

This Week in The Journal

● Cellular/Molecular

Dancing with the Astrocytes

Hideko Nishida and Shigeo Okabe

(see pages 331–340)

Time-lapse imaging has revealed that virtually all aspects of neuronal migration and synaptic function involve dynamic interactions with surrounding glial processes. This week, Nishida et al. looked at the role of astrocyte-neuronal contact in the stabilization and maturation of dendritic spines. The authors used two-photon time-lapse imaging of cultured hippocampal slices to visualize fluorescently labeled dendrites and green fluorescent protein-expressing astrocytes. Dendritic protrusions stabilized after making contact with astrocytes, such that protrusion lifetimes were longer if contact occurred. Viral expression of a mutant Rac1 decreased astrocyte motility and increased the length of dendritic filopodia but not their motility or lifetimes. Viral expression of chimeric molecules interfered with the association between the dendritic EphA4 receptor and its astrocytic ephrin-A3 ligand and shortened the lifetime of protrusions that contacted astrocytes. The results are consistent with contact-dependent signaling between dendritic protrusions and astrocyte processes during the formation of dendritic spines.

▲ Development/Plasticity/Repair

Guiding GnRH-1 Neurons

Paolo Giacobini, Andrea Messina, Susan Wray, Costanza Giampietro, Tiziana Crepaldi, Peter Carmeliet, and Aldo Fasolo

(see pages 431–445)

Gonadotropin hormone-releasing hormone-1 (GnRH-1) neurons begin life with a long trek from their birthplace in the nasal placode along olfactory nerve tracts to their permanent home in the hypothalamus. This week, Giacobini et al. make a case for the cytokine hepatocyte growth factor (HGF) as a guidance molecule for these neurons. Nasal explant cul-

tures expressed HGF and its receptor Met in a spatiotemporal pattern that fitted GnRH-1 neuronal migration *in vivo*. Tissue-type plasminogen activator (tPA), which cleaves and activates pro-HGF, was also expressed by migrating GnRH-1 neurons. In explants treated with an HGF-neutralizing antibody, the number of GnRH-1 neurons was unaffected, but migration was considerably restricted. Likewise, treatment with exogenous HGF expanded the migration pattern in a manner that was sensitive to the gradient created by exogenous HGF. In mice lacking tPA, the adult GnRH-1 neuron population was reduced by about one-third, perhaps indicative of a migratory failure.

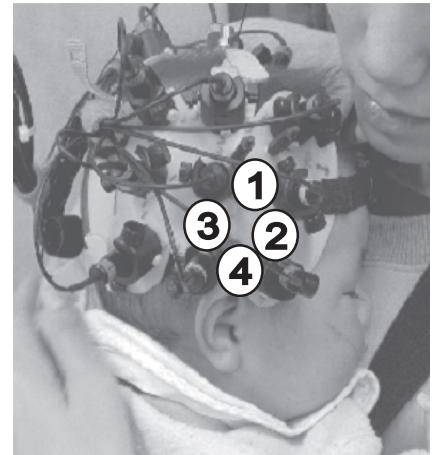
■ Behavioral/Systems/Cognitive

Japanese Infants Listening to Native Vowel Contrasts

Yasuyo Minagawa-Kawai, Koichi Mori, Nozomi Naoi, and Shozo Kojima

(see pages 315–321)

Human acoustic processing becomes attuned to the sounds of our native language within the first year of life. Minagawa-Kawai et al. used near-infrared spectroscopy (NIRS) to track acoustic processing in Japanese infants. Subjects were gently fitted with headgear containing near-infrared laser emission and detection probe arrays over the lateral auditory areas. Absorption of light by hemoglobin was used to estimate blood flow changes, providing a spatial resolution of 2–3 cm. NIRS measures only small vessels and thus may be less sensitive to systemic circulatory changes than functional magnetic resonance imaging. The stimuli consisted of two pairs of speech sounds or phonemes, in this case Japanese vowel sounds. The pairs had identical physical structure, but only one contained linguistic information. At 6 months, infants showed phonemic specificity, but this was no longer apparent by 10–11 months. After 12 months, the language specificity was again detectable but now was left lateralized, a pattern similar to adults.



Emission and detection probes were fitted in a 2×2 square lattice on the lateral side of the head for near-infrared spectroscopy measurement of auditory responses. See the article by Minagawa-Kawai et al. for details.

