

This Week in The Journal

● Cellular/Molecular

P2X2 Receptor Expression Differs in Primates and Rodents

Alexandre Serrano, Gary Mo, Rebecca Grant, Michel Paré, Dajan O'Donnell, et al.

(see pages 11890–11896)

ATP released by distension of the bladder, gut, and other visceral tissues activates homomeric P2X3 and heteromeric P2X2/3 receptors on mechanosensory and nociceptive neurons. ATP is also released in the spinal cord, where it acts on glia and neurons involved in pain pathways. All this is true in rodents, at least; Serrano et al. now suggest that primates are somewhat different. Although expression of P2X3 was similar in dorsal root ganglion (DRG) of rats, monkeys, and humans, the P2X2 subunit was expressed at very low levels in primates. Furthermore, monkey DRG neurons did not exhibit slowly desensitizing responses—characteristic of P2X2/3 currents—to agonist *in vitro*. More importantly, the potency of P2X2 and P2X2/3 antagonists was greatly reduced in monkey DRG neurons, as well as in HEK cells expressing human P2X3. These results suggest that antagonists of these receptors, which reduce hyperalgesia in rodent models of chronic pain, may be less effective in humans.

▲ Development/Plasticity/Repair

Continuous Estrogen Treatment Does Not Affect Spine Density

Daniel T. Ohm, Erik B. Bloss, William G. Janssen, Karen C. Dietz, Shannon Wadsworth, et al.

(see pages 11700–11705)

Women's cognitive abilities fluctuate during the menstrual cycle. When estrogen levels are high, performance on verbal working memory increases; when levels are low, spatial ability improves. Working memory also declines after menopause, but whether hormone replacement therapy reverses this effect is controversial. Inconsistent results have been obtained

partly because progesterone—which opposes estrogen actions in the brain—is usually prescribed along with estrogen. Nonetheless, an influential study found that unopposed estrogen treatment worsened cognitive performance and increased risk of dementia in postmenopausal women. Estrogen appeared to improve cognition in women who began treatment at younger ages, however. Another factor that may affect cognitive benefits of estrogen is treatment schedule (continuous vs. cyclic). Although studies in ovariectomized monkeys have found that cyclic estrogen treatment improves cognition and increases dendritic spine density in the dorsolateral prefrontal cortex, Ohm et al. report that neither continuous estrogen treatment nor cyclic estrogen combined with progesterone affected spine density.

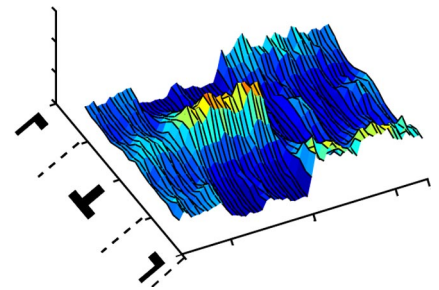
■ Behavioral/Systems/Cognitive

Two GABAergic Neurons Mediate Reversal Learning in Flies

Qingzhong Ren, Hao Li, Yanying Wu, Jing Ren, and Aike Guo

(see pages 11524–11538)

Animals must learn how to secure rewards and avoid punishment while remaining flexible enough to change their behavior when contingencies change. This flexibility is studied using reversal learning tasks: two cues are presented, one of which is associated with reward or punishment; after the association is learned, the reward or punishment is instead paired with the formerly neutral cue. To investigate the neural bases of such learning in *Drosophila*, Ren et al. used a visual discrimination task in which orientation toward one cue resulted in punishment. Normal flies quickly learned both the initial and the reversed association, but reversal learning was blocked by knocking down either GABA_A receptors in the mushroom bodies or GABA synthesis in a single pair of giant GABAergic neurons that innervate the mushroom bodies. Remarkably, these treatments were specific for reversal learning: initial learning, extinction, and learning to discriminate between two novel stimuli remained intact.



The percentage of time (*y*-axis) normal flies spent orienting toward different visual targets (*z*-axis) across trials (*x*-axis). After 6 baseline trials, punishment was associated with orientation toward an upright T for 10 trials. Punishment was then associated with the inverted T. Flies avoided the punished direction before and after reversal. See the article by Ren et al. for details.

◆ Neurobiology of Disease

NF-κB Impairs Ciliogenesis, Causing Hydrocephalus

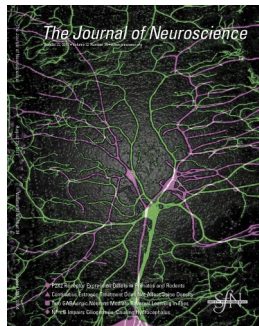
Michael Lattke, Alexander Magnutzki, Paul Walther, Thomas Wirth, and Bernd Baumann

(see pages 11511–11523)

Hydrocephalus is an accumulation of CSF that enlarges the cerebral ventricles and can impair development and function of adjacent brain regions. It typically results from increased CSF production, reduced absorption, or obstruction of CSF circulation. Although hydrocephalus often develops in association with neuroinflammation, the link between these phenomena is poorly understood. Lattke et al. examined this relationship in mice that conditionally expressed a constitutively active form of the IκB kinase complex (IKK2) in astrocytes and some ependymal cells. IKK2 activates nuclear factor κB (NF-κB), a transcription factor that triggers neuroinflammation. Early postnatal transgene expression activated NF-κB and caused upregulation of NF-κB target genes. This led to massive infiltration of macrophages into the ventricles, hydrocephalus formation, and abnormal hippocampal development. Neither obstruction of CSF flow nor fibrosis that could impair CSF resorption was detected; instead, poor development of cilia on ependymal cells that line the ventricles and promote CSF movement was the apparent cause of hydrocephalus.

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Cover legend: The complex dendritic arbors of the *Drosophila* class IV multidendritic neurons (green) are shown overlaid with the much simpler dendrite arbors of the class I neurons (magenta). The microtubule severing protein Kat-60L1 is required specifically in the somatodendritic compartment of the class IV neurons late in larval development. Kat-60L1 increases the number of growing microtubules and stabilizes the terminal branches of the class IV dendrites, thereby playing an essential role in the generation of their distinctive morphology and function. For more information, see the article by Stewart et al. (pages 11631–11642).

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A Little Goes a Long Way: How the Adult Brain Is Shaped by Musical Training in Childhood

Erika Skoe^{1,2} and Nina Kraus^{1,2,3,4,5}

¹Auditory Neuroscience Laboratory, ²Department of Communication Sciences, ³Institute for Neuroscience, ⁴Department of Neurobiology and Physiology, and ⁵Department of Otolaryngology, Northwestern University, Evanston, Illinois 60208

Playing a musical instrument changes the anatomy and function of the brain. But do these changes persist after music training stops? We probed this question by measuring auditory brainstem responses in a cohort of healthy young human adults with varying amounts of past musical training. We show that adults who received formal music instruction as children have more robust brainstem responses to sound than peers who never participated in music lessons and that the magnitude of the response correlates with how recently training ceased. Our results suggest that neural changes accompanying musical training during childhood are retained in adulthood. These findings advance our understanding of long-term neuroplasticity and have general implications for the development of effective auditory training programs.

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Clinically Relevant Hormone Treatments Fail to Induce Spinogenesis in Prefrontal Cortex of Aged Female Rhesus Monkeys

Daniel T. Ohm,^{1*} Erik B. Bloss,^{1*} William G. Janssen,¹ Karen C. Dietz,¹ Shannon Wadsworth,¹ Wendy Lou,⁴ Nancy A. Gee,⁵ Bill L. Lasley,⁵ Peter R. Rapp,⁶ and John H. Morrison^{1,2,3}

¹Fishberg Department of Neuroscience, The Friedman Brain Institute, Kastor Neurobiology of Aging Laboratory, ²Department of Geriatrics and Palliative Care, and ³Graduate School of Biological Sciences, Mount Sinai School of Medicine, New York, New York 10029, ⁴Dalla Lana School of Public Health, University of Toronto, Toronto, M5T 3M7 Ontario, Canada, ⁵Center for Health and the Environment and California National Primate Research Center, University of California, Davis, California 95616, and ⁶Laboratory of Experimental Gerontology, National Institute on Aging, Baltimore, Maryland 21224

Preclinical animal models have provided strong evidence that estrogen (E) therapy (ET) enhances cognition and induces spinogenesis in neuronal circuits. However, clinical studies have been inconsistent, with some studies revealing adverse effects of ET, including an increased risk of dementia. In an effort to bridge this disconnect between the preclinical and clinical data, we have developed a nonhuman primate (NHP) model of ET combined with high-resolution dendritic spine analysis of dorsolateral prefrontal cortical (dlPFC) neurons. Previously, we reported cyclic ET in aged, ovariectomized NHPs increased spine density on dlPFC neurons. Here, we report that monkeys treated with cyclic E treatment paired with cyclic progesterone (P), continuous E combined with P (either cyclic or continuous), or unopposed continuous E failed to increase spines on dlPFC neurons. Given that the most prevalent form of ET prescribed to women is a combined and continuous E and P, these data bring into convergence the human neuropsychological findings and preclinical neurobiological evidence that standard hormone therapy in women is unlikely to yield the synaptic benefit presumed to underlie the cognitive enhancement reported in animal models.

