

This Week in The Journal

● Cellular/Molecular

Mitochondrial Calcium Handling at Mossy Fiber Boutons

Doyun Lee, Kyu-Hee Lee, Won-Kyung Ho, and Suk-Ho Lee

(see pages 13603–13613)

Dentate granule cells essentially can speak with two tongues. The axonal branches of their mossy fibers innervate CA3 pyramidal cells and interneurons, each with distinct morphological and functional properties. Lee et al. stimulated mossy fibers and compared the response of putative large boutons at hilar mossy cells with smaller *en passant* boutons onto hilar interneurons. Following high-frequency stimulation (HFS), the intracellular residual calcium (Ca_{res}) was sustained for tens of seconds in large mossy fiber boutons (MFBs). Smaller *en passant* MFBs had a much quicker drop in intracellular calcium. Inhibitors of mitochondrial pumps increased Ca_{res} in large but not small MFBs, consistent with a buffering role for mitochondria in the large boutons. During HFS, calcium uptake depended on the inner mitochondrial membrane calcium uniporter, after which the mitochondrial Na^+/Ca^{2+} exchanger (mitoNCX) contributed to Ca_{res} . Post-tetanic potentiation at mossy cells, but not at interneurons, was affected by blocking the mitoNCX.

▲ Development/Plasticity/Repair

$\beta 1$ Integrin and Cortical Development

Richard Belvindrah, Diana Graus-Porta, Sandra Goebbels, Klaus-Armin Nave, and Ulrich Müller

(see pages 13854–13865)

In this week's *Journal*, Belvindrah et al. revisited the proposed role for the extracellular matrix receptor $\beta 1$ integrin in the developing cortex. The authors used a

Nex-CRE mouse line in which integrin subunits could be conditionally inactivated. *Itgb1-NEXko* mice lacked $\beta 1$ in precursors that generated migrating neurons. *Itga3-null* mice were deficient in $\alpha 3$ subunits in all cell types and thus did not express $\alpha 3\beta 1$ integrins. As expected, cortical layers were disrupted in brains of mice lacking $\alpha 3\beta 1$ in glia and neurons, but selective deletion in migrating pyramidal neurons did not affect their migration and cell layer formation, ruling out a pivotal role for integrins in migration. However, the expression of $\beta 1$ integrins in glia affected the morphological differentiation of glia and neurons.

■ Behavioral/Systems/Cognitive

Rotating and Translating in the Thalamus

Hui Meng, Paul J. May, J. David Dickman, and Dora E. Angelaki

(see pages 13590–13602)

In this week's *Journal*, Meng et al. mapped the projections that confer vestibular sensation to and from the thalamus in primates. Monkeys, seated in a vestibular turntable, experienced rotation in pitch, roll, and yaw dimensions, as well as translation in the horizontal plane. The authors made extracellular recordings from >1000 thalamic neurons, ~10% of which responded to vestibular stimulation. Although some cells responded exclusively to either tilt or translation, most showed intermediate responses to both stimuli, suggesting that they received signals from the otolith and semicircular canal. The vestibular responsive neurons were more widely dispersed than expected, with no apparent functional segregation. Injection of a neuronal tracer dye revealed that these thalamic neurons received input from cerebellar nuclei. The authors concluded that several thalamic nuclei contribute to precortical vestibular process-

ing and that their inputs come from cerebellar as well as vestibular nuclei.

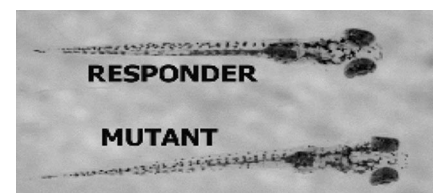
◆ Neurobiology of Disease

Cone-Specific Degeneration in Zebrafish

George Stearns, Meradelfa Evangelista, James M. Fadool, and Susan E. Brockerhoff

(see pages 13866–13874)

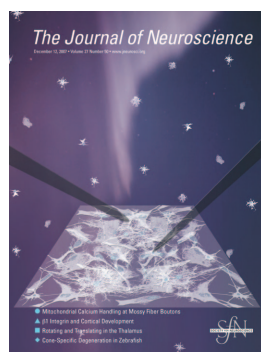
Dozens of mutations contribute to progressive blindness in humans, many of which result from photoreceptor degeneration. More of these identified mutations affect rods. This week, Stearns et al. identified a mutation in cone photoreceptors that caused cone degeneration as well as “bystander” death of some rods. F_3 generation progeny from fish mutagenized with ethyl nitrosourea were screened initially for their optokinetic response. The screen yielded a recessive mutation that affected the cone-specific phosphodiesterase *c* (*pde6c*) gene. Four days postfertilization, cones in mutant fish larvae had already degenerated. Cone degeneration resembled the rod degeneration seen in the mouse *rd1* mutation, which affects the rod-specific *pde6 β* . Location mattered to *pde6c* mutant photoreceptors, particularly to doomed rods unlucky enough to reside near cones. The lucky rods, those in densely packed cone-free areas, were spared degeneration.



The image shows a dorsal view of normal (responder) fish or fish that were blind as a result of a mutation in the cone phosphodiesterase (mutant). The size of the eye in the mutant was normal, but homozygous mutants were blind by 5 d postfertilization.

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Cover legend: The cover image is an artistic representation of neurons falling from the sky (Aurora Borealis backdrop) to land on a microstamped island of deposited chemicals that would sustain and restrict them into a functional network of cells of precisely controlled size and geometry. Similarly, in the experiments, hippocampal neurons were cultured from neonatal rat brains and then sprinkled onto patterned wafers engineered with sequences of these islands. Dual intracellular patch pipettes were then used as shown to probe synaptic connections from one cell to another in islands of different sizes, as well as quantify the strength, number, and excitatory/inhibitory targeting of synapses formed by the cells, depending on the size of the network in which they were situated. Interestingly, neurons seemed to decide how to distribute their synapses depending on the size of their network, either consolidating strong synapses with a few partners or spreading their synapses weakly among many partners. This suggests that the strength of a synapse may be influenced by network properties, such as the number of other partner cells providing input. For more information, see the article by Wilson et al. in this issue (pages 13581-13589).

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Correction: The article "Cell-Autonomous Inhibition of $\alpha 7$ -Containing Nicotinic Acetylcholine Receptors Prevents Death of Parasympathetic Neurons during Development," which appeared on pages 11501–11509 of the October 24, 2007 issue, was missing an author. The correct author line and affiliation section are as follows: Martin Hruska,¹ Rae Nishi,¹ and Inés Ibañez-Tallon²; ¹Department of Anatomy and Neurobiology, University of Vermont College of Medicine, Burlington, Vermont 05405, and ²Molecular Neurobiology Group, Max-Delbrück-Center, 13125 Berlin, Germany.