◆ Neurobiology of Disease

Mitochondrial Trafficking and CMT2 Neuropathy

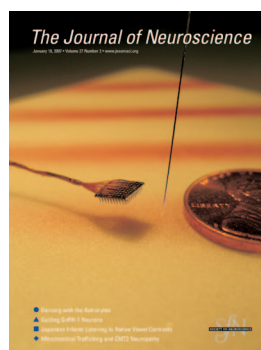
Robert H. Baloh, Robert E. Schmidt, Alan Pestronk, and Jeffrey Milbrandt

(see pages 422–430)

Hereditary neuropathies come in many shapes and sizes. Charcot-Marie-Tooth type 2 (CMT2) causes degeneration of peripheral sensory and motor neurons, particularly at the ends of these long axons. Many cases of CMT2 arise from mutations in a mitochondrial fusion protein mitofusin 2 (MFN2). This week, Baloh et al. propose that MFN2 mutations cause disease by altering mitochondrial trafficking. The authors expressed mutant MFN2 in cultured dorsal root ganglion neurons. Fragmented mitochondria clustered in cell bodies and proximal axons of these neurons. Time-lapse fluorescence imaging revealed disrupted mitochondrial trafficking, although ATP production and mitochondrial oxidative function remained intact. Likewise, oxidative activity was not disrupted in a muscle biopsy specimen from a patient with CMT2A. The transport failure may result from reduced attachment of mitochondria to the microtubule transport apparatus, thus limiting delivery of energy supplies to long axons.

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Cover legend: Photograph of the Cyberkinetics microelectrode ("Utah") array and a tungsten in glass microelectrode. The Utah array consists of a 4 mm square base with 100 silicon electrodes, each 1.0 mm in length. The exposed tips (50 μm) are metallized with platinum, whereas the remainder of each electrode is insulated with parylene C. A penny is included for perspective. For more information, see the article by Kelly et al. in this issue (pages 261–264).

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Bidirectional Modulation of Transmitter Release by Calcium Channel/Syntaxin Interactions *In Vivo*

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Protein interactions within the active zone of the nerve terminal are critical for regulation of transmitter release. The SNARE protein syntaxin 1A, primarily known for important interactions that control vesicle fusion, also interacts with presynaptic voltage-gated calcium channels. Based on recordings of calcium channel function *in vitro*, it has been hypothesized that syntaxin 1A–calcium channel interactions could alter calcium channel function at synapses. However, results at synapses *in vitro* suggest two potentially opposing roles: enhancement of neurotransmitter release by positioning docked vesicles near calcium channels and inhibition of calcium channel function by interaction with SNARE proteins. We have examined the possibility that these two effects of syntaxin can occur at synapses by studying the effects on transmitter release of manipulating syntaxin 1A–calcium channel interactions at *Xenopus* tadpole tail neuromuscular synapses *in vivo*. Introduction of synprint peptides, which competitively perturb syntaxin 1A–calcium channel interactions, decreased quantal content at these synapses and increased paired-pulse and tetanic facilitation. In contrast, injecting mRNA for mutant (A240V, V244A) syntaxin 1A, which reduces calcium channel modulation but not binding *in vitro*, increased quantal content and decreased paired-pulse and tetanic facilitation. Injection of wild-type syntaxin 1A mRNA had no effect. The opposing effects of synprint peptides and mutant syntaxin 1A provide *in vivo* support for the hypothesis that these interactions serve both to colocalize calcium channels with the release machinery and to modulate the functional state of the calcium channel. As such, these two effects of syntaxin on calcium channels modulate transmitter release in a bidirectional manner.

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Noncholinergic Lesions of the Medial Septum Impair Sequential Learning of Different Spatial Locations