The Journal of Neuroscience, August 22, 2012 • 32(34):11700–11705

Presynaptic But Not Postsynaptic GABA Signaling at Unitary Mossy Fiber Synapses

Carolina Cabezas,^{1,2,3} Theano Irinopoulou,^{1,2,3} Grégory Gauvain,^{1,2,3} and Jean Christophe Poncer^{1,2,3}

¹INSERM, UMR 839, F75005, Paris, France, ²Université Pierre et Marie Curie, F75005, Paris, France, and ³Institut du Fer à Moulin, F75005, Paris, France

Dentate gyrus granule cells have been suggested to corelease GABA and glutamate both in juvenile animals and under pathological conditions in adults. Although mossy fiber terminals (MFTs) are known to express glutamic acid decarboxylase (GAD) in early postnatal development, the functional role of GABA synthesis in MFTs remains controversial, and direct evidence for synaptic GABA release from MFTs is missing. Here, using GAD67-GFP transgenic mice, we show that GAD67 is expressed only in a population of immature granule cells in juvenile animals. We demonstrate that GABA can be released from these cells and modulate mossy fiber excitability through activation of GABAB autoreceptors. However, unitary postsynaptic currents generated by individual, GAD67-expressing granule cells are purely glutamatergic in all postsynaptic cell types tested. Thus GAD67 expression does not endow dentate gyrus granule cells with a full GABAergic phenotype and GABA primarily instructs the pre- rather than the postsynaptic element.

The Journal of Neuroscience, August 22, 2012 • 32(34):11835–11840

Articles

CELLULAR/MOLECULAR

PICK1 Mediates Transient Synaptic Expression of GluA2-Lacking AMPA Receptors during Glycine-Induced AMPA Receptor Trafficking

Nadia Jaafari, Jeremy M. Henley, and Jonathan G. Hanley

Medical Research Council Centre for Synaptic Plasticity and School of Biochemistry, Medical Sciences Building, University of Bristol, Bristol, BS8 1TD, United Kingdom

The number and subunit composition of postsynaptic AMPA receptors (AMPA) is a key determinant of synaptic transmission. The vast majority of AMPARs contain GluA2 subunit, which renders the channel impermeable to calcium. However, a small proportion are GluA2 lacking and therefore calcium permeable (CP-AMPA). It has been proposed recently that long-term potentiation (LTP) involves not only an increase in the total number of AMPARs at the synapse but also a transient switch to CP-AMPA in the first few minutes after LTP induction. The molecular mechanisms that underlie this switch to CP-AMPA and the subsequent switch back to calcium-impermeable AMPARs are unknown. Here, we show that endogenous GluA1 is rapidly inserted at the synaptic plasma membrane of rat hippocampal neurons immediately after stimulation with elevated glycine, a treatment known to induce LTP. In contrast, GluA2 is restricted from trafficking to the cell surface by a glycine-induced increase in PICK1–GluA2 binding on endosomal compartments. Between 5 and 20 min after stimulus, activation of CP-AMPA triggers a release of GluA2 from PICK1, allowing GluA2-containing AMPARs to traffic to the synaptic plasma membrane. These results define a PICK1-dependent mechanism that underlies transient alterations in the subunit composition and calcium permeability of synaptic AMPARs that is important during the early phase after stimulation with glycine and therefore is likely to be important during the expression of LTP.

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A Phosphatidylinositol Lipids System, Lamellipodin, and Ena/VASP Regulate Dynamic Morphology of Multipolar Migrating Cells in the Developing Cerebral Cortex

Satoshi Yoshinaga,¹ Takahiro Ohkubo,¹ Shinji Sasaki,¹ Mutsuo Nuriya,² Yukino Ogawa,¹ Masato Yasui,² Hidenori Tabata,¹ and Kazunori Nakajima¹

Departments of ¹Anatomy and ²Pharmacology, Keio University School of Medicine, Shinjuku-ku, Tokyo 160-8582, Japan

In the developing mammalian cerebral cortex, excitatory neurons are generated in the ventricular zone (VZ) and subventricular zone; these neurons migrate toward the pial surface. The neurons generated in the VZ assume a multipolar morphology and remain in a narrow region called the multipolar cell accumulation zone (MAZ) for ~24 h, in which they extend and retract multiple processes dynamically. They eventually extend an axon tangentially and begin radial migration using a migratory mode called locomotion. Despite the potential biological importance of the process movement of multipolar cells, the molecular mechanisms remain to be elucidated. Here, we observed that the processes of mouse multipolar cells were actin rich and morphologically resembled the filopodia and lamellipodia in growth cones; thus, we focused on the actin-remodeling proteins Lamellipodin (Lpd) and Ena/vasodilator-stimulated phosphoprotein (VASP). Lpd binds to phosphatidylinositol (3,4)-bisphosphate [PI(3,4)P₂] and recruits Ena/VASP, which promotes the assembly of actin filaments, to the plasma membranes. *In situ* hybridization and immunohistochemistry revealed that Lpd is expressed in multipolar cells in the MAZ. The functional silencing of either Lpd or Ena/VASP decreased the number of primary processes. Immunostaining and a Förster resonance energy transfer analysis revealed the subcellular localization of PI(3,4)P₂ at the tips of the processes. A knockdown experiment and treatment with an inhibitor for Src homology 2-containing inositol phosphatase-2, a 5-phosphatase that produces PI(3,4)P₂ from phosphatidylinositol (3,4,5)-triphosphate, decreased the number of primary processes. Our observations suggest that PI(3,4)P₂, Lpd, and Ena/VASP are involved in the process movement of multipolar migrating cells.

The Journal of Neuroscience, August 22, 2012 • 32(34):11643–11656

Organotypic Coculture Preparation for the Study of Developmental Synapse Elimination in Mammalian Brain

Naofumi Uesaka,¹ Takayasu Mikuni,¹ Kouichi Hashimoto,^{1,4,5} Hirokazu Hirai,² Kenji Sakimura,³ and Masanobu Kano¹

¹Department of Neurophysiology, Graduate School of Medicine, The University of Tokyo, Tokyo 113-0033, Japan, ²Department of Neurophysiology, Gunma University Graduate School of Medicine, Maebashi, Gunma 371-8511, Japan, ³Department of Cellular Neurobiology, Brain Research Institute, Niigata University, Niigata 951-8585, Japan, ⁴Department of Neurophysiology, Graduate School of Biomedical Sciences, Hiroshima University, Hiroshima 734-8551, Japan, and ⁵Precursory Research for Embryonic Science and Technology, Japan Science and Technology Agency, Saitama 332-0012, Japan

We developed an organotypic coculture preparation allowing fast and efficient identification of molecules that regulate developmental synapse elimination in the mammalian brain. This coculture consists of a cerebellar slice obtained from rat or mouse at postnatal day 9 (P9) or P10 and a medullary explant containing the inferior olive dissected from rat at embryonic day 15. We verified that climbing fibers (CFs), the axons of inferior olivary neurons, formed functional synapses onto Purkinje cells (PCs) in the cerebellum of cocultures. PCs were initially reinnervated by multiple CFs with similar strengths. Surplus CFs were eliminated subsequently, and the remaining CFs became stronger. These changes are similar to those occurring in developing cerebellum *in vivo*. Importantly, the changes in CF innervations in cocultures involved the same molecules required for CF synapse elimination *in vivo*, including NMDA receptor, type 1 metabotropic glutamate receptor and glutamate receptor $\delta 2$ (GluR $\delta 2$). We

demonstrate that gain- and loss-of-function analyses can be efficiently performed by lentiviral-mediated overexpression and RNAi-induced knockdown of GluR82. Using this approach, we identified neuroligin-2 as a novel molecule that promotes CF synapse elimination in postsynaptic PCs. Thus, our coculture preparation will greatly facilitate the elucidation of molecular mechanisms of synapse elimination.

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Paired-Pulse Plasticity in the Strength and Latency of Light-Evoked Lateral Inhibition to Retinal Bipolar Cell Terminals

Evan Vickers,¹ Mean-Hwan Kim,¹ Jozsef Vigh,² and Henrique von Gersdorff¹

¹The Vollum Institute, Oregon Health and Science University, Portland, Oregon 97239, and ²Department of Biomedical Sciences, Colorado State University, Ft. Collins, Colorado 80523

Synapses in the inner plexiform layer of the retina undergo short-term plasticity that may mediate different forms of adaptation to regularities in light stimuli. Using patch-clamp recordings from axotomized goldfish Mb bipolar cell (BC) terminals with paired-pulse light stimulation, we isolated and quantified the short-term plasticity of GABAergic lateral IPSCs (L-IPSCs). Bright light stimulation evoked ON and OFF L-IPSCs in axotomized BCs, which had distinct onset latencies (~50–80 and ~70–150 ms, respectively) that depended on background light adaptation. We observed plasticity in both the synaptic strength and latency of the L-IPSCs. With paired light stimulation, latencies of ON L-IPSCs increased at paired-pulse intervals (PPIs) of 50 and 300 ms, whereas OFF L-IPSC latencies decreased at the 300 ms PPI. ON L-IPSCs showed paired-pulse depression at intervals <1 s, whereas OFF L-IPSCs showed depression at intervals ≤1 s and amplitude facilitation at longer intervals (1–2 s). This biphasic form of L-IPSC plasticity may underlie adaptation and sensitization to surround temporal contrast over multiple timescales. Block of retinal signaling at GABA_ARs and AMPARs differentially affected ON and OFF L-IPSCs, confirming that these two types of feedback inhibition are mediated by distinct and convergent retinal pathways with different mechanisms of plasticity. We propose that these plastic changes in the strength and timing of L-IPSCs help to dynamically shape the time course of glutamate release from ON-type BC terminals. Short-term plasticity of L-IPSCs may thus influence the strength, timing, and spatial extent of amacrine and ganglion cell inhibitory surrounds.