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BRIEF COMMUNICATIONS

***NR2A*^{-/-} Mice Lack Long-Term Potentiation But Retain NMDA Receptor and L-Type Ca²⁺ Channel-Dependent Long-Term Depression in the Juvenile Superior Colliculus**

Jian-Ping Zhao and Martha Constantine-Paton

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Whether the subunit composition of NMDA receptors (NMDARs) controls the direction of long-term plasticity is currently disputed. In the visual layers of *NR2A*^{-/-} juvenile superior colliculus (SC), synapses lose miniature NMDAR currents, leaving NR2B-rich receptors in extrasynaptic regions. Compared with wild type (WT), evoked NMDAR currents in mutant neurons have slower rise and decay times and lower NMDAR/AMPA current ratios. Moreover, NMDAR and L-type Ca²⁺ channel-dependent SC long-term potentiation (LTP) is absent in *NR2A*^{-/-} cells, whereas both WT and mutant neurons show long-duration, low-frequency-induced, long-term depression (LLF-LTD) that is blocked by either AP-5, nimodipine, or Ro 25-6981 [*R*-(*R,S*)- α -(4-hydroxyphenyl)- β -methyl-4-(phenylmethyl)-1-piperidine propanol]. Thus, NMDAR currents or signaling localized at the postsynaptic density are essential to SC NMDAR-dependent LTP, whereas extrasynaptic or NR2B-rich NMDARs are necessary for LLF-LTD. However, synaptic NMDARs as well as the NR2A subunit are missing in *NR2A*^{-/-} mice. Therefore, NR2 subunit-specific ligand binding/channel properties and/or separate signaling pathways interacting with NMDARs at synaptic versus extrasynaptic receptors could underlie these results.

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Transient Mitogen-Activated Protein Kinase Activation Is Confined to a Narrow Temporal Window Required for the Induction of Two-Trial Long-Term Memory in *Aplysia*

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Although it is commonly appreciated that spaced training is superior to massed training in memory formation, the molecular mechanisms underlying this feature of memory are largely unknown. We previously described the selective benefit of multiple spaced (vs massed) training trials in the induction of long-term memory (LTM) for sensitization in *Aplysia californica*. We now report that LTM can be induced with only two spaced training trials [tail shocks (TSs)] when the second TS is administered 45 min after the first. In contrast, spacing intervals of 15 and 60 min are ineffective. This surprisingly narrow permissive training window for two-trial LTM is accompanied by an equally narrow window of transient mitogen-activated protein kinase (MAPK) activation, a necessary signaling molecule for LTM induction, at 45 min after a single TS. Thus, the transient recruitment of MAPK following a single TS may provide a narrow molecular window for two-trial LTM formation.

The Journal of Neuroscience, December 12, 2007 • 27(50):13701–13705

Neuronal Activity Related to Reward Size and Rewarded Target Position in Primate Supplementary Eye Field

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Several areas of the macaque brain are known to be related to the reward during the performance of saccadic eye-movement tasks. Neurons in the supplementary eye field (SEF) have been reported to be involved in the prediction and detection of a reward. We describe a group of neurons in the SEF that became active during the period of reward delivery after saccades toward a specific direction, but showed weaker activity in other directions, although the same amount of reward was given in each direction. Moreover, this directional reward activity was modulated by the reward size. Our results demonstrate that the SEF cells may reflect both reward amount and target positions toward which a movement was rewarded, and suggest that they may play an important role in providing information about the value of each saccade according to the spatial target location.

The Journal of Neuroscience, December 12, 2007 • 27(50):13750–13755

Semilunar Granule Cells: Glutamatergic Neurons in the Rat Dentate Gyrus with Axon Collaterals in the Inner Molecular Layer

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Synaptic reorganization of the dentate gyrus inner molecular layer (IML) is a pathophysiological process that may facilitate seizures in patients with temporal-lobe epilepsy. Two subtypes of IML neurons were originally described by Ramón y Cajal (1995), but have not been thoroughly studied. We used two-photon imaging, infrared-differential interference contrast microscopy and patch clamp recordings from rat hippocampal slices to define the intrinsic physiology and synaptic targets of spiny, granule-like neurons in the IML, termed semilunar granule cells (SGCs). These neurons resembled dentate granule cells but had axon collaterals in the molecular layer, significantly

larger dendritic arborization in the molecular layer, and a more triangular cell body than granule cells. Unlike granule cells, SGCs fired throughout long-duration depolarizing steps and had ramp-like depolarizations during interspike periods. Paired recordings demonstrated that SGCs are glutamatergic and monosynaptically excite both hilar interneurons and mossy cells. Semilunar granule cells appear to represent a distinct excitatory neuron population in the dentate gyrus that may be an important target for mossy fiber sprouting in patients and rodent models of temporal lobe epilepsy.

The Journal of Neuroscience, December 12, 2007 • 27(50):13756–13761

PICK1 and Phosphorylation of the Glutamate Receptor 2 (GluR2) AMPA Receptor Subunit Regulates GluR2 Recycling after NMDA Receptor-Induced Internalization

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Changes in surface trafficking of AMPA receptors play an important role in synaptic plasticity. Phosphorylation of the C terminus of the AMPA receptor (AMPA) subunit glutamate receptor 2 (GluR2) and the binding of GluR2 to the PDZ [postsynaptic density-95/Discs large/zona occludens-1]-domain containing protein, protein interacting with protein kinase C (PICK1), have been proposed to play an important role in NMDA receptor dependent internalization of GluR2. However, the fate of internalized GluR2 after NMDA receptor (NMDAR) activation is still unclear. Both recycling and degradation of GluR2 after the activation of NMDAR have been reported. Here, we used a pH-sensitive green fluorescent protein variant, pHluorin, tagged to the N terminus of GluR2 (pH-GluR2) to study the dynamic internalization and recycling of GluR2 after NMDAR activation. Using fluorescence recovery after photobleach (FRAP), we directly demonstrate that internalized pH-GluR2 subunits recycle back to the cell surface after NMDAR activation. We further demonstrate that changing the phosphorylation state of the S880 residue at the C terminus of GluR2 does not affect NMDAR-dependent GluR2 internalization, but alters the recycling of GluR2 after NMDAR activation. In addition, mutation of the *N*-ethylmaleimide-sensitive fusion protein (NSF) binding site in the pH-GluR2 slows receptor recycling. Finally, neurons lacking PICK1 display normal NMDAR dependent GluR2 internalization compared with wild-type neurons, but demonstrate accelerated GluR2 recycling after NMDAR activation. These results indicate that phosphorylation of GluR2 S880 and NSF and PICK1 binding to GluR2 dynamically regulate GluR2 recycling.

