This Week in The Journal

● Cellular/Molecular

Two Distinct Glutamate Signals in Bergmann Glia

Ko Matsui and Craig E. Jahr
(see pages 8932–8939)

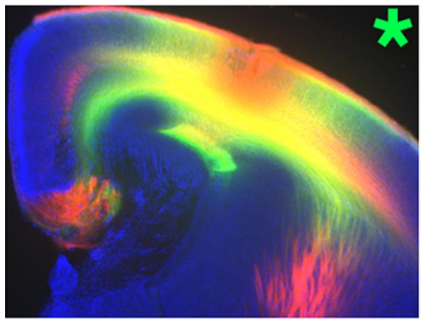
Synaptic transmission used to be simple: transmitter was released from axonal terminals and activated immediately adjacent postsynaptic receptors. Life got more complicated when it became clear that transmitter could be released from some dendrites and glia as well and could spill over to extrasynaptic membranes, to other synapses, or onto glial cells. Recently Matsui and Jahr reported a new form of neuronal–glial glutamate signaling. At the cerebellar climbing fiber synapse, they found that glutamate released from sites outside the active zone, called "ectopic" release, could activate Bergmann glial cells (BGs). This week they further define the features of this rapid neuronal–glial signaling. The ectopic release onto BGs showed marked paired-pulse depression and greater dependence on N-type calcium channels than conventional release onto Purkinje cells. The authors suggest that the local high concentrations of glutamate ectopically released onto BGs regulate the glial encasement of cerebellar synapses. This signal may get BGs in position to use their glutamate transporters to mop up transmitter around conventional synapses.

▲ Development/Plasticity/Repair

Forming Intracortical Projections

Kelly J. Huffman, Sonia Garel, and John L. R. Rubenstein
(see pages 8917–8923)

The neocortex is organized into areas with distinct functions, and this organization requires not only segregation of these areas but appropriate connectivity between and within cortical areas. The areas arise according to instructions from molecules such as FGF8, which is secreted in the rostral telencephalon during development. Although the *Fgf8* hypomorphic mutant mouse displays disordered neocortical patterning, thalamocortical projections are essentially intact, presumably because the latter rely on factors external to the cortex. This week Huffman et al. explore the generation of the intracortical wiring diagram. They used the retrograde-transported dyes DiA and DiI to compare projections from rostral and caudal regions. *Gbx2* mutants lacked thalamocortical projections but had appropriate intracortical projections. In contrast, in *Fgf8* hypomorphic mutants, caudal projections broke out of their intended regions. Thus formation of intracortical and thalamocortical connectivity appears to be under separate developmental control mechanisms.



Fgf8$^{neo/neo}$ mutants showed an abnormal pattern of intracortical projections, indicated by overlap labeling (yellow) of rostral and caudal placement of the dyes DiI (red) and DiA (green), respectively. See the article by Huffman et al. for details.

■ Behavioral/Systems/Cognitive

Hemodynamic Control by Single Cortical Interneurons

Bruno Cauli, Xin-Kang Tong, Armelle Rancillac, Nella Serluca, Bertrand Lambolez, Jean Rossier, and Edith Hamel
(see pages 8940–8949)

It makes sense that neuronal activity should be linked somehow to vascular perfusion, the source of necessary oxygen and glucose. In fact this relationship is the basis of functional neuroimaging. But how does it happen at the cellular level? This week, Cauli et al. use a meticulous combination of techniques to document that GABAergic interneurons locally integrate signals to microvessels. The authors used biocytin labeling and single-cell reverse transcriptase-multiplex PCR in rat cortical slices to characterize the morphology, electrophysiology, and peptide content of neurons contacting blood vessels. Although the cortex contains a diverse mix of interneurons, "vasomotor" neurons aggregated around the microvessels. Action potentials in single interneurons that expressed vasoactive intestinal peptide or nitric oxide synthase caused vessels to dilate, whereas those expressing somatostatin caused contraction. Vasoactive interneurons were innervated by serotonergic or cholinergic afferents, suggesting that the vasomotor interneurons can transduce neural activity into tight temporal and spatial control of cortical microvessels.

♦ Neurobiology of Disease

A Mouse Model of a Childhood Storage Disease

David E. Sleat, Jennifer A. Wiseman, Mukarram El-Banna, Kwi-Hye Kim, Qinwen Mao, Sandy Price, Shannon L. Macauley, Richard L. Sidman, Michael M. Shen, Qi Zhao, Marco A. Passini, Beverly L. Davidson, Gregory R. Stewart, and Peter Lobel
(see pages 9117–9126)

Neurodegenerative disorders are cruel at any age, but when they occur at the beginning of life their impact extends well beyond their relatively rare occurrence. Classical late-infantile neuronal ceroid lipofuscinosis (cLINCL) is one of the inherited lysosomal storage diseases, caused by mutations in the gene for tripeptidyl-peptidase I, a lysosomal serine protease. Autofluorescent material accumulates in neuronal lysosomes; affected children have seizures followed by blindness, ataxia, and death. Sleat et al. targeted the *CLN2* gene to create the first mouse model of cLINCL. The mice appeared healthy at birth, but by 7 weeks of age they developed constant tremors, followed by worsening locomotor abnormalities and premature death at 4–5 months. The cellular histopathology mimicked the human disease, with cytoplasmic autofluorescence inclusions and neurodegeneration in the brain, spinal cord, and periphery. Given the lack of effective treatments for cLINCL, this model may allow testing of future therapeutic strategies.

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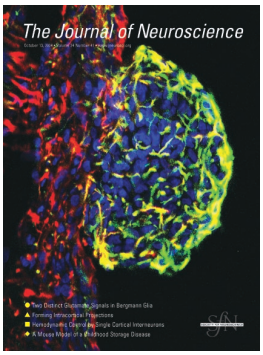

Cover picture: A hypercellular nodule in the lateral ventricle subventricular zone of a rat treated with an intrastriatal infusion of transforming growth factor α. These nodules contained both GFAP+ (red) and nestin+/GFAP+ colocalized (yellow) cells. For details, see the article by Cooper and Isacson in this issue (pages 8924–8931).

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9212 ***Erratum:*** The cover image for the September 29, 2004 issue (Volume 24, Number 39) was incorrect. Two of the autophosphorylation arrows that showed the activity between the subunits pointed incorrectly. The correct cover image is printed in this issue. For details, see Figure 2 in the article "Regulation of Calcium/Calmodulin-Dependent Protein Kinase II Activation by Intramolecular and Intermolecular Interactions," by Leslie C. Griffith, which appeared on pages 8391–8393 of the September 29, 2004 issue.

