

# This Week in The Journal

## ● Cellular/Molecular

### *Calcium and Vesicle Recruitment at the Calyx of Held*

Nobutake Hosoi, Takeshi Sakaba, and Erwin Neher

(see pages 14286–14298)

When it comes to synaptic vesicles, synapses seem to know a thing or two about supply and demand. High-frequency stimulation increases exocytosis and results in an accelerated recruitment of additional vesicles within the nerve terminal, a process thought to rely on intracellular calcium. This week, Hosoi et al. took advantage of the accessibility of the presynaptic terminal at the calyx of Held to examine the relationship between intracellular calcium and vesicle recruitment. The authors used paired presynaptic and postsynaptic recordings to measure simultaneously presynaptic calcium levels and postsynaptic responses. Replenishment of the fast-releasing vesicle pool increased with presynaptic calcium levels, thus helping to sustain release during high-frequency firing. This relationship was quasilinear, similar to the calcium dependence of facilitation and post-tetanic potentiation. These processes have much slower kinetics than the highly nonlinear calcium dependence of transmitter release and thus appear to be tuned to slowly changing global calcium levels in nerve terminals.

## ▲ Development/Plasticity/Repair

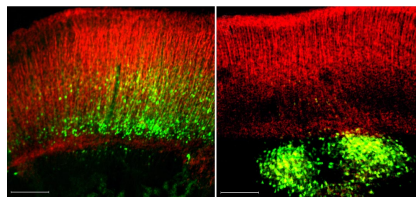
### *APP and Neuronal Migration*

Tracy L. Young-Pearse, Jilin Bai, Rui Chang, Jessica B. Zheng, Joseph J. LoTurco, and Dennis J. Selkoe

(see pages 14459–14469)

Most of the attention directed at  $\beta$ -amyloid precursor protein (APP) has focused on its cleavage and its cleavage products, such as  $A\beta$ , one of the hallmarks of Alzheimer's disease. However, there are clues that full-length APP has important

developmental roles. This week, Young-Pearse et al. revisited this issue by knocking down APP using *in utero* electroporation. In embryonic day 13 (E13) rat embryos, the authors electroporated APP shRNAs along with a fluorescent reporter and then examined cortical development at E19. The APP shRNA prevented migration of labeled cells from the ventricular zone. By E30, the labeled cells remained below the cortical plate as a heterotopia. The trapped cells initially expressed neuronal markers, suggesting that the defect was in migration rather than differentiation. The defect was rescued by full-length APP. In contrast, overexpression of wild-type APP at E13 accelerated migration of labeled cells into the cortical plate.



Knockdown of APP with a short-hairpin RNA caused the abnormal migration of GFP-labeled cells (right). The migration defect was rescued with overexpression of APP695 (left). See the article by Young-Pearse et al. for details.

## ■ Behavioral/Systems/Cognitive

### *Reversing Sleep Deprivation with a Whiff of Orexin-A*

Sam A. Deadwyler, Linda Porrino, Jerome M. Siegel, and Robert E. Hampson

(see pages 14239–14247)

This article might appeal to the beleaguered hospital intern or the college student during finals week, both of which must at times combat sleep deprivation. The loss of the hypothalamic neurons that produce orexin-A causes narcolepsy, and the administration of orexin-A produces arousal and increased attention. This week, Deadwyler et al. provide further evidence that orexin-A can counteract the effects of sleep deprivation. Adult rhesus

monkeys were sleep deprived for 30–36 h using a combination of videos, music, treats, gentle rattling of their cages, and constant supervision by laboratory personnel. Sounds a lot like a college dorm. The monkeys were then tested on a delayed match-to-sample short-term memory task. Monkeys that received orexin-A, particularly by intranasal spray, showed better performance. The differences were most apparent for trials that were classified as high-load cognitive processes. The superiority of the intranasal delivery may prove useful for potential clinical applications.