The Journal of Neuroscience, August 22, 2012 • 32(34):11688–11699

Arf6-GEF BRAG1 Regulates JNK-Mediated Synaptic Removal of GluA1-Containing AMPA Receptors: A New Mechanism for Nonsyndromic X-Linked Mental Disorder

Kenneth R. Myers,^{1*} Guangfu Wang,^{2*} Yanghui Sheng,^{2,4} Kathryn K. Conger,¹ James E. Casanova,^{1,2} and J. Julius Zhu^{2,3}

Departments of ¹Cell Biology, ²Pharmacology, and ³Neuroscience, University of Virginia Health System, Charlottesville, Virginia 22908-0732 and ⁴Yuanpei College, Peking University, Beijing, 100871, China

Activity-dependent modifications of excitatory synapses contribute to synaptic maturation and plasticity, and are critical for learning and memory. Consequently, impairments in synapse formation or synaptic transmission are thought to be responsible for several types of mental disabilities. BRAG1 is a guanine nucleotide exchange factor for the small GTP-binding protein Arf6 that localizes to the postsynaptic density of excitatory synapses. Mutations in BRAG1 have been identified in families with X-linked intellectual disability (XLID). These mutations mapped to either the catalytic domain or an IQ-like motif; however, the pathophysiological basis of these mutations remains unknown. Here, we show that the BRAG1 IQ motif binds apo-calmodulin (CaM), and that calcium-induced CaM release triggers a reversible conformational change in human BRAG1. We demonstrate that BRAG1 activity, stimulated by activation of NMDA-sensitive glutamate receptors, depresses AMPA receptor (AMPA-R)-mediated transmission via JNK-mediated synaptic removal of GluA1-containing AMPA-Rs in rat hippocampal neurons. Importantly, a BRAG1 mutant that fails to activate Arf6 also fails to depress AMPA-R signaling, indicating that Arf6 activity is necessary for this process. Conversely, a mutation in the BRAG1 IQ-like motif that impairs CaM binding results in hyperactivation of Arf6 signaling and constitutive depression of AMPA transmission. Our findings reveal a role for BRAG1 in response to neuronal activity with possible clinical relevance to nonsyndromic XLID.

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Ca²⁺-Dependent Regulation of Ca²⁺ Currents in Rat Primary Afferent Neurons: Role of CaMKII and the Effect of Injury

Qingbo Tang,¹ Madhavi Latha Yadav Bangaru,¹ Sandra Kostic,¹ Bin Pan,¹ Hsiang-En Wu,¹ Andrew S. Koopmeiners,¹ Hongwei Yu,¹ Gregory J. Fischer,¹ J. Bruce McCallum,¹ Wai-Meng Kwok,¹ Andy Hudmon,² and Quinn H. Hogan^{1,3}

¹Medical College of Wisconsin, Department of Anesthesiology, Milwaukee, Wisconsin 53226, ²Indiana University School of Medicine, Department of Biochemistry and Molecular Biology-Stark Neuroscience Research Institute, Indianapolis, IN 46202, ³Zablocki VA Medical Center, Milwaukee, Wisconsin 53295

Currents through voltage-gated Ca²⁺ channels (*I_{Ca}*) may be regulated by cytoplasmic Ca²⁺ levels ([Ca²⁺]_c), producing Ca²⁺-dependent inactivation (CDI) or facilitation (CDF). Since *I_{Ca}* regulates sensory neuron excitability, altered CDI or CDF could contribute to pain generation after peripheral nerve injury. We explored this by manipulating [Ca²⁺]_c while recording *I_{Ca}* in rat sensory neurons. In uninjured neurons, elevating [Ca²⁺]_c with a conditioning prepulse (−15 mV, 2 s) inactivated *I_{Ca}* measured during subsequent test pulses (−15 mV, 5 ms). This inactivation was Ca²⁺-dependent (CDI), since it was decreased with elimination of Ca²⁺ influx by depolarization to above the *I_{Ca}* reversal potential, with high intracellular Ca²⁺ buffering (EGTA 10 mM or BAPTA 20 mM), and with substitution of Ba²⁺ for extracellular Ca²⁺, revealing a residual voltage-dependent inactivation. At longer latencies after conditioning (>6 s), *I_{Ca}* recovered beyond baseline. This facilitation also proved to be Ca²⁺-dependent (CDF) using the protocols limiting cytoplasmic Ca²⁺ elevation. Ca²⁺/calmodulin-dependent protein kinase II (CaMKII) blockers applied by bath (KN-93, myristoyl-AIP)

or expressed selectively in the sensory neurons (AIP) reduced CDF, unlike their inactive analogues. Protein kinase C inhibition (chelerythrine) had no effect. Selective blockade of N-type Ca^{2+} channels eliminated CDF, whereas L-type channel blockade had no effect. Following nerve injury, CDI was unaffected, but CDF was eliminated in axotomized neurons. Excitability of sensory neurons in intact ganglia from control animals was diminished after a similar conditioning pulse, but this regulation was eliminated by injury. These findings indicate that I_{Ca} in sensory neurons is subject to both CDI and CDF, and that hyperexcitability following injury-induced loss of CDF may result from diminished CaMKII activity. The Journal of Neuroscience, August 22, 2012 • 32(34):11737–11749

Extracellular Alpha-Synuclein Oligomers Modulate Synaptic Transmission and Impair LTP Via NMDA-Receptor Activation

Maria José Diógenes,^{2,3*} Raquel B. Dias,^{2,3*} Diogo M. Rombo,^{2,3*} Hugo Vicente Miranda,¹ Francesca Maiolino,¹ Patrícia Guerreiro,¹ Thomas Näsström,⁶ Henri G. Franquelim,⁴ Luís M.A. Oliveira,⁵ Miguel A.R.B. Castanho,⁴ Lars Lannfelt,⁶ Joakim Bergström,⁶ Martin Ingelsson,⁶ Alexandre Quintas,⁵ Ana M. Sebastião,^{2,3} Luísa V. Lopes,^{2,3} and Tiago Fleming Outeiro^{1,7,8}

¹Cell and Molecular Neuroscience Unit, ²Institute of Pharmacology and Neurosciences, ³Neurosciences Unit, and ⁴Physical Biochemistry Unit, Instituto de Medicina Molecular, Faculdade de Medicina da Universidade de Lisboa, Ed. Egas Moniz, 1649-028 Lisboa, Portugal, ⁵Centro de Investigação Interdisciplinar Egas Moniz, Instituto Superior de Ciências da Saúde Egas Moniz, Monte de Caparica 2829-511 Caparica, Portugal, ⁶Department of Public Health/Geriatrics, Rudbeck Laboratory, Uppsala University, 751 24 Uppsala, Sweden, ⁷Instituto de Fisiologia, Faculdade de Medicina da Universidade de Lisboa, Ed. Egas Moniz, 1649-028 Lisboa, Portugal, and ⁸Department of NeuroDegeneration and Restorative Research, University Medizin Göttingen, 37073 Göttingen, Germany

Parkinson's disease (PD) is the most common representative of a group of disorders known as synucleinopathies, in which misfolding and aggregation of α -synuclein (a-syn) in various brain regions is the major pathological hallmark. Indeed, the motor symptoms in PD are caused by a heterogeneous degeneration of brain neurons not only in substantia nigra pars compacta but also in other extrastriatal areas of the brain. In addition to the well known motor dysfunction in PD patients, cognitive deficits and memory impairment are also an important part of the disorder, probably due to disruption of synaptic transmission and plasticity in extrastriatal areas, including the hippocampus.

Here, we investigated the impact of a-syn aggregation on AMPA and NMDA receptor-mediated rat hippocampal (CA3-CA1) synaptic transmission and long-term potentiation (LTP), the neurophysiological basis for learning and memory. Our data show that prolonged exposure to a-syn oligomers, but not monomers or fibrils, increases basal synaptic transmission through NMDA receptor activation, triggering enhanced contribution of calcium-permeable AMPA receptors. Slices treated with a-syn oligomers were unable to respond with further potentiation to theta-burst stimulation, leading to impaired LTP. Prior delivery of a low-frequency train reinstated the ability to express LTP, implying that exposure to a-syn oligomers drives the increase of glutamatergic synaptic transmission, preventing further potentiation by physiological stimuli.