9213 ***Correction:*** In the article "Functional Organization of Visual Cortex in the Owl Monkey," by Xiangmin Xu, William Bosking, Gyula Sáry, James Stefansic, Daniel Shima, and Vivien Casagrande, which appeared on pages 6237–6247 of the July 14, 2004 issue, Figure 2*C,D* inadvertently printed as identical panels. Also, in Figure 5, it should be noted that *A* and *B* and *C–F* are from two different cases. Figure 5, *A* and *B*, simply shows an example of how data were aligned. The gray levels in Figure 5*D* were adjusted to enhance contrast. The image was then bandpass filtered, thresholded, and posterized into three gray levels: dark (CO-blob proper), white (CO-interblob proper), and gray (border area). The scale bar (1 mm) for Figure 5*A,B* was missing in the printed version. Corrected versions of Figures 2 and 5, as well as each legend, are printed in this issue.

Corrections: In the article "The $GABA_A$ Receptor $\gamma 2$ Subunit R43Q Mutation Linked to Childhood Absence Epilepsy and Febrile Seizures Causes Retention of $\alpha 1\beta 2\gamma 2S$ Receptors in the Endoplasmic Reticulum," which appeared on pages 8672–8677 of the October 6, 2004 issue, the name of an author was spelled incorrectly. The first author's name should have

read Jing-Qiong Kang. In the article "Cycling of NMDA Receptors during Trafficking in Neurons before Synapse Formation," by Philip Washbourne, Xiao-Bo Liu, Edward G. Jones, and A. Kimberley McAllister, which appeared on pages 8253–8264 of the September 22, 2004 issue, the authors inadvertently used the wrong citation for a paper by K. R. Tovar and G. L. Westbrook that demonstrated lateral movements of NMDA receptors between synaptic and extrasynaptic pools in the plasma membrane of hippocampal neurons. The correct citation is as follows: Tovar KR, Westbrook GL (2002) Mobile NMDA receptors at hippocampal synapses. Neuron 34:255–264.

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Brief Communications

Olfaction in Olfactory Bulbectomized Rats

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Experimental rats had their right olfactory bulb removed on postnatal day 2 (P2) and their left olfactory bulb removed on P90. Control rats had one or both olfactory bulbs removed on P90. Before and after their adult-stage surgery, rats were trained using olfactometry and operant conditioning to detect and discriminate odors. Anterograde transport of horseradish peroxidase applied to the olfactory epithelium revealed numerous axons of olfactory sensory neurons in the right hemisphere of 27 experimental rats. These axons terminated in glomerular-like clusters within the frontal neocortex ($n = 5$) or anterior olfactory nucleus with some axons extending into the subventricular epithelium ($n = 22$). Seventeen of the experimental rats were able to detect a variety of odors and to discriminate between odors. Performance accuracy was related to the location and density of these anomalous inputs; experimental rats with inputs confined to frontal neocortex and those lacking any inputs to the forebrain were anosmic, as were adult-operated bilaterally bulbectomized rats. Our results provide strong support for the contention that, in the absence of the olfactory bulbs, olfactory connections to novel forebrain sites can support both odor detection and odor discrimination.

The Journal of Neuroscience, October 13, 2004 • 24(41):9195–9200

Articles

CELLULAR/MOLECULAR

Differential Control of Synaptic and Ectopic Vesicular Release of Glutamate

Ko Matsui and Craig E. Jahr

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Exocytosis of synaptic vesicles occurs not only at synaptic active zones but also at ectopic sites. Ectopic exocytosis provides a direct and rapid mechanism for neurons to communicate with glia that does not rely on transmitter spillover from the synaptic cleft. In the cerebellar cortex the processes of Bergmann glia cells encase synapses between presynaptic climbing fiber varicosities and postsynaptic Purkinje cell spines and express both AMPA receptors and electrogenic glutamate transporters. AMPA receptors expressed by Purkinje cells and Bergmann glia cells are activated predominantly by synaptic and ectopic release, respectively, and therefore can be used to compare the properties of the two release mechanisms. We report that vesicular release differs at synaptic and ectopic sites in the magnitude of short-term plasticity and the proportions of Ca^{2+} channel subtypes that trigger glutamate release. High-affinity glutamate transporter-mediated currents in Bergmann glia cells follow the rules of synaptic release more closely than the rules of ectopic release, indicating that the majority of glutamate is released from conventional synapses. On the other hand, ectopic release produces high-concentration glutamate transients at Bergmann glia cell membranes that are necessary to activate low-affinity AMPA receptors rapidly. Ectopic release may provide a geographical cue to guide Bergmann glia cell membranes to surround active synapses and ensure efficient uptake of glutamate that diffuses out of the synaptic cleft.

The Journal of Neuroscience, October 13, 2004 • 24(41):8932–8939

Excessive Expression of Acetylcholinesterase Impairs Glutamatergic Synaptogenesis in Hippocampal Neurons

Haiheng Dong,[1,2] Yun-Yan Xiang,[1,2] Noa Farchi,[4,5] William Ju,[3] Yaojiong Wu,[1,3] Liwen Chen,[1,3] Yutian Wang,[3] Binyamin Hochner,[4] Burton Yang,[1,3] Hermona Soreq,[5] and Wei-Yang Lu[1,2]

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Acetylcholinesterase (AChE) exerts noncatalytic activities on neural cell differentiation, adhesion, and neuritogenesis independently of its catalytic function. The noncatalytic functions of AChE have been attributed to its peripheral anionic site (PAS)-mediated protein–protein interactions. Structurally, AChE is highly homologous to the extracellular domain of neuroligin, a postsynaptic transmembrane molecule that interacts with presynaptic β-neurexins, thus facilitating synaptic formation and maturation. Potential effects of AChE expression on synaptic transmission, however, remain unknown. Using electrophysiology, immunocytochemistry, and molecular biological approaches, this study investigated the role of AChE in the regulation of synaptic formation and functions. We found that AChE was highly expressed in cultured embryonic hippocampal neurons at early culture days, particularly in dendritic compartments including the growth cone. Subsequently, the expression level of AChE declined, whereas synaptic activity and synaptic proteins progressively increased. Chronic blockade of the PAS of AChE with specific inhibitors selectively impaired glutamatergic functions and excitatory synaptic structures independently of cholinergic activation, while inducing AChE overexpression. Moreover, the PAS blockade-induced glutamatergic impairments were associated with a depressed expression of β-neurexins and an accumulation of other synaptic proteins, including neuroligins,

and were mostly preventable by antisense suppression of AChE expression. Our findings demonstrate that interference with the nonenzymatic features of AChE alters AChE expression, which impairs excitatory synaptic structure and functions.