## ◆ Neurobiology of Disease

### *AD, Omega-3 Fatty Acids, and a Lipoprotein Receptor*

Qiu-Lan Ma, Bruce Teter, Oliver J. Ubeda, Takashi Morihara, Dilsher Dhoot, Michael D. Nyby, Michael L. Tuck, Sally A. Frautschy, and Greg M. Cole

(see pages 14299–14307)

This is one of those good-fat–bad-fat stories for your holiday reading. Ma et al. examined the lipid regulation of an ApoE/low-density lipoprotein receptor, the neuronal sortilin-related receptor (SorLA or LR11). LR11 can reduce  $\beta$ -amyloid production by guiding APP in recycling Golgi and early endosome pathways, thus trafficking APP away from  $\beta$ - and  $\gamma$ -secretase. Polymorphisms that reduce LR11 expression also have been associated with increased Alzheimer's disease (AD) risk. The authors report that the essential omega-3 fatty acid docosahexaenoic acid (DHA) increases LR11 in a neuronal cell line and in primary neurons. DHA also increased LR11 in membrane fractions from aged normal mice and in transgenic mice that overexpressed APP. Dietary fish oil had similar effects in rats with increased AD risk. The authors suggest that this regulation may contribute to the reduced AD risk with increased fish consumption.

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**Cover legend:** An artistic rendering of optogenetic technologies in action. Blue and yellow lights can be used to evoke or inhibit electrical activity (represented by the intense glow in targeted neurons) in neurons. Illustration credit: Feng Zhang, Steve Dixon, Viviana Gradinaru, and Karl Deisseroth. For more information, see the article by Gradinaru et al. in this issue (pages 14231–14238).

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## Human Neuroma Contains Increased Levels of Semaphorin 3A, Which Surrounds Nerve Fibers and Reduces Neurite Extension *In Vitro*

Martijn R. Tannemaat,<sup>1,2</sup> Joanna Korecka,<sup>1</sup> Erich M. E. Ehlert,<sup>1</sup> Matthew R. J. Mason,<sup>1</sup> Sjoerd G. van Duinen,<sup>3</sup> Gerard J. Boer,<sup>1</sup> Martijn J. A. Malessy,<sup>2</sup> and Joost Verhaagen<sup>1</sup>

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Neuroma formation after peripheral nerve injury is detrimental to functional recovery and is therefore a significant clinical problem. The molecular basis for this phenomenon is not fully understood. Here, we show that the expression of the chemorepulsive protein semaphorin 3A (sema3A), but not semaphorin 3F, is increased in human neuroma tissue that has formed in severe obstetric brachial plexus lesions. Semaphorin 3A is produced by fibroblasts in the epineurial space and appears to be secreted into the extracellular matrix. It surrounds fascicles, minifascicles, or single axons, suggesting a role in fasciculation and inhibition of neurite outgrowth. Lentiviral vector-mediated knock-down of Neuropilin 1, the receptor for sema3A, leads to increased neurite outgrowth of F11 cells cultured on neuroma tissue, but not of F11 cells cultured on normal nerve tissue. These findings demonstrate the putative inhibitory role of sema3A in human neuroma tissue. Our observations are the first demonstration of the expression of sema3A in human neural scar tissue and support a role for this protein in the inhibition of axonal regeneration in injured human peripheral nerves. These findings contribute to the understanding of the outgrowth inhibitory properties of neuroma tissue.

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### Articles

#### CELLULAR/MOLECULAR

## Quantitative Analysis of Calcium-Dependent Vesicle Recruitment and Its Functional Role at the Calyx of Held Synapse

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Recruitment of release-ready vesicles at synapses is one of the important factors, which determine dynamic properties of signaling between neurons in the brain. It has been shown that the rate of vesicle recruitment is accelerated by strong synaptic activity. An elevated concentration of calcium ions in the presynaptic terminal ( $[Ca^{2+}]_i$ ) has been proposed to be responsible for this effect. However, the precise relationship between  $[Ca^{2+}]_i$  and recruitment has not been established yet, and the functional consequences of accelerated recruitment during synaptic activity have not been quantified experimentally. To probe the intracellular  $Ca^{2+}$  dependence of vesicle recruitment and to examine its functional role during trains of action potential (AP)-like stimuli, we monitored  $[Ca^{2+}]_i$  and synaptic responses simultaneously with paired recordings at the calyx of Held synapse. We found that a distinct, rapidly releasing vesicle pool is replenished with a rate that increases linearly with  $[Ca^{2+}]_i$ , without any apparent cooperativity. The slope factor for this increase is  $\sim 1$  pool/ $(\mu M \cdot s)$ . Blocking  $Ca^{2+}$ -dependent recruitment specifically with a calmodulin binding peptide revealed that the steady-state EPSCs during 100 Hz AP-like trains were maintained through this  $Ca^{2+}$ -dependent recruitment mechanism. Using a simple model of vesicle dynamics, we estimated that the recruitment rate accelerated 10-fold during the steady-state compared with the rate at resting  $[Ca^{2+}]_i$ . We could also demonstrate an approximate sixfold increase in release probability (facilitation) during the initial 5–15 AP-like stimuli of such trains in our experimental condition, regardless of EPSC depression.