Our novel findings provide mechanistic insight on how a-syn oligomers may trigger neuronal dysfunction and toxicity in PD and other synucleinopathies. The Journal of Neuroscience, August 22, 2012 • 32(34):11750–11762

Molecular and Functional Interaction between Protocadherin- γ C5 and GABA_A Receptors

Yanfang Li,¹ Haiyan Xiao,¹ Tzu-Ting Chiou,¹ Hongbing Jin,¹ Bevan Bonhomme,¹ Celia P. Miralles,¹ Noelia Pinal,¹ Rashid Ali,¹ Weisheng V. Chen,² Tom Maniatis,² and Angel L. De Blas¹

¹Department of Physiology and Neurobiology, University of Connecticut, Storrs, Connecticut 06269, and ²Department of Biochemistry and Molecular Biophysics, Columbia University Medical Center, New York, New York 10032

We have found that the $\gamma 2$ subunit of the GABA_A receptor ($\gamma 2$ -GABA_AR) specifically interacts with protocadherin- γ C5 (Pcdh- γ C5) in the rat brain. The interaction occurs between the large intracellular loop of the $\gamma 2$ -GABA_AR and the cytoplasmic domain of Pcdh- γ C5. In brain extracts, Pcdh- γ C5 coimmunoprecipitates with GABA_ARs. In cotransfected HEK293 cells, Pcdh- γ C5 promotes the transfer of $\gamma 2$ -GABA_AR to the cell surface. We have previously shown that, in cultured hippocampal neurons, endogenous Pcdh- γ C5 forms clusters, some of which associate with GABAergic synapses. Overexpression of Pcdh- γ C5 in hippocampal neurons increases the density of $\gamma 2$ -GABA_AR clusters but has no significant effect on the number of GABAergic contacts that these neurons receive, indicating that Pcdh- γ C5 is not synaptogenic. Deletion of the cytoplasmic domain of Pcdh- γ C5 enhanced its surface expression but decreased the association with both $\gamma 2$ -GABA_AR clusters and presynaptic GABAergic contacts. Cultured hippocampal neurons from the Pcdh- γ triple C-type isoform knock-out (TCKO) mouse (*Pcdh^{gcko/tcko}*) showed plenty of GABAergic synaptic contacts, although their density was reduced compared with sister cultures from wild-type and heterozygous mice. Knocking down Pcdh- γ C5 expression with shRNA decreased $\gamma 2$ -GABA_AR cluster density and GABAergic innervation. The results indicate that, although Pcdh- γ C5 is not essential for GABAergic synapse formation or GABA_AR clustering, (1) Pcdh- γ C5 regulates the surface expression of GABA_ARs via *cis*-cytoplasmic interaction with $\gamma 2$ -GABA_AR, and (2) Pcdh- γ C5 plays a role in the stabilization and maintenance of some GABAergic synapses.

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Projection Neurons in Lamina III of the Rat Spinal Cord Are Selectively Innervated by Local Dynorphin-Containing Excitatory Neurons

Najma Baseer,¹ Erika Polgár,¹ Masahiko Watanabe,² Takahiro Furuta,³ Takeshi Kaneko,³ and Andrew J. Todd¹

¹Spinal Cord Group, Institute of Neuroscience and Psychology, University of Glasgow, Glasgow G12 8QQ, United Kingdom; ²Department of Anatomy, Hokkaido University School of Medicine, Sapporo 060-8638, Japan; and ³Department of Morphological Brain Science, Graduate School of Medicine, Kyoto University, Kyoto 606-8501, Japan

Large projection neurons in lamina III of the rat spinal cord that express the neurokinin 1 receptor are densely innervated by peptidergic primary afferent nociceptors and more sparsely by low-threshold myelinated afferents. However, we know little about their input from other glutamatergic neurons. Here we show that these cells receive numerous contacts from nonprimary boutons that express the vesicular glutamate transporter 2 (VGLUT2), and form asymmetrical synapses on their dendrites and cell bodies. These synapses are significantly smaller than those formed by peptidergic afferents, but provide a substantial proportion of the glutamatergic synapses that the cells receive (over a third of those in laminae I–II and half of those in deeper laminae). Surprisingly, although the dynorphin precursor preprodynorphin (PPD) was only present in 4–7% of VGLUT2 boutons in laminae I–IV, it was found in 58% of the VGLUT2 boutons that contacted these cells. This indicates a highly selective targeting of the lamina III projection cells by glutamatergic neurons that express PPD, and these are likely to correspond to local neurons (interneurons and possibly projection cells). Since many PPD-expressing dorsal horn neurons respond to noxious stimulation, this suggests that the lamina III projection cells receive powerful monosynaptic and polysynaptic nociceptive input. Excitatory interneurons in the dorsal horn have been shown to possess I_A currents, which limit their excitability and can underlie a form of activity-dependent intrinsic plasticity. It is therefore likely that polysynaptic inputs to the lamina III projection neurons are recruited during the development of chronic pain states. *The Journal of Neuroscience*, August 22, 2012 • 32(34):11854–11863

Social, Communication, and Cortical Structural Impairments in Epac2-Deficient Mice

Deepak P. Srivastava,^{1,7*} Kelly A. Jones,^{1*} Kevin M. Woolfrey,^{1*} Jeffrey Burgdorf,⁴ Theron A. Russell,¹ Abigail Kalmbach,¹ Hyerin Lee,⁵ Connie Yang,⁵ Mazdak M. Bradberry,⁵ David Wokosin,¹ Joseph R. Moskal,⁴ Manuel F. Casanova,⁶ Jack Waters,¹ and Peter Penzes^{1,2,3}

¹Department of Physiology, ²Department of Psychiatry and Behavioral Sciences, and ³Lurie Cancer Research Center, Feinberg School of Medicine, Northwestern University, Chicago, Illinois 60611, ⁴Department of Biomedical Engineering and ⁵Weinberg College of Arts and Sciences, Northwestern University, Evanston, Illinois 60208, ⁶Department of Psychiatry, University of Louisville, Louisville, Kentucky, 40292, and ⁷Department of Neuroscience & Centre for the Cellular Basis of Behaviour, The James Black Centre, Institute of Psychiatry, King's College London, London, SE5 8AF, United Kingdom

Deficits in social and communication behaviors are common features of a number of neurodevelopmental disorders. However, the molecular and cellular substrates of these higher order brain functions are not well understood. Here we report that specific alterations in social and communication behaviors in mice occur as a result of loss of the *EPAC2* gene, which encodes a protein kinase A-independent cAMP target. Epac2-deficient mice exhibited robust deficits in social interactions and ultrasonic vocalizations, but displayed normal olfaction, working and reference memory, motor abilities, anxiety, and repetitive behaviors. Epac2-deficient mice displayed abnormal columnar organization in the anterior cingulate cortex, a region implicated in social behavior in humans, but not in somatosensory cortex. *In vivo* two-photon imaging revealed reduced dendritic spine motility and density on cortical neurons in Epac2-deficient mice, indicating deficits at the synaptic level. Together, these findings provide novel insight into the molecular and cellular substrates of social and communication behavior.

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Two *Drosophila* DEG/ENaC Channel Subunits Have Distinct Functions in Gustatory Neurons That Activate Male Courtship

Tong Liu, Elena Starostina, Vinoy Vijayan, and Claudio W. Pikielny

Department of Genetics and Neuroscience Center, Geisel School of Medicine at Dartmouth, Hanover, New Hampshire 03755-1404

Trimeric sodium channels of the DEG/ENaC family have important roles in neurons, but the specific functions of different subunits present in heteromeric channels are poorly understood. We previously reported that the *Drosophila* DEG/ENaC subunit Ppk25 is essential in a small subset of gustatory neurons for activation of male courtship behavior, likely through detection of female pheromones. Here we show that, like mutations in *ppk25*, mutations in another *Drosophila* DEG/ENaC subunit gene, *nope*, specifically impair male courtship of females. *nope* regulatory sequences drive reporter gene expression in gustatory neurons of the labellum wings, and legs, including all gustatory neurons in which *ppk25* function is required for male courtship of females. In addition, gustatory-specific knockdown of *nope* impairs male courtship. Further, the impaired courtship response of *nope* mutant males to females is rescued by targeted expression of *nope* in the subset of gustatory neurons in which *ppk25* functions. However, *nope* and *ppk25* have nonredundant functions, as targeted expression of *ppk25* does not compensate for the lack of *nope* and vice versa. Moreover, Nope and Ppk25 form specific complexes when coexpressed in cultured cells. Together, these data indicate that the Nope and Ppk25 polypeptides have specific, nonredundant functions in a subset of gustatory neurons required for activation of male courtship in response to females, and suggest the hypothesis that Nope and Ppk25 function as subunits of a heteromeric DEG/ENaC channel required for gustatory detection of female pheromones.