The Journal of Neuroscience, October 13, 2004 • 24(41):8950–8960

Presynaptic Glycine Receptors on GABAergic Terminals Facilitate Discharge of Dopaminergic Neurons in Ventral Tegmental Area

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GABA-mediated postsynaptic currents (IPSCs) were recorded from dopaminergic (DA) neurons of the ventral tegmental area (VTA) of rats, in acute brain slices, and from enzymatically or mechanically dissociated neurons. In young rats (3–10 d of age), where GABA is excitatory, glycine (1–3 μM) and taurine (10–30 μM) increased the amplitude of evoked IPSCs (eIPSCs) and the frequency of spontaneous IPSCs (sIPSCs) but had minimal postsynaptic effects. Strychnine (1 μM) blocked the action of glycine; when applied alone, it reduced the amplitude of eIPSCs and the frequency of sIPSCs, indicating a tonic facilitation of GABAergic excitation by some endogenous glycine agonist(s). In medium containing no Ca^{2+}, or with Cd^{2+} or tetrodotoxin added, the amplitude and especially the frequency of sIPSCs greatly diminished. In many cells, glycine had no effect on remaining miniature IPSCs, suggesting a preterminal site of glycine receptors (GlyRs). Fura-2 fluorescent imaging showed a glycine-induced increase of $[Ca^{2+}]$ in nerve terminals (on DA neurons), which was suppressed by strychnine or 3 μM ω-conotoxin MVIIA. Therefore, the presynaptic GlyR-mediated facilitation of GABAergic transmission seems to be mediated by N- and/or P/Q-type Ca^{2+} channels. In older rats (22–30 d of age), where GABA causes inhibition, the effect of strychnine on GABAergic IPSCs was reversed to facilitation, indicating a tonic glycinergic inhibition of GABA release. Furthermore, glycine (1–3 μM) reduced the amplitude of eIPSCs and the frequency of sIPSCs. Hence, the overall effect of the presynaptic action of glycine is to enhance the firing of DA cells, both in very young and older rats.

The Journal of Neuroscience, October 13, 2004 • 24(41):8961–8974

A Mosaic of Functional Kainate Receptors in Hippocampal Interneurons

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Although some physiological functions of kainate receptors (KARs) still remain unclear, recent advances have highlighted a role in synaptic physiology. In hippocampal slices, kainate depresses GABA-mediated synaptic inhibition and increases the firing rate of interneurons. However, the sensitivity to agonists of these responses differs, suggesting that the presynaptic and somatic KARs have a distinct molecular composition. Hippocampal interneurons express several distinct KAR subunits that can assemble into heteromeric receptors with a variety of pharmacological properties and that, in principle, could fulfill different roles. To address which receptor types mediate each of the effects of kainate in interneurons, we used new compounds and mice deficient for specific KAR subunits. In a recombinant assay, 5-carboxyl-2,4-di-benzamido-benzoic acid (NS3763) acted exclusively on homomeric glutamate receptor subunit 5 (GluR5), whereas 3*S*,4a*R*,6*S*,8a*R*-6-((4-carboxyphenyl)methyl) 1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid (LY382884) antagonized homomeric GluR5 and any heteromeric combination containing GluR5 subunits. In hippocampal slices, LY382884, but not NS3763, was able to prevent kainate-induced depression of evoked IPSC. In contrast, neither prevented the concomitant increase in spontaneous IPSC frequency. The selectivity of these compounds was seen additionally in knock-out mice, such that they were inactive in GluR5$^{-/-}$ mice but completely effective in GluR6$^{-/-}$ mice. Our data indicate that in wild-type mice, CA1 interneurons express heteromeric GluR6–KA2 receptors in their somatic compartments and GluR5–GluR6 or GluR5–KA2 at presynaptic terminals. However, functional compensation appears to take place in the null mutants, a new pharmacological profile emerging more compatible with the activity of homomeric receptors in both compartments: GluR5 in GluR6$^{-/-}$ mice and GluR6 in GluR5$^{-/-}$ mice.

The Journal of Neuroscience, October 13, 2004 • 24(41):8986–8993

α2-Chimaerin, Cyclin-Dependent Kinase 5/p35, and Its Target Collapsin Response Mediator Protein-2 Are Essential Components in Semaphorin 3A-Induced Growth-Cone Collapse

Matthew Brown,[1]* Tom Jacobs,[1]* Britta Eickholt,[3] Giovanna Ferrari,[1,2] Mabel Teo,[1,2] Clinton Monfries,[1,2] Robert Z. Qi,[4] Thomas Leung,[2] Louis Lim,[1,2] and Christine Hall[1]

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Neurite outgrowth is influenced by positive and negative signals that include the semaphorins, an important family of axonal outgrowth inhibitors. Here we report that the Rac GTPase activating protein (GAP) α2-chimaerin is involved in Semaphorin 3A (Sema 3A) signaling. In dorsal root ganglion neurons, Sema 3A-induced growth cone collapse was inhibited by α2-chimaerin mutated to eliminate GAP activity or interaction with phosphotyrosine. Activation of α2-chimaerin by phorbol ester caused growth cone collapse. Active α2-chimaerin interacts with collapsin response mediator protein-2 (CRMP-2) and cyclin-dependent kinase (Cdk) 5/p35 kinase through its SH2 and GAP domains, respectively. Cdk5 phosphorylates CRMP-2 at serine 522, possibly facilitating phosphorylation of serine 518 and threonine 514 by glycogen synthase kinase 3β (GSK3β), a kinase previously implicated in Sema 3A signaling. Phosphorylation of CRMP-2 serine 522 was essential for Sema 3A-induced growth cone collapse, which

is dependent on Cdk5 but not Rho kinase activity. α2-chimaerin, like CRMP-2, can associate with the Sema 3A receptor. These results indicate that active α2-chimaerin Rac GAP, Cdk5/p35, and its substrate CRMP-2, are implicated in the dynamics of growth cone guidance initiated through Sema 3A signaling.
The Journal of Neuroscience, October 13, 2004 • 24(41):8994–9004

Caenorhabditis elegans VEM-1, a Novel Membrane Protein, Regulates the Guidance of Ventral Nerve Cord-Associated Axons

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Departments of [1]Neuroscience and [2]Pathology, Albert Einstein College of Medicine, Bronx, New York 10461

In the developing CNS, pathfinding growth cones use intermediate target- and pioneer axon-associated guidance cues to navigate along stereotypical trajectories. We previously showed that the novel membrane-associated protein Vema is localized to the floor plate and the optic chiasm, intermediate targets located at the ventral midline of the spinal cord and diencephalon in the developing rodent CNS, respectively. Here, we report that the *Caenorhabditis elegans* ortholog of *vema*, *vem-1*, is expressed by the AVG pioneer midline neuron and by several neurons that extend longitudinally projecting axons into the ventral nerve cord (VNC). In *vem-1* mutants and *vem-1(RNAi)* animals, a subset of posteriorly projecting interneuron axons either fail to extend ventrally to the VNC and, instead, assume aberrant lateral positions or are inappropriately located in the left tract of the VNC. In addition, ventral motor neuron axons exhibit pathfinding errors within the VNC and along the dorsoventral body axis. The conserved UNC-40/DCC and SAX-3-/Robo receptors mediate signaling events that regulate axon guidance in a wide variety of systems. Double-mutant analyses reveal that *vem-1* genetically interacts with *unc-40* and is likely to function in parallel with *sax-3* to regulate the guidance of a subset of VNC-associated interneuron and motor neuron axons. Consistent with these genetic data, we also show that VEM-1 is capable of physically interacting with UNC-40 but not SAX-3.
The Journal of Neuroscience, October 13, 2004 • 24(41):9015–9026