The Journal of Neuroscience, December 12, 2007 • 27(50):13903–13908

Articles

CELLULAR/MOLECULAR

Target Cell-Specific Involvement of Presynaptic Mitochondria in Post-Tetanic Potentiation at Hippocampal Mossy Fiber Synapses

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Previous studies indicate that boutons from the same axon exhibit distinct Ca^{2+} dynamics depending on the postsynaptic targets. Mossy fibers of hippocampal granule cells innervate synaptic targets via morphologically distinct boutons. We investigated mitochondrial involvement in the generation of post-tetanic residual Ca^{2+} (Ca_{res}) at large and small *en passant* mossy fiber boutons (MFBs). Mitochondria limited the $[Ca^{2+}]_i$ build-up during high-frequency stimulation (HFS) at large MFBs, but not at small MFBs. The amount of Ca_{res} , quantified as a time integral of residual $[Ca^{2+}]_i$, was significantly larger at large MFBs than at small MFBs, and that at large MFBs was substantially attenuated by inhibitors of mitochondrial Ca^{2+} uniporter and mitochondrial Na^+/Ca^{2+} exchanger (mitoNCX). In contrast, blockers of mitoNCX had no effect on the Ca_{res} at small MFBs. Post-tetanic Ca_{res} has been proposed as a mechanism for post-tetanic potentiation (PTP). We examined mitochondrial involvement in PTP at mossy fiber synapses on hilar mossy cells (MF→MC synapse) and on hilar interneurons (MF→HI synapse), which are presumably innervated via large and small MFBs, respectively. Consistent with the differential contribution of mitochondria to Ca_{res} at large and small MFBs, mitoNCX blockers significantly reduced the PTP at the MF→MC synapse, but not at the MF→HI synapse. In contrast, protein kinase C (PKC) inhibitors significantly reduced the PTP at MF→HI synapse, but not at the MF→MC synapse. These results indicate that mitochondria- and PKC-dependent PTP are expressed at distinct hilar mossy fiber synapses depending on postsynaptic targets.

The Journal of Neuroscience, December 12, 2007 • 27(50):13603–13613

Close Homolog of L1 and Neuropilin 1 Mediate Guidance of Thalamocortical Axons at the Ventral Telencephalon

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We report a cooperation between the neural adhesion molecule close homolog of L1 (CHL1) and the semaphorin 3A (Sema3A) receptor, neuropilin 1 (Npn1), important for establishment of area-specific thalamocortical projections. CHL1 deletion in mice selectively disrupted the projection of somatosensory thalamic axons from the ventro-basal (VB) nuclei, causing them to shift caudally and target the visual cortex. At the ventral telencephalon, an intermediate target with graded Sema3A expression, VB axons were caudally shifted in CHL1⁻ embryos and in Npn1^{Sema-/-} mutants, in which axons are nonresponsive to Sema3A. CHL1 colocalized with Npn1 on thalamic axons, and associated with Npn1 through a sequence in the CHL1 Ig1 domain that was required for Sema3A-induced growth cone collapse. These results identify a novel function for CHL1 in thalamic axon responsiveness to ventral telencephalic cues, and demonstrate a role for CHL1 and Npn1 in establishment of proper targeting of specific thalamocortical projections.

The Journal of Neuroscience, December 12, 2007 • 27(50):13667–13679

TRPM8 Mechanism of Cold Allodynia after Chronic Nerve Injury

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The cold- and menthol-sensitive receptor TRPM8 (transient receptor potential melastatin 8) has been suggested to play a role in cold allodynia, an intractable pain seen clinically. We studied how TRPM8 is involved in cold allodynia using rats with chronic constrictive nerve injury (CCI), a neuropathic pain model manifesting cold allodynia in hindlimbs. We found that cold allodynic response in the CCI animals was significantly attenuated by capsazepine, a blocker for both TRPM8 and TRPV1 (transient receptor potential vanilloid 1) receptors, but not by the selective TRPV1 antagonist I-RTX (5-iodoresiniferatoxin). In L5 dorsal root ganglion (DRG) sections of the CCI rats, immunostaining showed an increase in the percentage of TRPM8-immunoreactive neurons when compared with the sham group. Using the Ca²⁺-imaging technique and neurons acutely dissociated from the L5 DRGs, we found that CCI resulted in a significant increase in the percentage of menthol- and cold-sensitive neurons and also a substantial enhancement in the responsiveness of these neurons to both menthol and innocuous cold. These changes occurred in capsaicin-sensitive neurons, a subpopulation of nociceptive-like neurons. Using patch-clamp recordings, we found that membrane currents evoked by both menthol and innocuous cold were significantly enhanced in the CCI group compared with the sham group. By retrograde labeling afferent neurons that target hindlimb skin, we showed that the skin neurons expressed TRPM8 receptors, that the percentage of menthol-sensitive/cold-sensitive/capsaicin-sensitive neurons increased, and that the menthol- and cold-evoked responses were significantly enhanced in capsaicin-sensitive neurons after CCI. Together, the gain of TRPM8-mediated cold sensitivity on nociceptive afferent neurons provides a mechanism of cold allodynia.

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Synaptic Vesicle Mobility in Mouse Motor Nerve Terminals with and without Synapsin

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We measured synaptic vesicle mobility using fluorescence recovery after photobleaching of FM 1-43 [N-(3-triethylammoniumpropyl)-4-(4-(dibutylamino)styryl) pyridinium dibromide] stained mouse motor nerve terminals obtained from wild-type (WT) and synapsin triple knock-out (TKO) mice at room temperature and physiological temperature. Vesicles were mobile in resting terminals at physiological temperature but virtually immobile at room temperature. Mobility was increased at both temperatures by blocking phosphatases with okadaic acid, decreased at physiological temperature by blocking kinases with staurosporine, and unaffected by disrupting actin filaments with latrunculin A or reducing intracellular calcium concentration with BAPTA-AM. Synapsin TKO mice showed reduced numbers of synaptic vesicles and reduced FM 1-43 staining intensity. Synaptic transmission, however, was indistinguishable from WT, as was synaptic vesicle mobility under all conditions tested. Thus, in TKO mice, and perhaps WT mice, a phospho-protein different from synapsin but otherwise of unknown identity is the primary regulator of synaptic vesicle mobility.

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GluR1 Links Structural and Functional Plasticity at Excitatory Synapses

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Long-term potentiation (LTP), a cellular model of learning and memory, produces both an enhancement of synaptic function and an increase in the size of the associated dendritic spine. Synaptic insertion of AMPA receptors is known to play an important role in mediating the increase in synaptic strength during LTP, whereas the role of AMPA receptor trafficking in structural changes remains unexplored. Here, we examine how the cell maintains the correlation between spine size and synapse strength during LTP. We found that cells exploit an elegant solution by linking both processes to a single molecule: the AMPA-type glutamate receptor subunit 1 (GluR1). Synaptic insertion of GluR1 is required to permit a stable increase in spine size, both in hippocampal slice cultures and *in vivo*. Synaptic insertion of GluR1 is not sufficient to drive structural plasticity. Although crucial to the expression of LTP, the ion channel function of GluR1 is not required for the LTP-driven spine size enhancement. Remarkably, a recombinant cytosolic C-terminal fragment (C-tail) of GluR1 is driven to the postsynaptic density after an LTP stimulus, and the synaptic incorporation of this isolated GluR1 C-tail is sufficient to permit spine enlargement even when postsynaptic exocytosis of endogenous GluR1 is blocked. We conclude that during plasticity, synaptic insertion of GluR1 has two functions: the established role of increasing synaptic strength via its ligand-gated ion channel, and a novel role through the structurally stabilizing effect of its C terminus that permits an increase in spine size.