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The medial septum and diagonal band of Broca (MSDB) are major afferents to the hippocampus and are important for learning, memory, and hippocampal theta rhythm. In the present study, we assessed the effect of cholinergic or noncholinergic MSDB lesions on the sequential learning of different goal locations in the same environment, a type of task that is proposed to require hippocampal theta rhythm. Rats were administered saline, 192-IgG saporin (SAP), or kainic acid (KA) into the MSDB and then behaviorally tested. On any day, a single arm of a radial maze was rewarded with food, but the location of this rewarded arm changed between days. As in previous studies, intraseptal SAP reduced the number of cholinergic neurons although sparing GABAergic septohippocampal neurons. KA had the reverse effect, reducing GABAergic septohippocampal neurons and sparing cholinergic neurons. KA, but not SAP, impaired performance on the repeated acquisition task. Saline and SAP rats showed rapid within-session learning, whereas KA rats were much slower to learn the goal location. Performance on a 30 min retention trial was also impaired, although this may be attributable to incomplete acquisition. These findings provide evidence that noncholinergic, but not cholinergic, MSDB neurons are important in helping the animal deal with high loads of memory interference, and provides partial support for the idea that hippocampal theta rhythm is involved.

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Vascular Endothelial Growth Factor Overexpression Delays Neurodegeneration and Prolongs Survival in Amyotrophic Lateral Sclerosis Mice

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We sought genetic evidence for the involvement of neuronal vascular endothelial growth factor (VEGF) in amyotrophic lateral sclerosis (ALS). Mice expressing human ALS mutant superoxide dismutase-1 (SOD1) were crossed with mice that overexpress VEGF in neurons (VEGF^{+/+}). We report that SOD1^{G93A}/VEGF^{+/+} double-transgenic mice show delayed motor neuron loss, delayed motor impairment, and prolonged survival compared with SOD1^{G93A} single transgenics. These findings indicate that neuronal VEGF protects against motor neuron degeneration, and may have therapeutic implications for ALS.

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Motion Integration by Neurons in Macaque MT Is Local, Not Global

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Direction-selective neurons in primary visual cortex have small receptive fields that encode the motions of local features. These motions often differ from the motion of the object to which they belong and must therefore be integrated elsewhere. A candidate site for this integration is visual cortical area MT (V5), in which cells with large receptive fields compute the motion of patterns. Previous studies of motion integration in MT have used stimuli that fill the receptive field, and thus do not test whether motion information is really integrated across this whole area. For each MT neuron, we identified two regions ("patches") within the receptive field that were approximately equally effective in driving responses. We then measured responses to plaids whose component gratings overlapped within a patch, and compared them with responses to the same component gratings presented in separate patches. Cells that were selective for the direction of motion of the whole pattern when the gratings overlapped lost this selectivity when the gratings were separated and became selective instead for the direction of motion of the individual components. If MT cells simply pooled all of the inputs that endow them with a receptive field, they would encode all of the motions in the receptive field as belonging to a single object. Our results indicate instead that critical elements of the computations underlying pattern-direction selectivity in MT are done locally, on a scale smaller than the whole receptive field.

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Articles

CELLULAR/MOLECULAR

Slow Conformational Changes of the Voltage Sensor during the Mode Shift in Hyperpolarization-Activated Cyclic-Nucleotide-Gated Channels

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Hyperpolarization-activated cyclic-nucleotide-gated (HCN) channels are activated by hyperpolarizations that cause inward movements of the positive charges in the fourth transmembrane domain (S4), which triggers channel opening. If HCN channels are held open for prolonged times (>50 ms), HCN channels undergo a mode shift, which in sea urchin (spHCN) channels induces a >50 mV shift in the midpoint of activation. The mechanism underlying the mode shift is unknown. The mode shift could be attributable to conformational changes in the pore domain that stabilize the open state of the channel, which would indirectly shift the voltage dependence of the channel, or attributable to conformational changes in the voltage-sensing domain that stabilize the inward position of S4, thereby directly shifting the voltage dependence of the channel. We used voltage-clamp fluorometry to detect S4 movements and to correlate S4 movements to the different activation steps in spHCN channels. We here show that fluorophores attached to S4 report on fluorescence changes during the mode shift, demonstrating that the mode shift is not simply attributable to a stabilization of the pore domain but that S4 undergoes conformational changes during the mode shift. We propose a model in which the mode shift is attributable to a slow, lateral movement in S4 that is triggered by the initial S4 gating-charge movement and channel opening. The mode shift gives rise to a short-term, activity-dependent memory in HCN channels, which has been shown previously to be important for the stable rhythmic firing of pacemaking neurons and could significantly affect synaptic integration.