In Vivo Trafficking and Targeting of N-Cadherin to Nascent Presynaptic Terminals

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N-cadherin is a prominent component of developing and mature synapses, yet very little is known about its trafficking within neurons. To investigate N-cadherin dynamics in developing axons, we used *in vivo* two-photon time-lapse microscopy of N-cadherin— green fluorescent protein (Ncad–GFP), which was expressed in Rohon–Beard neurons of the embryonic zebrafish spinal cord. Ncad–GFP was present as either stable accumulations or highly mobile transport packets. The mobile transport packets were of two types: tubulovesicular structures that moved preferentially in the anterograde direction and discrete–punctate structures that exhibited bidirectional movement. Stable puncta of Ncad–GFP accumulated in the wake of the growth cone with a time course. Colocalization of Ncad–GFP puncta with synaptic markers suggests that N-cadherin is a very early component of nascent synapses. Expression of deletion mutants revealed a potential role of the extracellular domain in appropriate N-cadherin trafficking and targeting. These results are the first to characterize the trafficking of a synaptic cell-adhesion molecule in developing axons *in vivo*. In addition, we have begun to investigate the cell biology of N-cadherin trafficking and targeting in the context of an intact vertebrate embryo.
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Two Interdependent TRPV Channel Subunits, Inactive and Nanchung, Mediate Hearing in *Drosophila*

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Hearing in *Drosophila* depends on the transduction of antennal vibration into receptor potentials by ciliated sensory neurons in Johnston's organ, the antennal chordotonal organ. We previously found that a *Drosophila* protein in the vanilloid receptor subfamily (TRPV) channel subunit, Nanchung (NAN), is localized to the chordotonal cilia and required to generate sound-evoked potentials (Kim et al., 2003). Here, we show that the only other *Drosophila* TRPV protein is mutated in the behavioral mutant *inactive* (*iav*). The IAV protein forms a hypotonically activated channel when expressed in cultured cells; in flies, it is specifically expressed in the chordotonal neurons, localized to their cilia and required for hearing. IAV and NAN are each undetectable in cilia of mutants lacking the other protein, indicating that they both contribute to a heteromultimeric transduction channel *in vivo*. A functional green fluorescence protein–IAV fusion protein shows that the channel is restricted to the proximal cilium, constraining models for channel activation.
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Optical Postsynaptic Measurement of Vesicle Release Rates for Hippocampal Synapses Undergoing Asynchronous Release during Train Stimulation

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Developing hippocampal neurons in microisland culture were found to undergo rapid depression of excitatory synaptic activity caused by consumption of their readily releasable pool (RRP) of vesicles in response to 20 Hz trains of stimulation. Associated with depression was a switch to an asynchronous release mode that maintained transmission at a high steady-state rate equivalent to ~2.1 RRPs per second. We have applied postsynaptic Ca^{2+} imaging to directly monitor these asynchronous release events to estimate both the steady rate of transmitter release and the number of quanta within the RRP at individual hippocampal synapses. Based on the frequency of asynchronous release measured at individual synapses postsynaptically using Ca^{2+} imaging (5–17 sec after train stimulation) and with knowledge of the time course by which asynchronous release rates decay, we estimate that individual hippocampal synapses exhibit (in response to train stimulation) peak release rates of up to 21 quanta per second from an RRP that contains, on average, 10 quanta. Use-dependent block of evoked synaptic activity by MK-801 [(+)-5-methyl-10,11-dihydro-5H-dibenzo [a,d]cyclohepten-5,10-imine maleate] confirmed that synapses undergoing asynchronous release are not significantly different from the general population with regard to their composition of NMDA receptor and/or release probability. Given that high-frequency trains deplete the synapse of readily releasable quanta (and that these release rates can only be maintained for a few seconds), these high rates of asynchronous release likely reflect refilling of vesicles from a reserve pool and not necessarily the continuous action of a relatively slow clathrin- and endosome-dependent process.

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Tyrosine Residues That Control Binding and Gating in the 5-Hydroxytryptamine$_3$ Receptor Revealed by Unnatural Amino Acid Mutagenesis

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The mechanism by which agonist binding triggers pore opening in ligand-gated ion channels is poorly understood. Here, we used unnatural amino acid mutagenesis to introduce subtle changes to the side chains of tyrosine residues (Tyr141, Tyr143, Tyr153, and Tyr234), which dominate the 5-HT_3 receptor binding site. Heterologous expression in oocytes, combined with radioligand binding data and a model of 5-HT (serotonin) computationally docked into the binding site, has allowed us to determine which of these residues are responsible for binding and/or gating. We have shown that Tyr 143 forms a hydrogen bond that is essential for receptor gating but does not affect binding, whereas a hydrogen bond formed by Tyr153 is involved in both binding and gating of the receptor. The aromatic group of Tyr234 is essential for binding and gating, whereas its hydroxyl does not affect binding but plays a steric role in receptor gating. Tyr141 is not involved in agonist binding or receptor gating but is important for antagonist interactions. These data, combined with a new model of the nonliganded 5-HT_3 receptor, lead to a mechanistic explanation of the interactions that initiate the conformational change leading to channel opening. Thus, we suggest that agonist entry into the binding pocket may displace Tyr143 and Tyr153 and results in their forming new hydrogen bonds. These bonds may form part of the network of bond rearrangements that trigger the conformational change leading to channel opening. Similar rearrangements may initiate gating in all Cys-loop receptors.