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Tonic Endovanilloid Facilitation of Glutamate Release in Brainstem Descending Antinociceptive Pathways

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Activation of transient receptor potential vanilloid-1 (TRPV1) channels in the periaqueductal gray (PAG) activates OFF antinociceptive neurons of the rostral ventromedial medulla (RVM). We examined in rats the effect of intra-ventrolateral (VL)-PAG injections of TRPV1 agonists and antagonists on the nocifensive response to heat in the plantar test, neurotransmitter (glutamate and GABA) release in the RVM, and spontaneous and tail flick-related activities of RVM neurons. The localization of TRPV1 in VL-PAG and RVM neurons was examined using various markers of glutamatergic and GABAergic neurons. Intra-VL-PAG injection of capsaicin increased the threshold of thermal pain sensitivity, whereas the selective TRPV1 antagonist 5'-iodo-resiniferatoxin (I-RTX) facilitated nociceptive responses, and blocked capsaicin analgesic effect at a dose inactive per se. Intra-VL PAG capsaicin evoked a robust release of glutamate in RVM microdialysates. I-RTX, at a dose inactive per se, blocked the effect of capsaicin, and inhibited glutamate release at a higher dose. Antinociception and hyperalgesia induced by capsaicin and I-RTX, respectively, correlated with enhanced or reduced activity of RVM OFF cells. Immunohistochemical analyses suggested that several TRPV1-immunoreactive (ir) neurons in both the VL-PAG and RVM are glutamatergic and surrounded by glutamatergic and GABAergic terminals. Our data suggest that VL-PAG neurons respond to TRPV1 stimulation by releasing glutamate into the RVM, thereby activating OFF cells and producing analgesia. The results obtained with the TRPV1 antagonist alone suggest that this pathway is tonically activated by endovanilloids.

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Activin Acutely Sensitizes Dorsal Root Ganglion Neurons and Induces Hyperalgesia via PKC-Mediated Potentiation of Transient Receptor Potential Vanilloid I

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Pain hypersensitivity is a cardinal sign of tissue damage, but how molecules from peripheral tissues affect sensory neuron physiology is incompletely understood. Previous studies have shown that activin A increases after peripheral injury and is sufficient to induce acute nociceptive behavior and increase pain peptides in sensory ganglia. This study was designed to test the possibility that the enhanced nociceptive responsiveness associated with activin involved sensitization of transient receptor potential vanilloid I (TRPV1) in primary sensory neurons. Activin receptors were found widely distributed among adult sensory neurons, including those that also express the capsaicin receptor. Whole-cell patch-clamp recording from sensory neurons showed that activin acutely sensitized capsaicin responses and depended on activin receptor kinase activity. Pharmacological studies revealed that the activin sensitization of capsaicin responses required PKC ϵ signaling, but not PI3K (phosphoinositide 3-kinase), ERK (extracellular signal-regulated protein kinase), PKA, PKC α/β , or Src. Furthermore, activin administration caused acute thermal hyperalgesia in wild-type mice, but not in TRPV1-null mice. These data suggest that activin signals through its own receptor, involves PKC ϵ signaling to sensitize the TRPV1 channel, and contributes to acute thermal hyperalgesia.

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Cx43 Hemichannels and Gap Junction Channels in Astrocytes Are Regulated Oppositely by Proinflammatory Cytokines Released from Activated Microglia

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Astrocytes have a role in maintaining normal neuronal functions, some of which depend on connexins, protein subunits of gap junction channels and hemichannels. Under inflammatory conditions, microglia release cytokines, including interleukin-1 β and tumor necrosis factor- α , that reduce intercellular communication via gap junctions. Now, we demonstrate that either conditioned medium harvested from activated microglia or a mixture of these two cytokines enhances the cellular exchange with the extracellular milieu via Cx43 hemichannels. These changes in membrane permeability were not detected in astrocytes cultured from Cx43 knock-out mice and were abrogated by connexin hemichannel blockers, including La³⁺, mimetic peptides, and niflumic acid. Both the reduction in gap junctional communication and the increase in membrane permeability were mediated by a p38 mitogen-activated protein kinase-dependent pathway. However, the increase in membrane permeability, but not the gap junction inhibition, was rapidly reversed by the sulfhydryl reducing agent dithiothreitol, indicating that final regulatory mechanisms are different. Treatment with proinflammatory cytokines reduced the total and cell surface Cx43 levels, suggesting that the increase in membrane permeability was attributable to an increase in hemichannels activity. Indeed, unitary events of \sim 220 pS corresponding to Cx43 hemichannels were much more frequent in astrocytes treated with microglia conditioned medium than under control conditions. Finally, the effect of cytokines enhanced the uptake and reduced the intercellular diffusion of glucose, which might explain changes in the metabolic status of astrocytes under inflammatory conditions. Accordingly, this opposite regulation may affect glucose trafficking and certainly will modify the metabolic status of astrocytes involved in brain inflammation.

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Regulation of the Inositol 1,4,5-Trisphosphate Receptor Type I by O-GlcNAc Glycosylation

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The inositol 1,4,5-trisphosphate (InsP₃) receptor type I (InsP₃R-I) is the principle channel for intracellular calcium (Ca²⁺) release in many cell types, including central neurons. It is regulated by endogenous compounds like Ca²⁺ and ATP, by protein partners, and by posttranslational modification. We report that the InsP₃R-I is modified by O-linked glycosylation of serine or threonine residues with β -N-acetylglucosamine (O-GlcNAc). The level of O-GlcNAcylation can be altered *in vitro* by the addition of the enzymes which add [OGT (O-GlcNAc transferase)] or remove (O-GlcNAcase) this sugar or by loading cells with UDP-GlcNAc. We monitored the effects of this modification on InsP₃R function at the single-channel level and on intracellular Ca²⁺ transients. Single-channel activity was monitored with InsP₃R incorporated into bilayers; Ca²⁺ signaling was monitored using cells loaded with a Ca²⁺-sensitive fluorophore. We found that channel activity was decreased by the addition of O-GlcNAc and that this decrease was reversed by removal of the sugar. Similarly, cells loaded with UDP-GlcNAc had an attenuated response to uncaging of InsP₃. These results show that O-GlcNAcylation is an important regulator of the InsP₃R-I and suggest a mechanism for neuronal dysfunction under conditions in which O-GlcNAc is high, such as diabetes or physiological stress.