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Phosphatidylinositol 3-Kinase and Akt Nonautonomously Promote Perineurial Glial Growth in *Drosophila* Peripheral Nerves

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Drosophila peripheral nerves, structured similarly to their mammalian counterparts, comprise a layer of motor and sensory axons wrapped by an inner peripheral glia (analogous to the mammalian Schwann cell) and an outer perineurial glia (analogous to the mammalian perineurium). Growth and proliferation within mammalian peripheral nerves are increased by Ras pathway activation: loss-of-function mutations in *Nf1*, which encodes the Ras inhibitor neurofibromin, cause the human genetic disorder neurofibromatosis, which is characterized by formation of neurofibromas (tumors of peripheral nerves). However, the signaling pathways that control nerve growth downstream of Ras remain incompletely characterized. Here we show that expression specifically within the *Drosophila* peripheral glia of the constitutively active *Ras*^{V12} increases perineurial glial thickness. Using chromosomal loss-of-function mutations and transgenes encoding dominant-negative and constitutively active proteins, we show that this nonautonomous effect of *Ras*^{V12} is mediated by the Ras effector phosphatidylinositol 3-kinase (PI3K) and its downstream kinase Akt. We also show that the nonautonomous, growth-promoting effects of activated PI3K are suppressed by coexpression within the peripheral glia of *FOXO*⁺ (forkhead box O) a transcription factor inhibited by Akt-dependent phosphorylation. We suggest that Ras–PI3K–Akt activity in the peripheral glia promotes growth of the perineurial glia by inhibiting FOXO. In mammalian peripheral nerves, the Schwann cell releases several growth factors that affect the proliferative properties of neighbors. Some of these factors are oversecreted in *Nf1* mutants. Our results raise the possibility that neurofibroma formation in individuals with neurofibromatosis might result in part from a Ras–PI3K–Akt-dependent inhibition of FOXO within Schwann cells.

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Direct Astrocytic Contacts Regulate Local Maturation of Dendritic Spines

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Astrocytes contribute on both development and function of synapses, but it remains unclear whether direct astrocytic contacts regulate development of individual synapses. Two-photon time-lapse imaging of astrocytic and dendritic protrusive activity revealed the correlation of astrocytic contacts with both lifetime and morphological maturation of dendritic protrusions. Astrocytic motility was essential in maturation of spines, because its suppression by manipulating Rac1-dependent signaling in astrocytes resulted in induction of longer, filopodia-like dendritic protrusions. Manipulation of ephrin/Eph-dependent neuron-astrocyte signaling suggested involvement of this signaling pathway in astrocyte-dependent stabilization of newly generated dendritic protrusions. Our data support a model in which astrocytic protrusive activity in development acts as a key local regulator for stabilization of individual dendritic protrusions and subsequent maturation into spines.

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Fast Synaptic Vesicle Reuse Slows the Rate of Synaptic Depression in the CA1 Region of Hippocampus

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During short-term synaptic depression, neurotransmission rapidly decreases in response to repetitive action potential firing. Here, by blocking the vacuolar ATPase, alkalinizing the extracellular pH, or exposing hippocampal slices to pH buffers, we impaired neurotransmitter refilling, and electrophysiologically tested the role of vesicle reuse in synaptic depression. Under all conditions, synapses onto hippocampal CA1 pyramidal cells showed faster depression with increasing stimulation frequencies. At 20 Hz, compromising neurotransmitter refilling increased depression within 300 ms reaching completion within 2 s, suggesting a minimal contribution of reserve vesicles to neurotransmission. In contrast, at 1 Hz, depression emerged gradually and became significant within 100 s. Moreover, the depression induced by pH buffers was reversible with a similar frequency dependence, suggesting that the frequency-dependent increase in depression was caused by impairment of rapid synaptic vesicle reuse. These results indicate that synaptic vesicle trafficking impacts the kinetics of short-term synaptic plasticity at an extremely rapid time scale.