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The *Drosophila* Metabotropic Glutamate Receptor DmGluRA Regulates Activity-Dependent Synaptic Facilitation and Fine Synaptic Morphology

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In vertebrates, several groups of metabotropic glutamate receptors (mGluRs) are known to modulate synaptic properties. In contrast, the *Drosophila* genome encodes a single functional mGluR (DmGluRA), an ortholog of vertebrate group II mGluRs, greatly expediting the functional characterization of mGluR-mediated signaling in the nervous system. We show here that DmGluRA is expressed at the glutamatergic neuromuscular junction (NMJ), localized in periactive zones of presynaptic boutons but excluded from active sites. Null *DmGluRA* mutants are completely viable, and all of the basal NMJ synaptic transmission properties are normal. In contrast, *DmGluRA* mutants display approximately a threefold increase in synaptic facilitation during short stimulus trains. Prolonged stimulus trains result in very strongly increased (~10-fold) augmentation, including the appearance of asynchronous, bursting excitatory currents never observed in wild type. Both defects are rescued by expression of DmGluRA only in the neurons, indicating a specific presynaptic requirement. These phenotypes are reminiscent of hyperexcitable mutants, suggesting a role of DmGluRA signaling in the regulation of presynaptic excitability properties. The mutant phenotypes could not be replicated by acute application of mGluR antagonists, suggesting that DmGluRA regulates the development of presynaptic properties rather than directly controlling short-term modulation. *DmGluRA* mutants also display mild defects in NMJ architecture: a decreased number of synaptic boutons accompanied by an increase in mean bouton size. These morphological changes bidirectionally correlate with DmGluRA levels in the presynaptic terminal. These data reveal the

following two roles for DmGluRA in presynaptic mechanisms: (1) modulation of presynaptic excitability properties important for the control of activity-dependent neurotransmitter release and (2) modulation of synaptic architecture.
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Three Mechanisms Underlie KCNQ2/3 Heteromeric Potassium M-Channel Potentiation

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The non-inactivating potassium M-current exerts a strong influence on neuronal excitability. The channels responsible for this current are made up of KCNQ subunits, and mutations in most of these produce human pathologies. Notably, in terms of excitation, mutations in either KCNQ2 or KCNQ3 lead to benign neonatal familial convulsions. Although a mere reduction of 25% in KCNQ2/3 function can increase excitability to epileptogenic levels, the potentiation of these subunits has anti-epileptogenic effects. After KCNQ2/3 heteromerization, current levels can augment as much as 10-fold, and we have discovered that there are three processes underlying this potentiation. First, there is an increase in the number of channels inserted in the membrane after heteromerization of the C-terminal region. Second, the N-terminal domain from KCNQ2 exerts a negative influence on the current level. Finally, Ala 315 of KCNQ3, a residue located in the inner vestibule after the selectivity filter, plays a critical role in preventing current flow in KCNQ3 homomeric channels, whereas it is permissive in heteromers in combination with Thr at the equivalent 276 position of KCNQ2.
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Evidence That ΔNp73 Promotes Neuronal Survival by p53-Dependent and p53-Independent Mechanisms

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The p53 family member, p73, is essential for the survival of sympathetic neurons during the developmental period of naturally occurring neuronal death. Here, we have asked whether ΔNp73, which is the only p73 isoform expressed in sympathetic neurons, mediates this survival by p53-dependent and/or p53-independent mechanisms. Initially, we used a genetic approach and crossed p53 $^{+/-}$ and p73 $^{+/-}$ mice. Quantitation of neurons in the sympathetic superior cervical ganglion during the period of naturally occurring cell death revealed that the loss of p53 partially rescued the death of neurons seen in p73 $^{-/-}$ animals. Moreover, exogenous expression of ΔNp73 in cultured p53 $^{-/-}$ sympathetic neurons rescued these neurons from apoptosis after NGF withdrawal. Biochemical studies asking how ΔNp73 inhibited NGF withdrawal-induced apoptosis in wild-type neurons demonstrated that it prevented the upregulation of the direct p53 targets p21 and Apaf-1 as well as cleavage of caspase-3. It also inhibited events at the mitochondrial apoptotic checkpoint, suppressing the induction of BimEL and the release of mitochondrial cytochrome *c*. Interestingly, ΔNp73 expression also inhibited one very early event in the apoptotic cascade, the activation of c-Jun N-terminal protein kinase (JNK), likely by binding directly to JNK. Finally, we show that neuronal cell size is decreased in p73 $^{-/-}$ mice, and that this decrease is not rescued by the lack of p53, suggesting a role for p73 in regulating cell size that does not involve interactions with p53. Thus, ΔNp73 promotes neuronal survival via p53-dependent and -independent mechanisms, and it does so at multiple points, including some of the most proximal events that occur after NGF withdrawal.
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DEVELOPMENT/PLASTICITY/REPAIR

Fgf8 Regulates the Development of Intra-Neocortical Projections

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The process of generating functionally distinct neocortical areas requires the formation of an intra-neocortical connectivity map. Here, we explore the early development of murine intra-neocortical projections and find that axons from rostral and caudal neurons remain, respectively, within large rostral and caudal domains of the neonatal neocortex. Despite evidence that thalamic input can regulate neocortical areal properties, we found that the neonatal intra-neocortical projection pattern was not perturbed when thalamic input was absent in *Gbx2* mutants. On the contrary, in *Fgf8* hypomorphic mutants, the rostral neocortex of which acquires more caudal molecular properties, caudally located neurons ectopically project axons into the rostral cortex. Therefore, neocortical patterning by *Fgf8* also contributes to arealization through mediating early development of intra-neocortical connectivity.
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Requirement for the RIIβ Isoform of PKA, But Not Calcium-Stimulated Adenylyl Cyclase, in Visual Cortical Plasticity

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The cAMP-dependent protein kinase (PKA) signaling pathway plays a key role in visual cortical plasticity. Inhibitors that block activation of all PKA regulatory subunits (RIα, RIβ, RIIα, RIIβ) abolish long-term potentiation (LTP) and long-term depression (LTD) *in vitro* and ocular dominance plasticity (ODP) *in vivo*. The details of this signaling cascade, however, including the source of PKA signals and which PKA subunits are involved, are unknown. To investigate these issues we have examined LTP, LTD, and ODP in knock-out mice lacking either the two cortically expressed Ca^{2+}-stimulated adenylyl cyclases (AC1 and AC8) or the predominant neocortical subunit of PKA (RIIβ). Here we show that plasticity remains intact in AC1/AC8$-/-$ mice, whereas ODP and LTD, but not LTP, are absent in RII$\beta-/-$ mice. We conclude that (1) plasticity in the visual cortex does not require the activity of known Ca^{2+}-stimulated adenylyl cyclases, (2) the PKA dependence of ODP and LTD, but not LTP, is mediated by RIIβ-PKA, and (3) multiple isoforms of PKA contribute to LTD.

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Differential Requirements for Semaphorin 3F and Slit-1 in Axonal Targeting, Fasciculation, and Segregation of Olfactory Sensory Neuron Projections

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The formation of precise stereotypic connections in sensory systems is critical for defining accurate internal representations of the external world; however, the molecular mechanisms underlying the formation of sensory maps are poorly understood. Here, we examine the roles of two structurally unrelated repulsive guidance cues, semaphorin 3F (Sema3F) and Slit-1, in olfactory sensory axon fasciculation, targeting, and segregation. Using *sema3F*$^{-/-}$ mice, we show that Sema3F is critical for vomeronasal sensory neuron axonal fasciculation and for segregation of these sensory afferents from the main olfactory system; however, Sema3F plays only a minor role in targeting of apical vomeronasal neuron axons to the anterior accessory olfactory bulb (AOB). In addition, we show that Sema3F is required for lamina-specific targeting of olfactory sensory axons within the main olfactory system. In contrast to Sema3F, Slit-1 is dispensable for fasciculation of basal vomeronasal neuron axons but is critical for targeting these axons to the posterior AOB. These results reveal discrete and complementary roles for secreted semaphorins and slits in axonal targeting, fasciculation, and segregation of olfactory sensory neuron projections.