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Interaction of Extracellular Signal-Regulated Protein Kinase 1/2 with Actin Cytoskeleton in Supraoptic Oxytocin Neurons and Astrocytes: Role in Burst Firing

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Neuronal firing patterns determine the manner of neurosecretion, the underlying mechanisms of which are poorly understood. Using supraoptic nuclei in brain slices from lactating rats, we examined the involvement of extracellular signal-regulated protein kinase 1/2 (ERK1/2) and filamentous actin (F-actin) in burst generation by oxytocin (OT) neurons. Blocking phosphorylation of ERK1/2 (pERK1/2) decreased miniature EPSCs and blocked OT-evoked bursts, as did intracellularly loading an antibody against pERK1/2. OT (10 pM) increased cytosolic pERK1/2 close to the cell membrane within the first 5 min, subsiding by 30 min, whereas OT elicited pERK1/2 nuclear translocation in closely associated supraoptic astrocytes. The increased pERK1/2 was tightly correlated with spatiotemporal actin dynamics. In OT neurons, OT initially increased F-actin, particularly at membrane subcortical areas, and then decreased it after 30 min. Both polymerization and depolymerization of actin cytoskeleton were associated with bursts, but only polymerization facilitated OT-evoked bursts. Blocking ERK1/2 activation blocked OT-evoked actin polymerization, whereas depolymerizing F-actin increased pERK1/2 expression. These changes were further identified *in vivo*. In intact animals, suckling increased ERK1/2 activation in the cytosol and membrane subcortical area F-actin formation in OT neurons, whereas it increased F-actin concentration in astrocytic somata. Coimmunoprecipitation showed that suckling increased molecular interactions between pERK1/2 and actin. Finally, two different blockers of ERK1/2 kinase injected intracerebroventricularly reduced suckling-evoked milk ejections. This is the first demonstration that OT mediation of suckling-evoked bursts/milk ejections is via interactions between pERK1/2 and actin cytoskeleton.

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Stepwise Morphological and Functional Maturation of Mechanotransduction in Rat Outer Hair Cells

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Inner ear mechanosensory hair cells convert mechanical vibrations into electrical signals via the coordinated interaction of multiple proteins precisely positioned within the sensory hair bundle. Present work identifies the time course for the acquisition and maturation of mechanoelectric transduction (MET) in rat cochlea outer hair cells maintained in organotypic cultures. A spatiotemporal developmental progression was observed morphologically and functionally with basal cochlea maturation preceding apical cochlea by 2–3 d in all measured properties. The fraction of mechanosensitive cells increased rapidly, with a midpoint at postnatal day 0 for basal cells, and correlated with myosin IIIa immunoreactivity. MET current magnitude increased over several days. Adaptation lagged the onset of transduction by a day and matured more slowly, overlapping but preceding the rise in myosin Ic immunoreactivity. Less than ~25% of myosin Ic expression was required for the mature adaptation response, suggesting multiple roles for this protein in hair bundle function. Directional sensitivity, lacking in immature responses, developed rapidly and correlated with the pruning of radial links and an increase in tenting of stereociliary tips. Morphological and electrophysiological data support a hypothesis in which key elements arrive independently at the site of MET, with a mature response occurring as membrane tension increases, likely by the increased tensioning of the tip link with the onset of adaptation. Organotypic cultures developed normal, tonotopically specific, MET response properties, suggesting that maturation was not influenced significantly by external factors such as innervation, endolymph, normal mechanical stimulation, or an intact organ of Corti.

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DEVELOPMENT/PLASTICITY/REPAIR

Synaptic Reorganization in Scaled Networks of Controlled Size

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Neurons in plastic regions of the brain undergo fundamental changes in the number of cells connecting to them as a result of development, plasticity and disease. Across these same time periods, functional changes in cellular and synaptic physiology are known to occur and are often characterized as developmental features of these periods. However, it remains possible that many such changes are direct consequences of the modified degree of partnering, and that neurons intrinsically scale their physiological parameters with network size. To systematically vary a recurrent network's number of neurons while measuring its synaptic properties, we used microfabricated extracellular matrix adhesive islands created with soft lithography to culture neuronal clusters of precise sizes, and assessed their intrinsic connectivity using intracellular recordings and confocal microscopy. Both large and small clusters supported constant densities of excitatory and inhibitory neurons. However, neurons that were provided with more potential partners (larger clusters) formed more connections per cell via an expanded dendritic surface than cocultured smaller clusters. Electrophysiologically, firing rate was preserved across clusters even as size and synapse number increased, due in part to synapses in larger networks having reduced unitary strengths, and sparser paired connectivity. Larger networks also featured a particular increase in the number of excitatory connections onto inhibitory dendrites. We suggest that these specific homeostatic mechanisms, which match the number, strength, and architecture of connections to the number of total available cellular partners in the network, could account for several known phenomena implicated in the formation, organization and degeneration of neuronal circuits.

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The Neonatal Ventromedial Hypothalamus Transcriptome Reveals Novel Markers with Spatially Distinct Patterning

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The ventromedial hypothalamus (VMH) is a distinct morphological nucleus involved in feeding, fear, thermoregulation, and sexual activity. It is essentially unknown how VMH circuits underlying these innate responses develop, in part because the VMH remains poorly defined at a cellular and molecular level. Specifically, there is a paucity of cell-type-specific genetic markers with which to identify neuronal subgroups and manipulate development and signaling *in vivo*. Using gene profiling, we now identify ~200 genes highly enriched in neonatal (postnatal day 0) mouse VMH tissue. Analyses of these VMH markers by real or virtual (Allen Brain Atlas; <http://www.brain-map.org>) experiments revealed distinct regional patterning within the newly formed VMH. Top neonatal markers include transcriptional regulators such as Vgl2, SF-1, Sox14, Satb2, Fezf1, Dax1, Nkx2-2, and COUP-TFII, but interestingly, the highest expressed VMH transcript, the transcriptional coregulator Vgl2, is completely absent in older animals. Collective results from zebrafish knockdown experiments and from cellular studies suggest that a subset of these VMH markers will be important for hypothalamic development and will be downstream of SF-1, a critical factor for normal VMH differentiation. We show that at least one VMH marker, the AT-rich binding protein Satb2, was responsive to the loss of leptin signaling (*Lep^{ob/ob}*) at postnatal day 0 but not in the adult, suggesting that some VMH transcriptional programs might be

influenced by fetal or early postnatal environments. Our study describing this comprehensive “VMH transcriptome” provides a novel molecular toolkit to probe further the genetic basis of innate neuroendocrine behavioral responses.

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Electrical Stimulation of Spared Corticospinal Axons Augments Connections with Ipsilateral Spinal Motor Circuits after Injury

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Activity-dependent competition shapes corticospinal (CS) axon outgrowth in the spinal cord during development. An important question in neural repair is whether activity can be used to promote outgrowth of CS axons in maturity. After injury, spared CS axons sprout and make new connections, but often not enough to restore function. We propose that electrically stimulating spared axons after injury will enhance sprouting and strengthen connections with spinal motor circuits. To study the effects of activity, we electrically stimulated CS tract axons in the medullary pyramid. To study the effects of injury, one pyramid was lesioned. We studied sparse ipsilateral CS projections of the intact pyramid as a model of the sparse connections preserved after CNS injury. We determined the capacity of CS axons to activate ipsilateral spinal motor circuits and traced their spinal projections. To understand the separate and combined contributions of injury and activity, we examined animals receiving stimulation only, injury only, and injury plus stimulation. Both stimulation and injury alone strengthened CS connectivity and increased outgrowth into the ipsilateral gray matter. Stimulation of spared axons after injury promoted outgrowth that reflected the sum of effects attributable to activity and injury alone. CS terminations were densest within the ventral motor territories of the cord, and connections in these animals were significantly stronger than after injury alone, indicating that activity augments injury-induced plasticity. We demonstrate that activity promotes plasticity in the mature CS system and that the interplay between activity and injury preferentially promotes connections with ventral spinal motor circuits.