The Journal of Neuroscience, January 10, 2007 • 27(2):341–354

A WAVE-1 and WRP Signaling Complex Regulates Spine Density, Synaptic Plasticity, and Memory

Scott H. Soderling,^{1,2} Eric S. Guire,² Stefanie Kaech,³ Jon White,^{1,2} Fang Zhang,^{1,2} Kevin Schutz,^{1,2} Lorene K. Langeberg,^{1,2} Gary Banker,³ Jacob Raber,⁴ and John D. Scott^{1,2}

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The scaffolding protein WAVE-1 (Wiskott-Aldrich syndrome protein family member 1) directs signals from the GTPase Rac through the Arp2/3 complex to facilitate neuronal actin remodeling. The WAVE-associated GTPase activating protein called WRP is implicated in human mental retardation, and WAVE-1 knock-out mice have altered behavior. Neuronal time-lapse imaging, behavioral analyses, and electrophysiological recordings from genetically modified mice were used to show that WAVE-1 signaling complexes control aspects of neuronal morphogenesis and synaptic plasticity. Gene targeting experiments in mice demonstrate that WRP anchoring to WAVE-1 is a homeostatic mechanism that contributes to neuronal development and the fidelity of synaptic connectivity. This implies that signaling through WAVE-1 complexes is essential for neural plasticity and cognitive behavior.

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Intersectin Is a Negative Regulator of Dynamin Recruitment to the Synaptic Endocytic Zone in the Central Synapse

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Intersectin is a multidomain dynamin-binding protein implicated in numerous functions in the nervous system, including synapse formation and endocytosis. Here, we demonstrate that during neurotransmitter release in the central synapse, intersectin, like its binding partner dynamin, is redistributed from the synaptic vesicle pool to the periaxonal zone. Acute perturbation of the intersectin–dynamin interaction by microinjection of either intersectin antibodies or Src homology 3 (SH3) domains inhibited endocytosis at the fission step. Although the morphological effects induced by the different reagents were similar, antibody injections resulted in a dramatic increase in

dynamin immunoreactivity around coated pits and at constricted necks, whereas synapses microinjected with the GST (glutathione S-transferase)-SH3C domain displayed reduced amounts of dynamin in the neck region. Our data suggest that intersectin controls the amount of dynamin released from the synaptic vesicle cluster to the periaxonal zone and that it may regulate fission of clathrin-coated intermediates.

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Cholinergic Interneurons Control the Excitatory Input to the Striatum

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How the extent and time course of presynaptic inhibition depend on the action potentials of the neuron controlling the terminals is unknown. We investigated this issue in the striatum using paired recordings from cholinergic interneurons and projection neurons. Glutamatergic EPSCs were evoked in projection neurons and cholinergic interneurons by stimulation of afferent fibers in the cortex and the striatum, respectively. A single spike in a cholinergic interneuron caused significant depression of the evoked glutamatergic EPSC in 34% of projection neurons located within 100 μm and 41% of cholinergic interneurons located within 200 μm . The time course of these effects was similar in the two cases, with EPSC inhibition peaking 20–30 ms after the spike and disappearing after 40–80 ms. Maximal depression of EPSC amplitude was up to 27% in projection neurons and to 19% in cholinergic interneurons. These effects were reversibly blocked by muscarinic receptor antagonists (atropine or methoctramine), which also significantly increased baseline EPSC (evoked without a preceding spike in the cholinergic interneuron), suggesting that some tonic cholinergic presynaptic inhibition was present. This was confirmed by the fact that lowering extracellular potassium, which silenced spontaneously active cholinergic interneurons, also increased baseline EPSC amplitude, and these effects were occluded by previous application of muscarinic receptor antagonists. Collectively, these results show that a single spike in a cholinergic interneuron exerts a fast and powerful inhibitory control over the glutamatergic input to striatal neurons.

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Activity-Dependent Control of Slow Synaptic Vesicle Endocytosis by Cyclin-Dependent Kinase 5

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The stimulated dephosphorylation of the dephosphin group of endocytic proteins by calcineurin and their subsequent rephosphorylation by cyclin-dependent kinase 5 (cdk5) is required for synaptic vesicle (SV) retrieval in central nerve terminals. However, the specific endocytic pathway(s) controlled by these enzymes is unknown. To address this issue, we combined functional and morphological assays of endocytosis in primary neuronal cultures with pharmacological and molecular ablation of calcineurin and cdk5 activity. During strong stimulation, inhibition of calcineurin or cdk5 blocked uptake of the activity-dependent membrane marker FM1–43, but not the more hydrophilic FM2–10. However, FM2–10 uptake-measured poststimulation was sensitive to cdk5 and calcineurin inhibition, indicating that a slow form of endocytosis persists after termination of stimulation. In parallel EM studies, inhibition of cdk5 during strong stimulation greatly reduced horseradish peroxidase labeling of plasma membrane-derived nerve terminal endosomes, but not SVs. Furthermore, during mild stimulation, FM1–43 uptake was unaffected by cdk5 inhibition and the SV membrane was exclusively retrieved via a single SV route, suggesting that recruitment of the endosomal route of membrane retrieval is activity dependent. Thus, we propose that the calcineurin/cdk5-dependent phosphorylation cycle of the dephosphins specifically controls a slow endocytic pathway that proceeds via endosomal intermediates and is activated by strong physiological stimulation in central nerve terminals.