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Differential Expression and Pharmacology of Native P2X Receptors in Rat and Primate Sensory Neurons

Alexandre Serrano,^{1*} Gary Mo,^{1,2*} Rebecca Grant,^{1*} Michel Paré,¹ Dajan O'Donnell,¹ Xiao Hong Yu,¹ Mirosław J. Tomaszewski,¹ Martin N. Perkins,¹ Philippe Séguéla,² and Chang Qing Cao¹

¹AstraZeneca R&D Montréal, Ville St-Laurent (Montréal) Québec H4S 1Z9, Canada, and ²Montreal Neurological Institute and the Alan Edwards Centre for Research on Pain, Department of Neurology & Neurosurgery, McGill University, Montréal, Québec H3A 2B4, Canada

Evidence suggesting the involvement of P2X2 and P2X3 in chronic pain has been obtained mostly from rodent models. Here we show that rodents may be poor predictors of P2X3 pharmacology in human. We demonstrate that monkey and human dorsal root ganglion (DRG) neurons do not express appreciable levels of P2X2 subunit, contrary to rat sensory neurons. Additionally, we report functional P2X3 activity in monkey DRG neurons and confirm the absence of functional P2X2/3 receptors. Interestingly, native P2X3 receptors in rat and monkey DRGs show similar agonist potency, but different antagonist potencies for TNP-ATP [2-O-(2,4,6-trinitrophenyl)-ATP] and R051. This unexpected difference in antagonist potency was confirmed by comparing rat and human P2X3 receptors in HEK293 cells. Mutagenesis studies reveal that two extracellular residues, A197 and T202, are synergistically responsible for the potency drop in primate P2X3 receptors. These results uncover species-specific P2X3 pharmacology and identify key mechanisms impacting the translatability of potential analgesics targeting P2X3 receptors.

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DEVELOPMENT/PLASTICITY/REPAIR

Microglia Proliferation Is Controlled by P2X7 Receptors in a Pannexin-1-Independent Manner during Early Embryonic Spinal Cord Invasion

Chiara Rigato,^{1,2,3*} Nina Swinnen,^{1,2,3,4*} Roeland Buckinx,^{1,2,3,5} Isabelle Couillin,⁶ Jean-Marie Mangin,^{1,2,3} Jean-Michel Rigo,⁴ Pascal Legendre,^{1,2,3*} and Hervé Le Corronc^{1,2,3,7*}

¹Institut National de la Santé et de la Recherche Médicale, U952, Université Pierre et Marie Curie, Paris, Ile de France, France, ²Centre National de la Recherche Scientifique (CNRS), UMR 7224, Université Pierre et Marie Curie, Paris, Ile de France, France, ³UPMC Université Paris 06, Paris, Ile de France, France, ⁴Hasselt University, BIOMED-Cell Physiology, Agoralaan (Gebouw C), Diepenbeek B-3590, Belgium, ⁵University of Antwerp, Laboratory of Cell Biology and Histology, Belgium, ⁶UMR-IEM 6218 Molecular Immunology and Embryology, Transgenose Institute, CNRS, 45071 Orleans, France, and ⁷Université d'Angers, 49000 Angers, France.

Microglia are known to invade the mammalian spinal cord (SC) at an early embryonic stage. While the mechanisms underlying this early colonization of the nervous system are still unknown, we recently found that it is associated, at least partially, with the ability of microglia to proliferate at the onset of motoneuron developmental cell death and of synaptogenesis in mouse embryo (E13.5). *In vitro* studies have shown that the proliferation and activation of adult microglia can be influenced by the purinergic ionotropic receptor P2X7 via a coupling with Pannexin-1. By performing patch-clamp recordings *in situ* using a whole-mouse embryonic SC preparation, we show here that embryonic microglia already express functional P2X7R. P2X7R activation evoked a biphasic current in embryonic microglia, which is supposed to reflect large plasma membrane pore opening. However, although embryonic microglia express pannexin-1, this biphasic current was still recorded in microglia of pannexin-1 knock-out embryos, indicating that it rather reflected P2X7R intrinsic pore dilatation. More important, we found that proliferation of embryonic SC microglia, but not their activation state, depends almost entirely on P2X7R by comparing wild-type and P2X7R $-/-$ embryos. Absence of P2X7R led also to a decrease in microglia density. Pannexin-1 $-/-$ embryos did not exhibit any difference in microglial proliferation, showing that the control of embryonic microglial proliferation by P2X7R does not depend on pannexin-1 expression. These results reveal a developmental role of P2X7R by controlling embryonic SC microglia proliferation at a critical developmental state in the SC of mouse embryos.

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Netrin-1 Attracts Axons through FAK-Dependent Mechanotransduction

Simon W. Moore, Xian Zhang, Christopher D. Lynch, and Michael P. Sheetz

Department of Biological Sciences, Columbia University, New York, New York 10027

The mechanism by which extracellular cues influence intracellular biochemical cascades that guide axons is important, yet poorly understood. Because of the mechanical nature of axon extension, we explored whether the physical interactions of growth cones with their guidance cues might be involved. In the context of mouse spinal commissural neuron axon attraction to netrin-1, we found that mechanical attachment of netrin-1 to the substrate was required for axon outgrowth, growth cone expansion, axon attraction and phosphorylation of focal adhesion kinase (FAK) and Crk-associated substrate (CAS). Myosin II activity was necessary for traction forces >30 pN on netrin-1. Interestingly, while these myosin II-dependent forces on netrin-1 substrates or beads were needed to increase the kinase activity and phosphorylation of FAK, they were not necessary for netrin-1 to increase CAS phosphorylation. When FAK kinase activity was inhibited, the growth cone's ability to recruit additional adhesions and to generate forces >60 pN on netrin-1 was disrupted. Together, these findings demonstrate an important role for mechanotransduction during chemoattraction to netrin-1 and that mechanical activation of FAK reinforces interactions with netrin-1 allowing greater forces to be exerted.

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Teneurin-4 Is a Novel Regulator of Oligodendrocyte Differentiation and Myelination of Small-Diameter Axons in the CNS

Nobuharu Suzuki,^{1,2} Masaya Fukushi,¹ Keisuke Kosaki,¹ Andrew D. Doyle,¹ Susana de Vega,^{1,3} Keigo Yoshizaki,¹ Chihiro Akazawa,² Eri Arikawa-Hirasawa,³ and Yoshihiko Yamada¹

¹The Laboratory of Cell and Developmental Biology, National Institute of Dental and Craniofacial Research, National Institutes of Health, Bethesda, Maryland 20814, ²Department of Biochemistry and Biophysics, Graduate School of Health Care Sciences, Tokyo Medical and Dental University, Tokyo 113-8510, Japan, and ³Research Institute for Diseases of Old Age and Department of Neurology, Faculty of Medicine, Juntendo University, Tokyo 113-8421, Japan

Myelination is essential for proper functioning of the CNS. In this study, we have identified a mouse mutation, designated *furue*, which causes tremors and hypomyelination in the CNS, particularly in the spinal cord, but not in the sciatic nerve of the PNS. In the spinal cord of the *furue* mice, myelination of small-diameter axons was dramatically reduced, and differentiation of oligodendrocytes, the myelin-forming cells in the CNS, was inhibited. We subsequently found that the *furue* mutation was associated with a transgene insertion into the teneurin-4 (*Ten-4*, *Ten-m4/Odz4*) gene, encoding a transmembrane protein of unknown function. *Ten-4* was strongly expressed in the spinal cord of wild-type mice and was induced during normal oligodendrocyte differentiation. In contrast, in the *furue* mice, the expression of *Ten-4* was absent. Differentiation and cellular process formation of oligodendrocytes were inhibited in primary cell culture from the *furue* mice. Cell differentiation and process formation were also inhibited in the oligodendrocyte progenitor cell line CG-4 after suppression of *Ten-4* expression by shRNA. Furthermore, *Ten-4* positively regulated focal adhesion kinase, an essential signaling molecule for oligodendrocyte process formation and myelination of small-diameter axons. These findings suggest that *Ten-4* is a novel regulator of oligodendrocyte differentiation and that it plays a critical role in the myelination of small-diameter axons in the CNS.