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β 1 Integrins in Radial Glia But Not in Migrating Neurons Are Essential for the Formation of Cell Layers in the Cerebral Cortex

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Radial glial cells in the cerebral cortex serve as progenitors for neurons and glia and guide the migration of cortical neurons. The integrin α 3 β 1 is thought to mediate interactions of migrating neurons with radial glial cells and to function as a receptor for the reelin signaling molecule. Here, we challenge this view and demonstrate that β 1 integrins in migrating neurons are not essential for the formation of cell layers in the cerebral cortex. Cortical cell layers also form normally in mice deficient in the integrin α 3 β 1. However, we provide evidence that β 1 integrins in radial glia control the morphological differentiation of both glia and neurons. We conclude that β 1 integrins in radial glia are required for the proper development of the cerebral cortex, whereas β 1 integrins in migrating neurons are not essential for glial-guided migration and reelin signaling.

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cAMP Response Element-Binding Protein-Mediated Gene Expression Increases the Intrinsic Excitability of CA1 Pyramidal Neurons

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To investigate the role of CREB-mediated gene expression on the excitability of CA1 pyramidal neurons, we obtained intracellular recordings from pyramidal neurons of transgenic mice expressing a constitutively active form of CREB, VP16–CREB, in a regulated and restricted manner. We found that transgene expression increased the neuronal excitability and inhibited the slow and medium afterhyperpolarization currents. These changes may contribute to the reduced threshold for LTP observed in these mice. When strong transgene expression was turned on for prolonged period of time, these mice also showed a significant loss of hippocampal neurons and sporadic epileptic seizures. These deleterious effects were dose dependent and could be halted, but not reversed by turning off transgene expression. Our experiments reveal a new role for hippocampal CREB-mediated gene expression, identify the slow afterhyperpolarization as a primary target of CREB action, provide a new mouse model to investigate temporal lobe epilepsy and associated neurodegeneration, and illustrate the risks of cell death associated to a sustained manipulation of this pathway. As a result, our study has important implications for both the understanding of the cellular bases of learning and memory and the consideration of therapies targeted to the CREB pathway.

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Vestibular Signals in Primate Thalamus: Properties and Origins

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Vestibular activation is found in diverse cortical areas. To characterize the pathways and types of signals supplied to cortex, we recorded responses to rotational and/or translational stimuli in the macaque thalamus. Few cells responded to rotation alone, with most showing convergence between semicircular canal and otolith signals. During sinusoidal rotation, thalamic responses lead head velocity by $\sim 30^\circ$ on average at frequencies between 0.01–4 Hz. During translation, neurons encoded combinations of linear acceleration and velocity. In general, thalamic responses were similar to those recorded in the vestibular and cerebellar nuclei using identical testing paradigms, but differed from those of vestibular afferents. Thalamic responses represented a biased continuum: most cells more strongly encoded translation and fewer cells modulated primarily in response to net gravito-inertial acceleration. Responsive neurons were scattered within a large area that included regions of the ventral posterior and ventral lateral nuclei, and so were not restricted to the known vestibular nuclei projection zones. To determine the origins of these responses, a retrograde tracer was injected into a dorsolateral thalamic site where rotation/translation-sensitive cells were encountered. This injection labeled neurons in the rostral contralateral anterior interposed and fastigial nuclei, but did not label cells within the vestibular nuclei. Examination of thalamic terminations after tracer injections into the cerebellar and vestibular nuclei indicated that most vestibular responsive units fall within the thalamic terminal zones of these nuclei. Thus, vestibular signals, which are supplied to the thalamus from both vestibular and cerebellar nuclei, are positioned for distribution to widespread cortical areas.

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Order-Dependent Modulation of Directional Signals in the Supplementary and Presupplementary Motor Areas

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To maximize reward and minimize effort, animals must often execute multiple movements in a timely and orderly manner. Such movement sequences must be usually discovered through experience, and during this process, signals related to the animal's action, its ordinal position in the sequence, and subsequent reward need to be properly integrated. To investigate the role of the primate medial frontal cortex in planning and controlling multiple movements, monkeys were trained to produce a series of hand movements instructed by visual stimuli. We manipulated the number of movements in a sequence across trials, making it possible to dissociate the effects of the ordinal position of a given movement and the number of remaining movements necessary to obtain reward. Neurons in the supplementary and presupplementary motor areas modulated their activity according to the number of remaining movements, more often than in relation to the ordinal position, suggesting that they might encode signals related to the timing of reward or its temporally discounted value. In both cortical areas, signals related to the number of remaining movements and those related to movement direction were often combined multiplicatively, suggesting that the gain of the signals related to movements might be modulated by motivational factors. Finally, compared with the supplementary motor area, neurons in the presupplementary motor area were more likely to increase their activity when the number of remaining movements is large. These results suggest that these two areas might play complementary roles in controlling movement sequences.

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The Neural Cost of the Auditory Perception of Language Switches: An Event-Related Functional Magnetic Resonance Imaging Study in Bilinguals

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One of the most remarkable abilities of bilinguals is to produce and/or to perceive a switch from one language to the other without any apparent difficulty. However, several psycholinguistic studies indicate that producing, recognizing, and integrating a linguistic code different from the one in current use may entail a processing cost for the speaker/listener. Up to now, the underlying neural substrates of perceiving language switches are unknown. In the present study, we investigated the neural mechanisms of language switching during auditory perception in bilinguals. Event-related functional magnetic resonance imaging was performed in 12 early, highly proficient Italian/French bilinguals, who were more exposed to their second language. Subjects had to listen to narratives containing “switched passages” that could either respect (i.e., regular switches) or violate (i.e., irregular switches) the constituents of sentence structure. The results indicate that switching engages an extensive neural network, including bilateral prefrontal and temporal associative regions. Moreover, a clear dissociation is observed for the types of switches. Regular switches entail a pattern of brain activity closely related to lexical processing, whereas irregular switches engage brain structures involved in syntactic and phonological aspects of language processing. Noteworthy, when switching into the less-exposed language, we observed the selective engagement of subcortical structures and of the anterior cingulate cortex, putatively involved in cognitive and executive control. This suggests that switching into a less-exposed language requires controlled processing resources. This pattern of brain activity may constitute an important neural signature of language dominance in bilinguals.