The Journal of Neuroscience, January 10, 2007 • 27(2):401–411

DEVELOPMENT/PLASTICITY/REPAIR

Lack of Hypoxia-Inducible Factor-1 α Impairs Midbrain Neural Precursor Cells Involving Vascular Endothelial Growth Factor Signaling

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Oxygen tension is critical for proliferation of human and murine midbrain-derived neural precursor cells (mNPCs). Here, we conditionally inactivated the hypoxia-responsive transcription factor hypoxia-inducible factor-1 α (HIF-1 α) in murine NPCs to determine its role in proliferation, survival, and dopaminergic differentiation *in vitro* as well as survival of murine dopaminergic neurons *in vivo*. HIF-1 α conditional knock-out (HIF-1 α CKO) mNPCs showed midbrain-specific impairment of survival and proliferation. Dopaminergic differentiation of HIF-1 α CKO mNPCs *in vitro* was markedly reduced. Expression of vascular endothelial growth factor (VEGF) mRNA was reduced in HIF-1 α CKO mNPCs, whereas erythropoietin signaling was not affected. Treatment of HIF-1 α CKO mNPCs with 50 ng/ml VEGF partially recovered proliferation and dopaminergic differentiation *in vitro*. In substantia nigra (SN) of adult HIF-1 α CKO mice, protein levels of dopaminergic marker molecules such as tyrosine hydroxylase (TH) and aldehyde dehydrogenase were reduced by 41 and 61%, respectively. The cell survival marker Bcl-2 was reduced by 58% while caspase-3 was activated. Nonbiased stereological cell counts of TH-positive neurons in SN of young adult HIF-1 α CKO mice revealed a reduction of 31% compared with cre/wt mice (in which the wild-type *Hif1a* allele is expressed in parallel with the Cre recombinase allele). However, we found no impairment of striatal dopamine concentrations or locomotor

behavior. In conclusion, HIF-1 α seems to be a transcription factor relevant to the development and survival of substantia nigra dopaminergic neurons involving VEGF signaling.

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Hepatocyte Growth Factor Acts as a Motogen and Guidance Signal for Gonadotropin Hormone-Releasing Hormone-1 Neuronal Migration

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Reproduction in mammals is under the control of the hypothalamic neuropeptide gonadotropin hormone-releasing hormone-1 (GnRH-1). GnRH-1-secreting neurons originate during embryonic development in the nasal placode and migrate into the forebrain along olfactory nerves. Gradients of secreted molecules may play a role in this migratory process. In this context, hepatocyte growth factor (HGF) is a potential candidate, because it promotes cell motility in developing brain and has been shown previously to act as a motogen on immortalized GnRH-1 neurons (GN11). In this study, the role of HGF and its receptor Met during development of the GnRH-1 system was examined. GnRH-1 cells express Met during their migration and downregulate its expression once they complete this process. Tissue-type plasminogen activator (tPA), a known HGF activator, is also detected in migratory GnRH-1 neurons. Consistent with *in vivo* expression, HGF is present in nasal explants, and GnRH-1 neurons express Met. HGF-neutralizing antibody was applied to explants to examine the role of the endogenous growth factor. Migration of GnRH-1 cells and olfactory axon outgrowth were significantly reduced, in line with disruption of a guidance gradient. Exogenous application of HGF to explants increased the distance that GnRH-1 cells migrated, suggesting that HGF also acts as a motogen to GnRH-1 neurons. Functional experiments, performed on organotypic slice cultures, show that creation of an opposing HGF gradient inhibits GnRH-1 neuronal migration. Finally, tPA^{-/-}:uPA^{-/-} (urokinase-type plasminogen activator^{-/-}) knock-out mice exhibit strong reduction of the GnRH-1 cell population. Together, these data indicate that HGF signaling via Met receptor influences the development of GnRH-1.