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BEHAVIORAL/SYSTEMS/COGNITIVE

Cortical GABA Interneurons in Neurovascular Coupling: Relays for Subcortical Vasoactive Pathways

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The role of interneurons in neurovascular coupling was investigated by patch-clamp recordings in acute rat cortical slices, followed by single-cell reverse transcriptase-multiplex PCR (RT-mPCR) and confocal observation of biocytin-filled neurons, laminin-stained microvessels, and immunodetection of their afferents by vasoactive subcortical cholinergic (ACh) and serotonergic (5-HT) pathways. The evoked firing of single interneurons in whole-cell recordings was sufficient to either dilate or constrict neighboring microvessels. Identification of vasomotor interneurons by single-cell RT-mPCR revealed expression of vasoactive intestinal peptide (VIP) or nitric oxide synthase (NOS) in interneurons inducing dilatation and somatostatin (SOM) in those eliciting contraction. Constrictions appeared spatially restricted, maximal at the level of neurite apposition, and were associated with contraction of surrounding smooth muscle cells, providing the first evidence for neural regulation of vascular sphincters. Direct perfusion of VIP and NO donor onto the slices dilated microvessels, whereas neuropeptide Y (NPY) and SOM induced vasoconstriction. RT-PCR analyses revealed expression of specific subtypes of neuropeptide receptors in smooth muscle cells from intracortical microvessels, compatible with the vasomotor responses they elicited. By triple and quadruple immunofluorescence, the identified vasomotor interneurons established contacts with local microvessels and received, albeit to a different extent depending on interneuron subtypes, somatic and dendritic afferents from ACh and 5-HT pathways. Our results demonstrate the ability of specific subsets of cortical GABA

interneurons to transmute neuronal signals into vascular responses and further suggest that they could act as local integrators of neurovascular coupling for subcortical vasoactive pathways.

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Retinotopic Organization and Functional Subdivisions of the Human Lateral Geniculate Nucleus: A High-Resolution Functional Magnetic Resonance Imaging Study

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Functional magnetic resonance imaging (fMRI) has provided intriguing insights into the topography and functional organization of visual cortical areas in the human brain. However, little is known about the functional anatomy of subcortical nuclei. Here, we used high-resolution fMRI ($1.5 \times 1.5 \times 2\ mm^3$) at 3 tesla to investigate the retinotopic organization of the human lateral geniculate nucleus (LGN). The central 15° of the visual field were mapped using periodic flickering checkerboard stimuli that evoked a traveling wave of activity. The contralateral visual hemifield was represented with the lower field in the medial-superior portion and the upper field in the lateral-inferior portion of each LGN. The horizontal meridian was significantly overrepresented relative to the vertical meridian. The fovea was represented in posterior and superior portions, with increasing eccentricities represented more anteriorly. The magnification of the fovea relative to the periphery was similar to that described for human primary visual cortex. The magnocellular regions of the LGN were distinguished based on their sensitivity to low stimulus contrast and tended to be located in its inferior and medial portions. Our results demonstrate striking similarities in the topographic organization of the macaque and human LGN and support accounts of a constant magnification from the retina through the cortex in both species.

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A Population Decoding Framework for Motion Aftereffects on Smooth Pursuit Eye Movements

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Both perceptual and motor systems must decode visual information from the distributed activity of large populations of cortical neurons. We have sought a common framework for understanding decoding strategies for visually guided movement and perception by asking whether the strong motion aftereffects seen in the perceptual domain lead to similar expressions in motor output. We found that motion adaptation indeed has strong sequelae in the direction and speed of smooth pursuit eye movements. After adaptation with a stimulus that moves in a given direction for 7 sec, the direction of pursuit is repelled from the direction of pursuit targets that move within 90° of the adapting direction. The speed of pursuit decreases for targets that move at the direction and speed of the adapting stimulus and is repelled from the adapting speed in the sense that the decrease either becomes greater or smaller (eventually turning to an increase) when tracking targets move slower or faster than the adapting speed. The effects of adaptation are spatially specific and fixed to the retinal location of the adapting stimulus. The magnitude of adaptation of pursuit speed and direction is uncorrelated, suggesting that the two parameters are decoded independently. Computer simulation of motion adaptation in the middle temporal visual area (MT) shows that vector-averaging decoding of the population response in MT can account for the effects of adaptation on the direction of pursuit. Our results suggest a unified framework for thinking, in terms of population decoding, about motion adaptation for both perception and action.

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Phase Sensitivity of Synaptic Modifications in Oscillating Cells of Rat Visual Cortex

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Synaptic modifications depend on the amplitude and temporal relations of presynaptic and postsynaptic activation. The interactions among these variables are complex and hard to predict when neurons engage in synchronized high-frequency oscillations in the β and γ frequency range, as is often observed during signal processing in the cerebral cortex. Here we investigate in layer II/III pyramidal cells of rat visual cortex slices how synapses change when synchronized, oscillatory multifiber activity impinges on postsynaptic neurons during membrane potential (V_m) oscillations at 20 and 40 Hz. Synapses underwent long-term potentiation (LTP) when EPSPs coincided with the peaks of the V_m oscillations but exhibited long-term depression (LTD) when EPSPs coincided with the troughs. The induction of LTP but not of LTD was NMDA receptor dependent, required additional activation of muscarinic receptors in older animals, and persisted in a kainate-driven increased conductance state. Thus, even when neuronal networks engage in high-frequency oscillations, synaptic plasticity remains exquisitely sensitive to the timing of discharges. This is an essential prerequisite for theories which assume that precise synchronization of discharges serves as signature of relatedness in distributed processing.