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Balanced Excitatory and Inhibitory Inputs to Cortical Neurons Decouple Firing Irregularity from Rate Modulations

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In vivo cortical neurons are known to exhibit highly irregular spike patterns. Because the intervals between successive spikes fluctuate greatly, irregular neuronal firing makes it difficult to estimate instantaneous firing rates accurately. If, however, the irregularity of spike timing is decoupled from rate modulations, the estimate of firing rate can be improved. Here, we introduce a novel coding scheme to make the firing irregularity orthogonal to the firing rate in information representation. The scheme is valid if an interspike interval distribution can be well fitted by the gamma distribution and the firing irregularity is constant over time. We investigated in a computational model whether fluctuating external inputs may generate gamma process-like spike outputs, and whether the two quantities are actually decoupled. Whole-cell patch-clamp recordings of cortical neurons were performed to confirm the predictions of the model. The output spikes were well fitted by the gamma distribution. The firing irregularity remained approximately constant regardless of the firing rate when we injected a balanced input, in which excitatory and inhibitory synapses are activated concurrently while keeping their conductance ratio fixed. The degree of irregular firing depended on the effective reversal potential set by the balance between excitation and inhibition. In contrast, when we modulated conductances out of balance, the irregularity varied with the firing rate. These results indicate that the balanced input may improve the efficiency of neural coding by clamping the firing irregularity of cortical neurons. We demonstrate how this novel coding scheme facilitates stimulus decoding.

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Interactions between the NR2B Receptor and CaMKII Modulate Synaptic Plasticity and Spatial Learning

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The NR2B subunit of the NMDA receptor interacts with several prominent proteins in the postsynaptic density, including calcium/calmodulin-dependent protein kinase II (CaMKII). To determine the function of these interactions, we derived transgenic mice expressing a ligand-activated carboxy-terminal NR2B fragment (cNR2B) by fusing this fragment to a tamoxifen (TAM)-dependent mutant of the estrogen receptor ligand-binding domain LBD^{G521R}. Here, we show that induction by TAM allows the transgenic cNR2B fragment to bind to endogenous CaMKII in neurons. Activation of the LBD^{G521R}-cNR2B transgenic protein in mice leads to the disruption of CaMKII/NR2B interactions at synapses. The disruption decreases Thr286 phosphorylation of α CaMKII, lowers phosphorylation of a key CaMKII substrate in the postsynaptic membrane (AMPA receptor subunit glutamate receptor 1), and produces deficits in hippocampal long-term potentiation and spatial learning. Together our results demonstrate the importance of interactions between CaMKII and NR2B for CaMKII activity, synaptic plasticity, and learning.

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Exuberant Neuronal Convergence onto Reduced Taste Bud Targets with Preservation of Neural Specificity in Mice Overexpressing Neurotrophin in the Tongue Epithelium

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A mouse fungiform taste bud is innervated by only four to five geniculate ganglion neurons; their peripheral fibers do not branch to other buds. We examined whether the degree or specificity of this exclusive innervation pattern is influenced by brain-derived neurotrophic factor (BDNF), a prominent lingual neurotrophin implicated in taste receptoneural development. Labeled ganglion cells were counted after injecting single buds with different color markers in BDNF-lingual-overexpressing (OE) mice. To evaluate the end-organs, taste buds and a class of putative taste receptor cells were counted from progeny of BDNF-OE mice crossbred with green fluorescent protein (GFP) (gustducin) transgenic mice. Fungiform bud numbers in BDNF-OE mice are 35%, yet geniculate neuron numbers are 195%, of wild-type mice. Neurons labeled by single-bud injections in BDNF-OE animals were increased fourfold versus controls. Injecting three buds, each with different color markers, resulted in predominantly single-labeled ganglion cells, a discrete innervation pattern similar to controls. Thus, hyper-innervation of BDNF-OE buds involves many neurons innervating single buds, not increased fiber branching. Therefore, both wild-type and BDNF-OE mice exhibit, in fungiform buds, the same, “discrete” receptoneural pattern, this despite dramatic neurotrophin overexpression-related decreases in bud numbers and increases in innervation density. Hyperinnervation did not affect GFP positive cell numbers; proportions of GFP cells in BDNF-OE buds were the same as in wild-type mice. Total numbers of ganglion cells innervating buds in transgenic mice are similar to controls; the density of taste input to the brain appears maintained despite dramatically reduced receptor organs and increased ganglion cells.

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Genetic Contributions to Long-Range Temporal Correlations in Ongoing Oscillations

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The amplitude fluctuations of ongoing oscillations in the electroencephalographic (EEG) signal of the human brain show autocorrelations that decay slowly and remain significant at time scales up to tens of seconds. We call these long-range temporal correlations (LRTC). Abnormal LRTC have been observed in several brain pathologies, but it has remained unknown whether genetic factors influence the temporal correlation structure of ongoing oscillations. We recorded the ongoing EEG during eyes-closed rest in 390 monozygotic and dizygotic twins and investigated the temporal structure of ongoing oscillations in the alpha- and beta-frequency bands using detrended fluctuation analysis (DFA). The strength of LRTC was more highly correlated in monozygotic than in dizygotic twins. Statistical analysis attributed up to ~60% of the variance in DFA to genetic factors, indicating a high heritability for the temporal structure of amplitude fluctuations in EEG oscillations. Importantly, the DFA and EEG power were uncorrelated. LRTC in ongoing oscillations are robust, heritable, and independent of power, suggesting that LRTC and oscillation power are governed by distinct biophysical mechanisms and serve different functions in the brain. We propose that the DFA method is an important complement to classical spectral analysis in fundamental and clinical research on ongoing oscillations.

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NEUROBIOLOGY OF DISEASE

Mitochondrial Sensitivity and Altered Calcium Handling Underlie Enhanced NMDA-Induced Apoptosis in YAC128 Model of Huntington's Disease

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Expansion of a CAG repeat in the Huntington's disease (HD) gene results in progressive neuronal loss, particularly of striatal medium-sized spiny neurons (MSNs). Studies in human HD autopsy brain tissue, as well as cellular and animal models of HD, suggest that increased activity of NMDA-type glutamate receptors and altered mitochondrial function contribute to selective neuronal degeneration. In this regard, the YAC128 mouse model, expressing full-length human huntingtin with 128 glutamine repeats, has been the focus of much interest. Although NMDA-induced apoptosis is enhanced in YAC128 MSNs, here we report that the initial steps in the death signaling pathway, including NMDA receptor (NMDAR) current and cytosolic Ca²⁺ loading, are similar to those observed in wild-type MSNs. In contrast, we found that the NMDAR-mediated Ca²⁺ load triggered a strikingly enhanced loss of mitochondrial membrane potential in YAC128 MSNs, suggesting that NMDAR signaling via the mitochondrial apoptotic pathway is altered. This effect was accompanied by impaired cytosolic Ca²⁺ clearance after removal of NMDA, a difference that was not apparent after high potassium-evoked depolarization-mediated Ca²⁺ entry. Inhibition of the mitochondrial permeability transition (mPT) reduced peak cytosolic Ca²⁺ and mitochondrial depolarization evoked by NMDA in YAC128 MSNs but not wild-type MSNs. Hence, in contrast to YAC models with moderate CAG expansions, the enhanced NMDA-induced apoptosis in YAC128 MSNs is predominantly determined by augmented mitochondrial sensitivity to Ca²⁺-induced activation of the mPT. These results suggest that the CAG repeat length influences the mechanism by which mHtt enhances NMDAR-mediated excitotoxicity.

