canada, Hebrew University, Jerusalem, 91120, Israel, and ⁴the Edmond and Lily Safra Center for Brain Sciences, Hebrew University, Jerusalem, 91904, Israel

The human primary motor cortex (M1) is robustly activated during visually guided hand movements. M1 multivoxel patterns of functional MRI activation are more correlated during repeated hand movements to the same targets than to greatly differing ones, and therefore potentially contain information about movement direction. It is unclear, however, whether direction specificity is due to the motor command, as implicitly assumed, or to the visual aspects of the task, such as the target location and the direction of the cursor's trajectory. To disambiguate the visual and motor components, different visual-to-motor transformations were applied during an fMRI scan, in which participants made visually guided hand movements in various directions. The first run was the "baseline" (i.e., visual and motor mappings were matched); in the second run ("rotation"), the cursor movement was rotated by 45° with respect to the joystick movement. As expected, positive correlations were seen between the M1 multivoxel patterns evoked by the baseline run and by the rotation run, when the two movements were matched in their movement direction but the visual aspects differed. Importantly, similar correlations were observed when the visual elements were matched but the direction of hand movement differed. This indicates that M1 is sensitive to both motor and visual components of the task. However, repeated observation of the cursor movement without concurrent joystick control did not elicit significant activation in M1 or any correlated patterns of activation. Thus, visual aspects of movement are encoded in M1 only when they are coupled with motor consequences.

The Journal of Neuroscience, August 24, 2011 • 31(34):12377–12384

NEUROBIOLOGY OF DISEASE

Leptin Action in the Dorsomedial Hypothalamus Increases Sympathetic Tone to Brown Adipose Tissue in Spite of Systemic Leptin Resistance

Pablo J. Enriori,¹ Puspha Sinnayah,² Stephanie E. Simonds,¹ Cecilia Garcia Rudaz,¹ and Michael A. Cowley¹

¹Department of Physiology, Faculty of Medicine, Monash University and Monash Obesity and Diabetes Institute, Melbourne, Victoria 3800, Australia, and

²School of Biomedical and Health Sciences, Victoria University, Victoria 3021, Australia

Leptin regulates body weight in mice by decreasing appetite and increasing sympathetic nerve activity (SNA), which increases energy expenditure in interscapular brown adipose tissue (iBAT). Diet-induced obese mice (DIO) are resistant to the anorectic actions of leptin. We evaluated whether leptin still stimulated sympathetic outflow in DIO mice. We measured iBAT temperature as a marker of SNA. We found that obese hyperleptinemic mice have higher iBAT temperature than mice on regular diet. Conversely, obese leptin-deficient *ob/ob* mice have lower iBAT temperature. Additionally, leptin increased SNA in obese (DIO and *ob/ob*) and control mice, despite DIO mice being resistant to anorectic action of leptin. We demonstrated that neurons in the dorsomedial hypothalamus (DMH) of DIO mice mediate the thermogenic responses to hyperleptinemia in obese mammals because blockade of leptin receptors in the DMH prevented the thermogenic effects of leptin.

Peripheral Melanin II (MTII) injection increased iBAT temperature, but it was blunted by blockade of DMH melanocortin receptors (MC4Rs) by injecting agouti-related peptide (AgRP) directly into the DMH, suggesting a physiological role of the DMH on temperature regulation in animals with normal body weight. Nevertheless, obese mice without a functional melanocortin system (MC4R KO mice) have an increased sympathetic outflow to iBAT compared with their littermates, suggesting that higher leptin levels drive sympathoexcitation to iBAT by a melanocortin-independent pathway.

Because the sympathetic nervous system contributes in regulating blood pressure, heart rate, and hepatic glucose production, selective leptin resistance may be a crucial mechanism linking adiposity and metabolic syndrome.

The Journal of Neuroscience, August 24, 2011 • 31(34):12189–12197

Antipsychotic Drugs Rapidly Induce Dopamine Neuron Depolarization Block in a Developmental Rat Model of Schizophrenia

Ornella Valenti,^{1,2,3} Pierangelo Cifelli,^{1,2,3,4} Kathryn M. Gill,^{1,2,3} and Anthony A. Grace^{1,2,3}

Departments of ¹Neuroscience, ²Psychiatry, and ³Psychology, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, and ⁴Ri.MED Foundation, 90134 Palermo, Italy

Repeated administration of antipsychotic drugs to normal rats has been shown to induce a state of dopamine neuron inactivation known as depolarization block, which correlates with the ability of the drugs to exhibit antipsychotic efficacy and extrapyramidal side effects in schizophrenia patients. Nonetheless, in normal rats depolarization block requires weeks of antipsychotic drug administration, whereas schizophrenia patients exhibit initial effects soon after initiating antipsychotic drug treatment. We now report that, in a developmental disruption rat model of schizophrenia [methyl-azoxymethanol acetate (20 mg/kg, i.p.) injected into G17 pregnant female rats, with offspring tested as adults], the extant hyperdopaminergic state combines with the excitatory actions of a first- (haloperidol; 0.6 mg/kg, i.p.) and a second- (sertindole; 2.5 mg/kg, i.p.) generation antipsychotic drug to rapidly induce depolarization block in ventral tegmental area dopamine neurons. Acute injection of either antipsychotic drug induced an immediate reduction in the number of spontaneously active dopamine neurons (cells per electrode track; termed population activity). Repeated administration of either antipsychotic drug for 1, 3, 7, 15, and 21 d continued to reduce dopamine neuron population activity. Both acute and repeated effects on population activity were reversed by acute apomorphine injections, which is consistent with the reversal of dopamine neuron depolarization block. Although this action may account for the effects of D2 antagonist drugs on alleviating psychosis and the lack of development of tolerance in humans, the drugs appear to do so by inducing an offsetting deficit rather than attacking the primary pathology present in schizophrenia.

The Journal of Neuroscience, August 24, 2011 • 31(34):12330–12338