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Spike Timing of Distinct Types of GABAergic Interneuron during Hippocampal Gamma Oscillations *In Vitro*

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Gamma frequency (30–100 Hz) network oscillations occur in the intact hippocampus during awake, attentive behavior. Here, we explored the underlying cellular mechanisms in an *in vitro* model of persistent gamma-frequency oscillations, induced by bath application of 20 μM carbachol in submerged hippocampal slices at 30 $\pm$ 1°C. Current-source density analysis of the field oscillation revealed a prominent alternating sink-source pair in the perisomatic and apical dendritic regions of CA3. To elucidate the active events generating these extracellular dipoles, we examined the firing properties of distinct neuron types. Visually guided unit recordings were obtained from individual CA3 neurons followed by intracellular labeling for anatomical identification. Pyramidal cells fired at 2.82 $\pm$ 0.7 Hz, close to the negative peak of the oscillation (0.03 $\pm$ 0.65 msec), and often in conjunction with a negative spike-like component of the field potential. In contrast, all phase-coupled interneurons fired after this negative peak. Perisomatic inhibitory interneurons fired at high frequency (18.1 $\pm$ 2.7 Hz), shortly after the negative peak (1.97 $\pm$ 0.95 msec) and were strongly phase-coupled. Dendritic inhibitory interneurons fired at lower frequency (8.4 $\pm$ 2.4 Hz) and with less fidelity and a longer delay after the negative peak (4.3 $\pm$ 1.1 msec), whereas interneurons with cell body in the stratum radiatum often showed no phase relationship with the field oscillation. The phase and spike time data of individual neurons, together with the current-source density analysis, support a synaptic feedback model of gamma oscillations primarily involving pyramidal cells and inhibitory cells targeting their perisomatic region.

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Role of Cerebellar Interpositus Nucleus in the Genesis and Control of Reflex and Conditioned Eyelid Responses

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The role of cerebellar circuits in the acquisition of new motor abilities is still a matter of intensive debate. To establish the contribution of posterior interpositus nucleus (PIN) to the performance and/or acquisition of reflex and classically conditioned responses (CRs) of the eyelid, the effects of microstimulation and/or pharmacological inhibition by muscimol of the nucleus were investigated in conscious cats. Microstimulation of the PIN in naive animals evoked ramp-like eyelid responses with a wavy appearance, without producing any noticeable plastic functional change in the cerebellar and brainstem circuits involved. Muscimol microinjections decreased the amplitude of reflex eyeblinks evoked by air puffs, both when presented alone or when paired with a tone as conditioned stimulus (CS). In half-conditioned animals, muscimol injections also decreased the amplitude and damped the typical wavy profile of CRs, whereas microstimulation of the same sites increased both parameters. However, neither muscimol injections nor microstimulation modified the expected percentage of CRs, suggesting a major role of the PIN in the performance of eyelid responses rather than in the learning process. Moreover, the simultaneous presentation of CS and microstimulation in well trained animals evoked CRs similar in amplitude to the added value of those evoked by the two stimuli presented separately. In contrast, muscimol-injected animals developed CRs to paired CS and microstimulation presentations, larger than those evoked by the two stimuli when presented alone. It is concluded that the PIN contributes to the enhancement of both reflex and conditioned eyelid responses and to the damping of resonant properties of neuromuscular elements controlling eyelid kinematics.

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The Role of the Insular Cortex in Pitch Pattern Perception: The Effect of Linguistic Contexts

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Auditory pitch patterns are significant ecological features to which nervous systems have exquisitely adapted. Pitch patterns are found embedded in many contexts, enabling different information-processing goals. Do the psychological functions of pitch patterns determine the neural mechanisms supporting their perception, or do all pitch patterns, regardless of function, engage the same mechanisms? This issue is pursued in the present study by using ^{15}0-water positron emission tomography to study brain activations when two subject groups discriminate pitch patterns in their respective native languages, one of which is a tonal language and the other of which is not. In a tonal language, pitch patterns signal lexical meaning. Native Mandarin-speaking and English-speaking listeners discriminated pitch patterns embedded in Mandarin and English words and also passively listened to the same stimuli. When Mandarin listeners discriminated pitch embedded in Mandarin lexical tones, the left anterior insular cortex was the most active. When they discriminated pitch patterns embedded in English words, the homologous area in the right hemisphere activated as it did in English-speaking listeners discriminating pitch patterns embedded in either Mandarin or English words. These results support the view that neural responses to physical acoustic stimuli depend on the function of those stimuli and implicate anterior insular cortex in auditory processing, with the left insular cortex especially responsive to linguistic stimuli.

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Group I Metabotropic Glutamate Receptor NMDA Receptor Coupling and Signaling Cascade Mediate Spinal Dorsal Horn NMDA Receptor 2B Tyrosine Phosphorylation Associated with Inflammatory Hyperalgesia

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Hindpaw inflammation induces tyrosine phosphorylation (tyr-P) of the NMDA receptor (NMDAR) 2B (NR2B) subunit in the rat spinal dorsal horn that is closely related to the initiation and development of hyperalgesia. Here, we show that in rats with Freund's adjuvant-induced inflammation, the increased dorsal horn NR2B tyr-P is blocked by group I metabotropic glutamate receptor (mGluR) antagonists [7-(hydroxyimino)cyclopropa[b] chromen-1a-carboxylate ethyl ester (CPCCOEt) and 2-methyl-6-(phenylethynyl)-pyridine (MPEP), by the Src inhibitor CGP 77675, but not by the MAP kinase inhibitor 2′-amino-3′-methoxyflavone. Analysis of the calcium pathways shows that the *in vivo* NR2B tyr-P is blocked by an IP_3 receptor antagonist 2-aminoethoxydiphenylborate (2APB) but not by antagonists of ionotropic glutamate receptors and voltage-dependent calcium channels, suggesting that the NR2B tyr-P is dependent on intracellular calcium release. In a dorsal horn slice preparation, the group I (dihydroxyphenylglycine), but not group II [(2*R*,4*R*)-4-aminopyrrolidine-2,3-dicarboxylate] and III [L-AP 4 (L-(+)-2-amino-4-phosphonobutyric acid)], mGluR agonists, an IP_3 receptor (D-IP_3) agonist, and a PKC (PMA) activator, induces NR2B tyr-P similar to that seen *in vivo* after inflammation. Coimmunoprecipitation indicates that Shank, a postsynaptic density protein associated with mGluRs, formed a complex involving PSD-95 (postsynaptic density-95), NR2B, and Src in the spinal dorsal horn. Double immunofluorescence studies indicated that NR1 is colocalized with mGluR5 in dorsal horn neurons. mGluR5 also coimmunoprecipitates with NR2B. Finally, intrathecal pretreatment of CPCCOEt, MPEP, and 2APB attenuates inflammatory hyperalgesia. Thus, inflammation and mGluR-induced NR2B tyr-P share similar mechanisms. The group I mGluR-NMDAR coupling cascade leads to phosphorylation of the NMDAR and appears necessary for the initiation of spinal dorsal horn sensitization and behavioral hyperalgesia after inflammation.