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Katanin p60-like1 Promotes Microtubule Growth and Terminal Dendrite Stability in the Larval Class IV Sensory Neurons of *Drosophila*

Andrea Stewart,¹ Asako Tsubouchi,² Melissa M. Rolls,³ W. Daniel Tracey,² and Nina Tang Sherwood⁴

¹Department of Biology, Duke University, Durham, North Carolina 27708, ²Departments of Anesthesiology, Cell Biology and Neurobiology, Duke University, Durham, North Carolina 27710, ³Department of Biochemistry and Molecular Biology, The Pennsylvania State University, University Park, Pennsylvania 16802, and ⁴Departments of Biology and Molecular Genetics and Microbiology, Duke University, Durham, North Carolina 27708

Dendrite shape is considered a defining component of neuronal function. Yet, the mechanisms specifying diverse dendritic morphologies, and the extent to which their function depends on these morphologies, remain unclear. Here, we demonstrate a requirement for the microtubule-severing protein katanin p60-like 1 (*Kat-60L1*) in regulating the elaborate dendrite morphology and nocifensive functions of *Drosophila* larval class IV dendritic arborization neurons. *Kat-60L1* mutants exhibit diminished responsiveness to noxious mechanical and thermal stimuli. Class IV dendrite branch number and length are also reduced, supporting a correspondence between neuronal function and the full extent of the dendritic arbor. These arborization defects occur particularly in late larval development, and live imaging reveals that *Kat-60L1* is required for dynamic, filopodia-like nascent branches to stabilize during this stage. Mutant dendrites exhibit fewer EB1-GFP-labeled microtubules, suggesting that *Kat-60L1* increases polymerizing microtubules to establish terminal branch stability and full arbor complexity. Although loss of the related microtubule-severing protein Spastin also reduces the class IV dendrite arbor, microtubule polymerization within dendrites is unaffected. Conversely, Spastin overexpression destroys stable microtubules within these neurons, while *Kat-60L1* has no effect. *Kat-60L1* thus sculpts the class IV dendritic arbor through microtubule regulatory mechanisms distinct from Spastin. Our data support differential roles of microtubule-severing proteins in regulating neuronal morphology and function, and provide evidence that dendritic arbor development is the product of multiple pathways functioning at distinct developmental stages.

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Effects of Temporary Functional Deafferentation on the Brain, Sensation, and Behavior of Stroke Patients

Elisabeth Sens,¹ Ulrike Teschner,^{1,2} Winfried Meissner,³ Christoph Preul,² Ralph Huonker,² Otto W. Witte,² Wolfgang H. R. Miltner,¹ and Thomas Weiss¹

¹Biological and Clinical Psychology, Friedrich Schiller University, Jena, D-07743, Germany, ²Department of Neurology, University Hospital, Jena, D-07747, Germany, and ³Department of Anesthesiology and Intensive Care, University Hospital, Jena, D-07747, Germany

Following stroke, many patients suffer from chronic motor impairment and reduced somatosensation in the stroke-affected body parts. Recent experimental studies suggest that temporary functional deafferentation (TFD) of parts of the stroke-affected upper limb or of the less-affected contralateral limb might improve the sensorimotor capacity of the stroke-affected hand. The present study sought evidence of cortical reorganization and related sensory and motor improvements following pharmacologically induced TFD of the stroke-affected forearm.

Examination was performed during 2 d of Constraint-Induced Movement Therapy. Thirty-six human patients were deafferented on the stroke-affected forearm by an anesthetic cream (containing lidocaine and prilocaine) on one of the 2 d, and a placebo cream was applied on the other. The order of TFD and placebo treatment was counterbalanced across patients. Somatosensory and motor performance were assessed using a Grating orienting task and a Shape-sorter-drum task, and with somatosensory-evoked magnetic fields. Evoked magnetic fields showed significant pre- to postevaluation magnitude increases in response to tactile stimulation of the thumb of the stroke-affected hand during TFD but not following placebo treatment. We also observed a rapid extension of the distance between cortical representations of the stroke-affected thumb and little finger following TFD but not following placebo treatment. Moreover, somatosensory and motor performance of the stroke-affected

hand was significantly enhanced during TFD but not during placebo treatment. Thus, pharmacologically induced TFD of a stroke-affected forearm might improve the somatosensory and motor functions of the stroke-affected upper limb, accompanied by cortical plasticity.
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BEHAVIORAL/SYSTEMS/COGNITIVE

A GABAergic Inhibitory Neural Circuit Regulates Visual Reversal Learning in *Drosophila*

Qingzhong Ren,^{1,2} Hao Li,^{1,2} Yanying Wu,^{1,2} Jing Ren,^{1,2} and Aike Guo^{1,3}

¹Institute of Neuroscience and State Key Laboratory of Neuroscience, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, Shanghai 200031, China, ²Graduate School of Chinese Academy of Sciences, Beijing 100049, China, and ³State Key Laboratory of Brain and Cognitive Science, Institute of Biophysics, Chinese Academy of Sciences, Beijing 100101, China

Inflexible cognition and behavior are prominent features of prefrontal cortex damage and several neuropsychiatric disorders. The ability to flexibly adapt cognitive processing and behavior to dynamically changing environmental contingencies has been studied using the reversal learning paradigm in mammals, but the complexity of the brain circuits precludes a detailed analysis of the underlying neural mechanism. Here we study the neural circuitry mechanism supporting flexible behavior in a genetically tractable model organism, *Drosophila melanogaster*. Combining quantitative behavior analysis and genetic manipulation, we found that inhibition from a single pair of giant GABAergic neurons, the anterior paired lateral (APL) neurons, onto the mushroom bodies (MBs) selectively facilitates behavioral flexibility during visual reversal learning. This effect was mediated by ionotropic GABA_A receptors in the MB. Moreover, flies with perturbed MB output recapitulated the poor reversal performance of flies with dysfunctional APL neurons. Importantly, we observed that flies with dysfunctional APL–MB circuit performed normally in simple forms of visual learning, including initial learning, extinction, and differential conditioning. Finally, we showed that acute disruption of the APL–MB circuit is sufficient to impair visual reversal learning. Together, these data suggest that the APL–MB circuit plays an essential role in the resolution of conflicting reinforcement contingencies and reveals an inhibitory neural mechanism underlying flexible behavior in *Drosophila*.

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Spatial Information Outflow from the Hippocampal Circuit: Distributed Spatial Coding and Phase Precession in the Subiculum

Steve M. Kim,* Surya Ganguli,* and Loren M. Frank

W.M. Keck Center for Integrative Neuroscience and Department of Physiology, University of California, San Francisco, San Francisco, California 94143-0444

Hippocampal place cells convey spatial information through a combination of spatially selective firing and theta phase precession. The way in which this information influences regions like the subiculum that receive input from the hippocampus remains unclear. The subiculum receives direct inputs from area CA1 of the hippocampus and sends divergent output projections to many other parts of the brain, so we examined the firing patterns of rat subicular neurons. We found a substantial transformation in the subicular code for space from sparse to dense firing rate representations along a proximal–distal anatomical gradient: neurons in the proximal subiculum are more similar to canonical, sparsely firing hippocampal place cells, whereas neurons in the distal subiculum have higher firing rates and more distributed spatial firing patterns. Using information theory, we found that the more distributed spatial representation in the subiculum carries, on average, more information about spatial location and context than the sparse spatial representation in CA1. Remarkably, despite the disparate firing rate properties of subicular neurons, we found that neurons at all proximal–distal locations exhibit robust theta phase precession, with similar spiking oscillation frequencies as neurons in area CA1. Our findings suggest that the subiculum is specialized to compress sparse hippocampal spatial codes into highly informative distributed codes suitable for efficient communication to other brain regions. Moreover, despite this substantial compression, the subiculum maintains finer scale temporal properties that may allow it to participate in oscillatory phase coding and spike timing-dependent plasticity in coordination with other regions of the hippocampal circuit.

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Role of Orbitofrontal Cortex Neuronal Ensembles in the Expression of Incubation of Heroin Craving

Sanya Fanous, Evan M. Goldart, Florence R. M. Theberge, Jennifer M. Bossert, Yavin Shaham, and Bruce T. Hope

Behavioral Neuroscience Branch, Intramural Research Program/National Institute on Drug Abuse/National Institutes of Health/Department of Health and Human Services, Baltimore, Maryland 21224

In humans, exposure to cues previously associated with heroin use often provokes relapse after prolonged withdrawal periods. In rats, cue-induced heroin seeking progressively increases after withdrawal (incubation of heroin craving). Here, we examined the role of orbitofrontal cortex (OFC) neuronal ensembles in the enhanced response to heroin cues after prolonged withdrawal or the expression of incubation of heroin craving. We trained rats to self-administer heroin (6 h/d for 10 d) and assessed cue-induced heroin seeking in extinction tests after 1 or 14 withdrawal days. Cue-induced heroin seeking increased from 1 to 14 d and was accompanied by increased Fos expression in ~12% of OFC neurons. Nonselective inactivation of OFC neurons with the GABA agonists baclofen + muscimol decreased cue-induced heroin seeking on withdrawal day 14 but not day 1. We then used the Daun02 inactivation procedure to assess a causal role of the minority of selectively activated Fos-expressing OFC neurons (that presumably form cue-encoding neuronal ensembles) in cue-induced heroin seeking after 14 withdrawal days. We trained *c-fos*–*lacZ* transgenic rats to self-administer

heroin and 11 d later reexposed them to heroin-associated cues or novel cues for 15 min (induction day), followed by OFC Daun02 or vehicle injections 90 min later; we then tested the rats in extinction tests 3 d later. Daun02 selectively decreased cue-induced heroin seeking in rats previously reexposed to the heroin-associated cues on induction day but not in rats exposed previously to novel cues. Results suggest that heroin-cue-activated OFC neuronal ensembles contribute to the expression of incubation of heroin craving.