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Insulin Dysfunction Induces *In Vivo* Tau Hyperphosphorylation through Distinct Mechanisms

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Hyperphosphorylated tau is the major component of paired helical filaments in neurofibrillary tangles found in Alzheimer's disease (AD) brains, and tau hyperphosphorylation is thought to be a critical event in the pathogenesis of the disease. The large majority of AD cases is late onset and sporadic in origin, with aging as the most important risk factor. Insulin resistance, impaired glucose tolerance, and diabetes mellitus (DM) are other common syndromes in the elderly also strongly age dependent, and there is evidence supporting a link between insulin dysfunction and AD. To investigate the possibility that insulin dysfunction might promote tau pathology, we induced insulin deficiency and caused DM in mice with streptozotocin (STZ). A mild hyperphosphorylation of tau could be detected 10, 20, and 30 d after STZ injection, and a massive hyperphosphorylation of tau was observed after 40 d. The robust hyperphosphorylation of tau was localized in the axons and neuropil, and prevented tau binding to microtubules. Neither mild nor massive tau phosphorylation induced tau aggregation. Body temperature of the STZ-treated mice did not differ from control animals during 30 d, but dropped significantly thereafter. No change in β -amyloid (A β) precursor protein (APP), APP C-terminal fragments, or A β levels were observed in STZ-treated mice; however, cellular protein phosphatase 2A activity was significantly decreased. Together, these data indicate that insulin dysfunction induced abnormal tau hyper-

phosphorylation through two distinct mechanisms: one was consequent to hypothermia; the other was temperature-independent, inherent to insulin depletion, and probably caused by inhibition of phosphatase activity.

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The Cell-Selective Neurotoxicity of the Alzheimer's A β Peptide Is Determined by Surface Phosphatidylserine and Cytosolic ATP Levels. Membrane Binding Is Required for A β Toxicity

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Measurement of A β toxicity of cells in culture exposes a subpopulation of cells with resistance to A β , even at high concentrations and after long periods of treatment. The cell-selective toxicity of A β resembles the selective damage observed in cells of specific regions of the Alzheimer's disease (AD) brain and suggests that there must be particular characteristics or stages of these cells that make them exceptionally sensitive or resistant to the effect of A β . Using flow cytometry and cell sorting, we efficiently separated and analyzed the A β -sensitive and the A β -resistant subpopulations within a variety of neuronal cell lines (PC12, GT1–7) and primary cultured neurons (hippocampal, cortex). We found that this distinctive sensitivity to A β was essentially associated with cell membrane A β binding. This selective A β binding was correlated to distinctive cell characteristics, such as cell membrane exposure of the apoptotic signal molecule phosphatidyl serine, larger cell size, the G₁ cell cycle stage, and a lower than normal cytosolic ATP level. The response to A β by the cells with high A β binding affinity was characterized by a larger calcium response and increased mortality, lactate dehydrogenase release, caspase activation, and DNA fragmentation. The distinctive sensitivity or resistance to A β of the different subpopulations was maintained even after multiple cell divisions. We believe that these distinctive cell characteristics are the determining factors for the selective attack of A β on cells in culture and in the AD brain.

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Autonomic Denervation of Lymphoid Organs Leads to Epigenetic Immune Atrophy in a Mouse Model of Krabbe Disease

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Lysosomal β -galactosylceramidase deficiency results in demyelination and inflammation in the nervous system causing the neurological Krabbe disease. In the *Twitchee* mouse model of this disease, we found that neurological symptoms parallel progressive and severe lymphopenia. Although lymphopoiesis is normal before disease onset, primary and secondary lymphoid organs progressively degenerate afterward. This occurs despite preserved erythropoiesis and leads to severe peripheral lymphopenia caused by reduced numbers of T cell precursors and mature lymphocytes. Hematopoietic cell replacement experiments support the existence of an epigenetic factor in mutant mice reconcilable with a progressive loss of autonomic axons that hampers thymic functionality. We propose that degeneration of autonomic nerves leads to the irreversible thymic atrophy and loss of immune-competence. Our study describes a new aspect of Krabbe disease, placing patients at risk of immune-related pathologies, and identifies a novel target for therapeutic interventions.

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Thalamic Shape Abnormalities in Individuals with Schizophrenia and Their Nonpsychotic Siblings

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Deficits in the volume of the thalamus have been observed in both individuals with schizophrenia and their nonpsychotic relatives. However, no studies to date have examined the underlying pattern of thalamic shape change in relatives of individuals with schizophrenia. This study examined the volume and shape of the thalamus in schizophrenia subjects, their siblings, and healthy control individuals. T1-weighted magnetic resonance scans were collected in a group of young subjects with schizophrenia (mean age, 23 years) and their nonpsychotic siblings ($n = 25$ pairs), and control subjects and their siblings ($n = 40$ pairs). Thalamic surfaces were generated using high-dimensional brain mapping. A canonical weighting function was derived from the contrast between schizophrenia and control subjects and then used to generate a canonical shape score for all subjects. Maps of the estimated surface displacement between groups were also created to visualize the thalamic shape differences between groups. The thalamic canonical scores of the siblings of the schizophrenia probands were intermediate between the probands and healthy control subjects. These siblings also displayed an intermediate degree of the inward surface deformation of the anterior and posterior thalamus that was present between schizophrenia probands and controls. There was no main effect of group status on thalamic volume and no significant correlations of the structural measures with measures of psychopathology or cognitive function. Our results indicate that thalamic shape abnormalities are present in relatively young individuals with schizophrenia and their siblings. Inward deformation of the anterior and posterior regions of the thalamus represents a potential neuroanatomical endophenotype of schizophrenia.

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A Mutation in the Cone-Specific *pde6* Gene Causes Rapid Cone Photoreceptor Degeneration in Zebrafish

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Photoreceptor degeneration is a common cause of inherited blindness worldwide. We have identified a blind zebrafish mutant with rapid degeneration of cone photoreceptors caused by a mutation in the cone phosphodiesterase ϵ (*pde6c*) gene, a key regulatory component in cone phototransduction. Some rods also degenerate, primarily in areas with a low density of rods. Rod photoreceptors in areas of the retina that always have a high density of rods are protected from degeneration. Our findings demonstrate that, analogous to what happens to rod photoreceptors in the *rd1* mouse model, loss of cone phosphodiesterase leads to rapid degeneration of cone photoreceptors. Furthermore, we propose that cell density plays a key role in determining whether rod photoreceptors degenerate as a secondary consequence to cone degeneration. Our zebrafish mutant serves as a model for developing therapeutic treatments for photoreceptor degeneration in humans.

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