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The Integration of Multiple Stimulus Features by V1 Neurons

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We investigated how V1 neurons integrate two stimulus features by presenting stimuli from a stimulus set made up of all combinations of eight different directions of motion and nine binocular disparities. We investigated the occurrence and shape of the resulting joint tuning function. Among V1 neurons, ~80% were jointly tuned for disparity with orientation or direction. The joint tuning function of all jointly tuned neurons was separable into distinct tuning for disparity on the one hand, and orientation or direction tuning on the other. The degree of separability and the mutual information between the stimulus and the firing rates were strongly correlated. The mutual information of jointly tuned neurons when both features were decoded together was highly correlated with the mutual information when the two features were decoded separately, and the information was then summed. Jointly tuned neurons were just as good at representing information about single features as neurons tuned for only a single feature. The tuning properties of most jointly tuned neurons did not dynamically evolve over time, nor did jointly tuned neurons respond earlier than neurons tuned for only a single feature. The response selectivity of V1 neurons is low and decreases the information that a neuron represents about a stimulus. Together these results suggest that distinct stimulus features are integrated very early in visual processing. Furthermore, V1 generates a distributed representation through low response selectivity that avoids the curse of dimensionality by using separable joint tuning functions.

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Modulation Power and Phase Spectrum of Natural Sounds Enhance Neural Encoding Performed by Single Auditory Neurons

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We examined the neural encoding of synthetic and natural sounds by single neurons in the auditory system of male zebra finches by estimating the mutual information in the time-varying mean firing rate of the neuronal response. Using a novel parametric method for estimating mutual information with limited data, we tested the hypothesis that song and song-like synthetic sounds would be preferentially encoded relative to other complex, but non-song-like synthetic sounds. To test this hypothesis, we designed two synthetic stimuli: synthetic songs that matched the power of spectral–temporal modulations but lacked the modulation phase structure of zebra finch song and noise with uniform band-limited spectral–temporal modulations. By defining neural selectivity as relative mutual information, we found that the auditory system of songbirds showed selectivity for song-like sounds. This selectivity increased in a hierarchical manner along ascending processing stages in the auditory system. Midbrain neurons responded with highest information rates and efficiency to synthetic songs and thus were selective for the spectral–temporal modulations of song. Primary forebrain neurons showed increased information to zebra finch song and synthetic song equally over noise stimuli. Secondary forebrain neurons responded with the highest information to zebra finch song relative to other stimuli and thus were selective for its specific modulation phase relationships. We also assessed the relative contribution of three response properties to this selectivity: (1) spiking reliability, (2) rate distribution entropy, and (3) bandwidth. We found that rate distribution and bandwidth but not reliability were responsible for the higher average information rates found for song-like sounds.

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Intrastriatal Transforming Growth Factor α Delivery to a Model of Parkinson's Disease Induces Proliferation and Migration of Endogenous Adult Neural Progenitor Cells without Differentiation into Dopaminergic Neurons

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We examined the cell proliferative, neurogenic, and behavioral effects of transforming growth factor α (TGFα) in a 6-OHDA Parkinson's disease model when compared with naive rats. Intrastriatal TGFα infusion induced significant proliferation, hyperplastic nodules, and substantial migratory waves of nestin-positive progenitor cells from the adult subventricular zone (SVZ) of dopamine-denervated rats. Interestingly, SVZ cells in naive rats displayed proliferation but minimal migration in response to the TGFα infusion. The cells in the expanded SVZ accumulated cytoplasmic β-catenin, indicating activation of classical Wnt signaling. However, no evidence of any neuronal differentiation was found of these recruited progenitor cells anywhere examined in the brain. Consequently, no evidence of dopaminergic (DA) neurogenesis was found in the striatum or substantia nigra in any experimental group, and amphetamine-induced behavioral rotations did not improve. In summary, the cells in the TGFα-induced migratory cellular wave remain undifferentiated and do not differentiate into midbrain-like DA neurons.

The Journal of Neuroscience, October 13, 2004 • 24(41):8924–8931

Physiological and Morphological Characterization of Dentate Granule Cells in the p35 Knock-Out Mouse Hippocampus: Evidence for an Epileptic Circuit

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There is a high correlation between pediatric epilepsies and neuronal migration disorders. What remains unclear is whether there are intrinsic features of the individual dysplastic cells that give rise to heightened seizure susceptibility, or whether these dysplastic cells contribute to seizure activity by establishing abnormal circuits that alter the balance of inhibition and excitation. Mice lacking a functional *p35* gene provide an ideal model in which to address these questions, because these knock-out animals not only exhibit aberrant neuronal migration but also demonstrate spontaneous seizures.

Extracellular field recordings from hippocampal slices, characterizing the input–output relationship in the dentate, revealed little difference between wild-type and knock-out mice under both normal and elevated extracellular potassium conditions. However, in the presence of the $GABA_A$ antagonist bicuculline, p35 knock-out slices, but not wild-type slices, exhibited prolonged depolarizations in response to stimulation of the perforant path. There were no significant differences in the intrinsic properties of dentate granule cells (i.e., input resistance, time constant, action potential generation) from wild-type versus knock-out mice. However, antidromic activation (mossy fiber stimulation) evoked an excitatory synaptic response in over 65% of granule cells from p35 knock-out slices that was never observed in wild-type slices. Ultrastructural analyses identified morphological substrates for this aberrant excitation: recurrent axon collaterals, abnormal basal dendrites, and mossy fiber terminals forming synapses onto the spines of neighboring granule cells. These studies suggest that granule cells in p35 knock-out mice contribute to seizure activity by forming an abnormal excitatory feedback circuit.

The Journal of Neuroscience, October 13, 2004 • 24(41):9005–9014

A Mouse Model of Classical Late-Infantile Neuronal Ceroid Lipofuscinosis Based on Targeted Disruption of the CLN2 Gene Results in a Loss of Tripeptidyl-Peptidase I Activity and Progressive Neurodegeneration

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Mutations in the CLN2 gene, which encodes a lysosomal serine protease, tripeptidyl-peptidase I (TPP I), result in an autosomal recessive neurodegenerative disease of children, classical late-infantile neuronal ceroid lipofuscinosis (cLINCL). cLINCL is inevitably fatal, and there currently exists no cure or effective treatment. In this report, we provide the characterization of the first CLN2-targeted mouse model for cLINCL. CLN2-targeted mice were fertile and apparently healthy at birth despite an absence of detectable TPP I activity. At ~7 weeks of age, neurological deficiencies became evident with the onset of a tremor that became progressively more severe and was eventually

accompanied by ataxia. Lifespan of the affected mice was greatly reduced (median survival, 138 d), and extensive neuronal pathology was observed including a prominent accumulation of cytoplasmic storage material within the lysosomal-endosomal compartment, a loss of cerebellar Purkinje cells, and widespread axonal degeneration. The CLN2-targeted mouse therefore recapitulates much of the pathology and clinical features of cLINCL and represents an animal model that should provide clues to the normal cellular function of TPP I and the pathogenic processes that underlie neuronal death in its absence. In addition, the CLN2-targeted mouse also represents a valuable model for the evaluation of different therapeutic strategies.
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This Week in The Journal
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