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BEHAVIORAL/SYSTEMS/COGNITIVE

Involvement of Non-NMDA Glutamate Receptors in Central Amygdala in Synaptic Actions of Ethanol and Ethanol-Induced Reward Behavior

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The central nucleus of the amygdala (CeA) plays a critical role in positive emotional responses that involve stimulus-reward learning and are induced by the reinforcing effects of many drugs of abuse, including alcohol. Behavioral studies have implicated CeA as a key brain structure in alcohol reward, but the underlying mechanisms are still poorly understood. Recent studies have demonstrated that both NMDA and non-NMDA receptors in CeA neurons are targets of acute and chronic alcohol in naive and alcohol-dependent animals. However, little is known about the role of CeA non-NMDA receptors in synaptic actions of alcohol and, particularly, in the behavior of alcohol reward. In the present study with both whole-cell voltage-clamp recordings in CeA slices *in vitro* and analysis of an animal model of conditioned place preference (CPP) *in vivo*, we investigated the synaptic mechanisms for actions of acute and chronic ethanol on CeA non-NMDA receptor functions and their contribution to ethanol-induced reward behavior. Acute ethanol significantly inhibited evoked and miniature synaptic currents mediated by non-NMDA receptors through inhibitions of both postsynaptic non-NMDA receptors and presynaptic glutamate release involving N-type Ca²⁺ channels. CeA neurons from rats exhibiting the ethanol-induced CPP behavior showed a significant increase in non-NMDA synaptic transmission. Blockade of this increased synaptic transmission through CeA microinjection abolished the CPP behavior. These results suggest that acute alcohol inhibits CeA non-NMDA synaptic transmission through both presynaptic and postsynaptic mechanisms, and chronic alcohol upregulates this synaptic activity, which is required for the alcohol-induced reward behavior.

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Action Representation of Sound: Audiomotor Recognition Network While Listening to Newly Acquired Actions

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The discovery of audiovisual mirror neurons in monkeys gave rise to the hypothesis that premotor areas are inherently involved not only when observing actions but also when listening to action-related sound. However, the whole-brain functional formation underlying such “action-listening” is not fully understood. In addition, previous studies in humans have focused mostly on relatively simple and overexperienced everyday actions, such as hand clapping or door knocking. Here we used functional magnetic resonance imaging to ask whether the human action-recognition system responds to sounds found in a more complex sequence of newly acquired actions. To

address this, we chose a piece of music as a model set of acoustically presentable actions and trained non-musicians to play it by ear. We then monitored brain activity in subjects while they listened to the newly acquired piece. Although subjects listened to the music without performing any movements, activation was found bilaterally in the frontoparietal motor-related network (including Broca's area, the premotor region, the intraparietal sulcus, and the inferior parietal region), consistent with neural circuits that have been associated with action observations, and may constitute the human mirror neuron system. Presentation of the practiced notes in a different order activated the network to a much lesser degree, whereas listening to an equally familiar but motorically unknown music did not activate this network. These findings support the hypothesis of a "hearing–doing" system that is highly dependent on the individual's motor repertoire, gets established rapidly, and consists of Broca's area as its hub. *The Journal of Neuroscience*, January 10, 2007 • 27(2):308–314

Neural Attunement Processes in Infants during the Acquisition of a Language-Specific Phonemic Contrast

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To elucidate the developmental neural attunement process in the language-specific phonemic repertoire, cerebral hemodynamic responses to a Japanese durational vowel contrast were measured in Japanese infants using near-infrared spectroscopy. Because only relative durational information distinguishes this particular vowel contrast, both first and second language learners have difficulties in acquiring this phonemically crucial durational difference. Previous cross-linguistic studies conducted on adults showed that phoneme-specific, left-dominant neural responses were observed only for native Japanese listeners. Using the same stimuli, we show that a larger response to the across-category changes than to the within-category changes occurred transiently in the 6- to 7-month-old group before stabilizing in the groups older than 12 months. However, the left dominance of the phoneme-specific response in the auditory area was observed only in the groups of 13 months and above. Thus, the durational phonemic contrast is most likely processed first by a generic auditory circuit at 6–7 months as a result of early auditory experience. The neural processing of the contrast is then switched over to a more linguistic circuit after 12 months, this time with a left dominance similar to native adult listeners.