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Dynamic Modulation of Cerebellar Excitability for Abrupt, But Not Gradual, Visuomotor Adaptation

John E. Schlerf,¹ Joseph M. Galea,³ Amy J. Bastian,^{2,4} and Pablo A. Celnik^{1,2}

Departments of ¹Physical Medicine and Rehabilitation and ²Neuroscience, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205,

³Sobell Department of Motor Neuroscience and Movement Disorders, UCL Institute of Neurology, University College London, London, WC1N 3BG, United Kingdom, and ⁴The Kennedy Krieger Institute, Baltimore, Maryland 21205

The cerebellum is critically important for error-driven adaptive motor learning, as evidenced by the fact that cerebellar patients do not adapt well to sudden predictable perturbations. However, recent work has shown that cerebellar patients adapt much better if the perturbation is gradually introduced. Here we explore physiological mechanisms that underlie this distinction between abrupt and gradual motor adaptation in humans. We used transcranial magnetic stimulation to evaluate whether neural mechanisms within the cerebellum contribute to either process during a visuomotor reach adaptation. When a visuomotor rotation was introduced abruptly, cerebellar excitability changed early in learning and approached baseline levels near the end of the adaptation block. However, we observed no modulation of cerebellar excitability when we presented the visuomotor rotation gradually during learning. Similarly, we did not observe cerebellar modulation during trial-by-trial adaptation to random visuomotor displacements or during reaches without perturbations. This suggests that the cerebellum is most active during the early phases of adaptation when large perturbations are successfully compensated.

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Recurrent Interactions between the Input and Output of a Songbird Cortico-Basal Ganglia Pathway Are Implicated in Vocal Sequence Variability

Kosuke Hamaguchi and Richard Mooney

Department of Neurobiology, Duke University, Durham, North Carolina, 27710

Complex brain functions, such as the capacity to learn and modulate vocal sequences, depend on activity propagation in highly distributed neural networks. To explore the synaptic basis of activity propagation in such networks, we made dual *in vivo* intracellular recordings in anesthetized zebra finches from the input (nucleus HVC, used here as a proper name) and output [lateral magnocellular nucleus of the anterior nidopallium (LMAN)] neurons of a songbird cortico-basal ganglia (BG) pathway necessary to the learning and modulation of vocal motor sequences. These recordings reveal evidence of bidirectional interactions, rather than only feedforward propagation of activity from HVC to LMAN, as had been previously supposed. A combination of dual and triple recording configurations and pharmacological manipulations was used to map out circuitry by which activity propagates from LMAN to HVC. These experiments indicate that activity travels to HVC through at least two independent ipsilateral pathways, one of which involves fast signaling through a midbrain dopaminergic cell group, reminiscent of recurrent mesocortical loops described in mammals. We then used *in vivo* pharmacological manipulations to establish that augmented LMAN activity is sufficient to restore high levels of sequence variability in adult birds, suggesting that recurrent interactions through highly distributed forebrain–midbrain pathways can modulate learned vocal sequences.

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Evidence for Hyperbolic Temporal Discounting of Reward in Control of Movements

Adrian M. Haith,^{1,2*} Thomas R. Reppert,^{1*} and Reza Shadmehr¹

Departments of ¹Biomedical Engineering and ²Neurology, Johns Hopkins School of Medicine, Baltimore, Maryland 21287

Suppose that the purpose of a movement is to place the body in a more rewarding state. In this framework, slower movements may increase accuracy and therefore improve the probability of acquiring reward, but the longer durations of slow movements produce devaluation of reward. Here we hypothesize that the brain decides the vigor of a movement (duration and velocity) based on the expected discounted reward associated with that movement. We begin by showing that durations of saccades of varying amplitude can be accurately predicted by a model in which motor commands maximize expected discounted reward. This result suggests that reward is temporally discounted even in timescales of tens of milliseconds. One interpretation of temporal discounting is that the true objective of the brain is to maximize the rate of reward—which is equivalent to a specific form of hyperbolic discounting. A consequence of this idea is that the vigor of saccades should change as one alters the intertrial intervals between movements. We find experimentally that in healthy humans, as intertrial intervals are varied, saccade peak velocities and durations change on a trial-by-trial basis precisely as predicted by a model in which the objective is to maximize the rate of reward. Our results are inconsistent with theories in which reward is discounted exponentially. We suggest that there exists a single cost, rate of reward, which provides a unifying principle that may govern control of movements in timescales of milliseconds, as well as decision making in timescales of seconds to years.

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Prevalence of Selectivity for Mirror-Symmetric Views of Faces in the Ventral and Dorsal Visual Pathways

Tim C. Kietzmann,^{1,2} Jascha D. Swisher,¹ Peter König,² and Frank Tong¹

¹Psychology Department and Vanderbilt Vision Research Center, Vanderbilt University, Nashville, Tennessee 37240, and ²Institute of Cognitive Science, University of Osnabrück, 49076 Osnabrück, Germany

Although the ability to recognize faces and objects from a variety of viewpoints is crucial to our everyday behavior, the underlying cortical mechanisms are not well understood. Recently, neurons in a face-selective region of the monkey temporal cortex were reported to be selective for mirror-symmetric viewing angles of faces as they were rotated in depth (Freiwald and Tsao, 2010). This property has been suggested to constitute a key computational step in achieving full view-invariance. Here, we measured functional magnetic resonance imaging activity in nine observers as they viewed upright or inverted faces presented at five different angles (-60° , -30° , 0° , 30° , and 60°). Using multivariate pattern analysis, we show that sensitivity to viewpoint mirror symmetry is widespread in the human visual system. The effect was observed in a large band of higher order visual areas, including the occipital face area, fusiform face area, lateral occipital cortex, mid fusiform, parahippocampal place area, and extending superiorly to encompass dorsal regions V3A/B and the posterior intraparietal sulcus. In contrast, early retinotopic regions V1–hV4 failed to exhibit sensitivity to viewpoint symmetry, as their responses could be largely explained by a computational model of low-level visual similarity. Our findings suggest that selectivity for mirror-symmetric viewing angles may constitute an intermediate-level processing step shared across multiple higher order areas of the ventral and dorsal streams, setting the stage for complete viewpoint-invariant representations at subsequent levels of visual processing.

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The Spiking Component of Oscillatory Extracellular Potentials in the Rat Hippocampus

Erik W. Schomburg,¹ Costas A. Anastassiou,² György Buzsáki,³ and Christof Koch^{2,4}

¹Department of Physics and ²Division of Biology, California Institute of Technology, Pasadena, California 91125, ³New York University Neuroscience Institute and Center for Neural Science, New York University, New York, New York 10016, and ⁴Allen Institute for Brain Science, Seattle, Washington 98103

When monitoring neural activity using intracranial electrical recordings, researchers typically consider the signals to have two primary components: fast action potentials (APs) from neurons near the electrode, and the slower local field potential (LFP), thought to be dominated by postsynaptic currents integrated over a larger volume of tissue. In general, a decrease in signal power with increasing frequency is observed for most brain rhythms. The 100–200 Hz oscillations in the rat hippocampus, including “fast gamma” or “epsilon” oscillations and sharp wave-ripples (SPW-Rs), are one exception, showing an increase in power with frequency within this band. We have used detailed biophysical modeling to investigate the composition of extracellular potentials during fast oscillations in rat CA1. We find that postsynaptic currents exhibit a decreasing ability to generate large-amplitude oscillatory signals at high frequencies, whereas phase-modulated spiking shows the opposite trend. Our estimates indicate that APs and postsynaptic currents contribute similar proportions of the power contained in 140–200 Hz ripples, and the two combined generate a signal that closely resembles *in vivo* SPW-Rs. Much of the AP-generated signal originates from neurons further than 100 μm from the recording site, consistent with ripples appearing similarly strong regardless of whether or not they contain recognizable APs. Additionally, substantial power can be generated in the 90–150 Hz epsilon band by the APs of rhythmically firing pyramidal neurons. Thus, high-frequency LFPs may generally contain signatures of local cell assembly activation.

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Neural Evidence for Distracter Suppression during Visual Search in Real-World Scenes

Katharina N. Seidl,^{1,2*} Marius V. Peelen,^{1,2,3*} and Sabine Kastner^{1,2}

¹Department of Psychology and ²Princeton Neuroscience Institute, Princeton University, Princeton, New Jersey 08544, and ³Center for Mind/Brain Sciences, University of Trento, 38068 Rovereto, Trentino, Italy

Selecting visual information from cluttered real-world scenes involves the matching of visual input to the observer’s attentional set—an internal representation of objects that are relevant for current behavioral goals. When goals change, a new attentional set needs to be instantiated, requiring the suppression of the previous set to prevent distraction by objects that are no longer relevant. In the present fMRI study, we investigated how such suppression is implemented at the neural level. We measured human brain activity in response to natural scene photographs that could contain objects from (1) a currently relevant (target) category, (2) a previously but not presently relevant (distracter) category, and/or (3) a never relevant (neutral) category. Across conditions, multivoxel response patterns in object-selective cortex carried information about objects present in the scenes. However, this information strongly depended on the task relevance of the objects. As expected, information about the target category was significantly increased relative to the neutral category, indicating top-down enhancement of task-relevant information. Importantly, information about the distracter category was significantly reduced relative to the neutral category, indicating that the processing of previously relevant objects was suppressed. Such active suppression at the level of high-order visual cortex may serve to prevent the erroneous selection of, or interference from, objects that are no longer relevant to ongoing behavior. We conclude that the enhancement of relevant information and the suppression of distracting information both contribute to the efficient selection of visual information from cluttered real-world scenes.

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Spinal and Pontine Relay Pathways Mediating Respiratory Rhythm Entrainment by Limb Proprioceptive Inputs in the Neonatal Rat

Aurore Giraudin, Morgane Le Bon-Jégo, Marie-Jeanne Cabirol, John Simmers,* and Didier Morin*

Université Bordeaux, Institut de Neurosciences Cognitives et Intégratives d'Aquitaine, Centre National de la Recherche Scientifique Unité Mixte de Recherche 5287, F-33000 Bordeaux, France

The coordination of locomotion and respiration is widespread among mammals, although the underlying neural mechanisms are still only partially understood. It was previously found in neonatal rat that cyclic electrical stimulation of spinal cervical and lumbar dorsal roots (DRs) can fully entrain (1:1 coupling) spontaneous respiratory activity expressed by the isolated brainstem/spinal cord. Here, we used a variety of preparations to determine the type of spinal sensory inputs responsible for this respiratory rhythm entrainment, and to establish the extent to which limb movement-activated feedback influences the medullary respiratory networks via direct or relayed ascending pathways. During *in vivo* overground locomotion, respiratory rhythm slowed and became coupled 1:1 with locomotion. In hindlimb-attached semi-isolated preparations, passive flexion–extension movements applied to a single hindlimb led to entrainment of fictive respiratory rhythmicity recorded in phrenic motoneurons, indicating that the recruitment of limb proprioceptive afferents could participate in the locomotor-respiratory coupling. Furthermore, in correspondence with the regionalization of spinal locomotor rhythm-generating circuitry, the stimulation of DRs at different segmental levels in isolated preparations revealed that cervical and lumbosacral proprioceptive inputs are more effective in this entraining influence than thoracic afferent pathways. Finally, blocking spinal synaptic transmission and using a combination of electrophysiology, calcium imaging and specific brainstem lesioning indicated that the ascending entraining signals from the cervical or lumbar limb afferents are transmitted across first-order synapses, probably monosynaptic, in the spinal cord. They are then conveyed to the brainstem respiratory centers via a brainstem pontine relay located in the parabrachial/Kölliker-Fuse nuclear complex.

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NEUROBIOLOGY OF DISEASE

Nuclear Factor κ B Activation Impairs Ependymal Ciliogenesis and Links Neuroinflammation to Hydrocephalus Formation

Michael Lattke,¹ Alexander Magnutzki,¹ Paul Walther,² Thomas Wirth,¹ and Bernd Baumann¹

¹Institute of Physiological Chemistry and ²Central Facility for Electron Microscopy, Ulm University, 89081 Ulm, Germany

Hydrocephalus formation is a frequent complication of neuropathological insults associated with neuroinflammation. However, the mechanistic role of neuroinflammation in hydrocephalus development is unclear. We have investigated the function of the proinflammatory acting inhibitor of κ B kinase (IKK)/nuclear factor κ B (NF- κ B) signaling system in neuroinflammatory processes and generated a novel mouse model that allows conditional activation of the IKK/NF- κ B system in astrocytes. Remarkably, NF- κ B activation in astrocytes during early postnatal life results in hydrocephalus formation and additional defects in brain development. NF- κ B activation causes global neuroinflammation characterized by a strong, astrocyte-specific expression of proinflammatory NF- κ B target genes as well as a massive infiltration and activation of macrophages. In this animal model, hydrocephalus formation is specifically induced during a critical time period of early postnatal development, in which IKK/NF- κ B-induced neuroinflammation interferes with ependymal ciliogenesis. Our findings demonstrate for the first time that IKK/NF- κ B activation is sufficient to induce hydrocephalus formation and provides a potential mechanistic explanation for the frequent association of neuroinflammation and hydrocephalus formation during brain development, namely impairment of ependymal cilia formation. Therefore, our study might open up new perspectives for the treatment of certain types of neonatal and childhood hydrocephalus associated with hemorrhages and infections.

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Lipopolysaccharide-Induced Microglial Activation and Neuroprotection against Experimental Brain Injury Is Independent of Hematogenous TLR4

Zhihong Chen, Walid Jalabi, Karl B. Shpargel, Kenneth T. Farabaugh, Ranjan Dutta, Xinghua Yin, Grahame J. Kidd, Cornelia C. Bergmann, Stephen A. Stohlgan, and Bruce D. Trapp

Department of Neurosciences, Lerner Research Institute, Cleveland Clinic, Cleveland, Ohio 44195

Intraperitoneal injection of the Gram-negative bacterial endotoxin lipopolysaccharide (LPS) elicits a rapid innate immune response. While this systemic inflammatory response can be destructive, tolerable low doses of LPS render the brain transiently resistant to subsequent injuries. However, the mechanism by which microglia respond to LPS stimulation and participate in subsequent neuroprotection has not been documented. In this study, we first established a novel LPS treatment paradigm where mice were injected intraperitoneally with 1.0 mg/kg LPS for four consecutive days to globally activate CNS microglia. By using a reciprocal bone marrow transplantation procedure between wild-type and Toll-like receptor 4 (TLR4) mutant mice, we demonstrated that the presence of LPS receptor (TLR4) is not required on hematogenous immune cells but is required on cells that are not replaced by bone marrow transplantation, such as vascular endothelia and microglia, to transduce microglial activation and neuroprotection. Furthermore, we showed that activated microglia physically ensheath cortical projection neurons, which have reduced axosomatic inhibitory synapses from the neuronal perikarya. In line with previous reports that inhibitory synapse reduction protects neurons from degeneration and injury, we show here that neuronal cell death and lesion volumes are significantly reduced in LPS-treated animals following experimental brain injury. Together, our results suggest that activated microglia participate in neuroprotection and that this neuroprotection is likely achieved through reduction of inhibitory axosomatic synapses. The therapeutic significance of these findings rests not only in identifying neuroprotective functions of microglia, but also in establishing the CNS location of TLR4 activation.

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Ryanodine Receptor Blockade Reduces Amyloid- β Load and Memory Impairments in Tg2576 Mouse Model of Alzheimer Disease

Bénédicte Oulès,^{1,2*} Dolores Del Prete,^{3,4*} Barbara Greco,³ Xuexin Zhang,⁵ Inger Lauritzen,⁴ Jean Sevalle,⁴ Sebastien Moreno,⁴ Patrizia Paterlini-Bréchet,^{1,2} Mohamed Trebak,⁵ Frédéric Checler,⁴ Fabio Benfenati,³ and Mounia Chami⁴

¹Institut National de la Santé et de la Recherche Médicale U807 and ²Paris V University, Paris, F-75015, France, ³Department of Neuroscience and Brain Technologies, Italian Institute of Technology, 16163 Genova, Italy, ⁴Fondation pour la Recherche Médicale and Laboratory of Excellence “Distalz,” Institut de Pharmacologie Moléculaire et Cellulaire, UMR7275 CNRS/University of Nice Sophia Antipolis, 06560 Valbonne, France, and ⁵Center for Cardiovascular Sciences, Albany Medical College, Albany, New York 12208

In Alzheimer disease (AD), the perturbation of the endoplasmic reticulum (ER) calcium (Ca^{2+}) homeostasis has been linked to presenilins, the catalytic core in γ -secretase complexes cleaving the amyloid precursor protein (APP), thereby generating amyloid- β ($\text{A}\beta$) peptides. Here we investigate whether APP contributes to ER Ca^{2+} homeostasis and whether ER Ca^{2+} could in turn influence $\text{A}\beta$ production. We show that overexpression of wild-type human APP (APP_{695}), or APP harboring the Swedish double mutation (APP_{swe}) triggers increased ryanodine receptor (RyR) expression and enhances RyR-mediated ER Ca^{2+} release in SH-SY5Y neuroblastoma cells and in APP_{swe} -expressing (Tg2576) mice. Interestingly, dantrolene-induced lowering of RyR-mediated Ca^{2+} release leads to the reduction of both intracellular and extracellular $\text{A}\beta$ load in neuroblastoma cells as well as in primary cultured neurons derived from Tg2576 mice. This $\text{A}\beta$ reduction can be accounted for by decreased Thr-668-dependent APP phosphorylation and β - and γ -secretases activities. Importantly, dantrolene diminishes $\text{A}\beta$ load, reduces $\text{A}\beta$ -related histological lesions, and slows down learning and memory deficits in Tg2576 mice. Overall, our data document a key role of RyR in $\text{A}\beta$ production and learning and memory performances, and delineate RyR-mediated control of Ca^{2+} homeostasis as a physiological paradigm that could be targeted for innovative therapeutic approaches.

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