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Reinforcement Learning Signals Predict Future Decisions

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Optimal behavior in a competitive world requires the flexibility to adapt decision strategies based on recent outcomes. In the present study, we tested the hypothesis that this flexibility emerges through a reinforcement learning process, in which reward prediction errors are used dynamically to adjust representations of decision options. We recorded event-related brain potentials (ERPs) while subjects played a strategic economic game against a computer opponent to evaluate how neural responses to outcomes related to subsequent decision-making. Analyses of ERP data focused on the feedback-related negativity (FRN), an outcome-locked potential thought to reflect a neural prediction error signal. Consistent with predictions of a computational reinforcement learning model, we found that the magnitude of ERPs after losing to the computer opponent predicted whether subjects would change decision behavior on the subsequent trial. Furthermore, FRNs to decision outcomes were disproportionately larger over the motor cortex contralateral to the response hand that was used to make the decision. These findings provide novel evidence that humans engage a reinforcement learning process to adjust representations of competing decision options.

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NEUROBIOLOGY OF DISEASE

The I–II Loop Controls Plasma Membrane Expression and Gating of Ca_v3.2 T-Type Ca²⁺ Channels: A Paradigm for Childhood Absence Epilepsy Mutations

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Calcium currents via low-voltage-activated T-type channels mediate burst firing, particularly in thalamic neurons. Considerable evidence supports the hypothesis that overactive T-channels may contribute to thalamocortical dysrhythmia, including absence epilepsy. Single nucleotide polymorphisms in one of the T-channel genes (*CACNA1H*, which encodes Ca_v3.2) are associated with childhood absence epilepsy in a Chinese population. Because only a fraction of these polymorphisms are predicted to increase channel activity and neuronal firing, we hypothesized that other channel properties may be affected. Here we describe that all the polymorphisms clustered in the intracellular loop connecting repeats I and II (I–II loop) increase the surface expression of extracellularly tagged Ca_v3.2 channels. The functional domains within the I–II

loop were then mapped by deletion analysis. The first 62 amino acids of the loop (post IS6) are involved in regulating the voltage dependence of channel gating and inactivation. Similarly, the last 15 amino acids of the loop (pre IIS1) are involved in channel inactivation. In contrast, the central region of I-II loop regulates surface expression, with no significant effect on channel biophysics. Electrophysiology, luminometry, fluorescence-activated cell sorting measurements, and confocal microscopy studies demonstrate that deletion of this central region leads to enhanced surface expression of channels from intracellular compartments to the plasma membrane. These results provide novel insights into how *CACNA1H* polymorphisms may contribute to Ca_v3.2 channel overactivity and consequently to absence epilepsy and establish the I-II loop as an important regulator of Ca_v3.2 channel function and expression.

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Altered Axonal Mitochondrial Transport in the Pathogenesis of Charcot-Marie-Tooth Disease from Mitofusin 2 Mutations

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Mutations in the mitochondrial fusion protein mitofusin 2 (MFN2) are the most commonly identified cause of Charcot-Marie-Tooth type 2 (CMT2), a dominantly inherited disease characterized by degeneration of peripheral sensory and motor axons. However, the mechanism by which mutations in this ubiquitously expressed mitochondrial fusion protein lead to neuropathy has not yet been elucidated. To explore how MFN2 mutations lead to degeneration of peripheral axons, we expressed neuropathy-associated forms of MFN2 in cultured dorsal root ganglion neurons, cells preferentially affected in CMT2. Disease-associated MFN2 mutant proteins induced abnormal clustering of small fragmented mitochondria in both neuronal cell bodies and proximal axons. Interestingly, transport of mitochondria in axons was significantly impaired in neurons expressing disease-mutated forms of MFN2. The diminished axonal mitochondrial transport was not attributable to diminished ATP levels in the neurons, and oxidative respiration was normal in mutant MFN2-expressing cells. Additionally, mitochondrial oxidative enzyme activity was normal in muscle mitochondria from a CMT2 patient with an MFN2 mutation, further supporting that abnormal mitochondrial transport in neurons is independent from an energy production defect. This abnormal mitochondrial trafficking provides a likely explanation for the selective susceptibility of the longest peripheral axons to MFN2 mutations, in which proper localization of mitochondria is critical for axonal and synaptic function.

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