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## NMDA Receptor Activation Potentiates Inhibitory Transmission through GABA Receptor-Associated Protein-Dependent Exocytosis of GABA<sub>A</sub> Receptors

Kurt C. Marsden,<sup>1</sup> Jennifer B. Beattie,<sup>1</sup> Jenna Friedenthal,<sup>2</sup> and Reed C. Carroll<sup>1</sup>

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The trafficking of postsynaptic AMPA receptors (AMPA<sub>R</sub>s) is a powerful mechanism for regulating the strength of excitatory synapses. It has become clear that the surface levels of inhibitory GABA<sub>A</sub> receptors (GABA<sub>A</sub>R<sub>s</sub>) are also subject to regulation and that GABA<sub>A</sub>R trafficking may contribute to inhibitory plasticity, although the underlying mechanisms are not fully understood. Here, we report that NMDA receptor activation, which has been shown to drive excitatory long-term depression through AMPAR endocytosis, simultaneously increases expression of GABA<sub>A</sub>R<sub>s</sub> at the dendritic surface of hippocampal neurons. This NMDA stimulus increases miniature IPSC amplitudes and requires the activity of  $Ca^{2+}$  calmodulin-dependent kinase II and the trafficking proteins *N*-ethylmaleimide-sensitive factor, GABA receptor-associated protein

(GABARAP), and glutamate receptor interacting protein (GRIP). These data demonstrate for the first time that endogenous GABARAP and GRIP contribute to the regulated trafficking of GABA<sub>A</sub>Rs. In addition, they reveal that the bidirectional trafficking of AMPA and GABA<sub>A</sub> receptors can be driven by a single glutamatergic stimulus, providing a potent postsynaptic mechanism for modulating neuronal excitability.

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## Olig1 and Sox10 Interact Synergistically to Drive *Myelin Basic Protein* Transcription in Oligodendrocytes

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The oligodendrocyte lineage genes (*Olig1/2*), encoding basic helix-loop-helix transcription factors, were first identified in screens for master regulators of oligodendrocyte development. OLIG1 is important for differentiation of oligodendrocyte precursors into myelin-forming oligodendrocytes during development and is thought to play a crucial role in remyelination during multiple sclerosis. However, it is still unclear how OLIG1 interacts with its transcriptional cofactors and DNA targets. OLIG1 was reportedly restricted to mammals, but we demonstrate here that zebrafish and other teleosts also possess an OLIG1 homolog. In zebrafish, as in mammals, Olig1 is expressed in the oligodendrocyte lineage. Olig1 associates physically with another myelin-associated transcription factor, Sox10, and the Olig1/Sox10 complex activates *mbp* (myelin basic protein) transcription via conserved DNA sequence motifs in the *mbp* promoter region. In contrast, Olig2 does not bind to Sox10 in zebrafish, although both OLIG1 and OLIG2 bind SOX10 in mouse.

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## A TAT–DEF–Elk-1 Peptide Regulates the Cytonuclear Trafficking of Elk-1 and Controls Cytoskeleton Dynamics

Jérémie Lavour,<sup>1,3</sup> Frédéric Bernard,<sup>2,3</sup> Pierre Trifilieff,<sup>1,3,4,5</sup> Vincent Pascoli,<sup>1,3</sup> Vincent Kappes,<sup>1,3</sup> Christiane Pagès,<sup>1,3</sup> Peter Vanhoutte,<sup>1,3</sup> and Jocelyne Caboche<sup>1,3</sup>

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The transcription factor Elk-1 plays a key role in cell differentiation, proliferation and apoptosis. This role is thought to arise from its phosphorylation by activated extracellular signal-regulated kinases (ERKs), a critical posttranslational event for the transcriptional activity of the ternary complex composed of Elk-1 and a dimer of serum response factor (SRF) at the serum response element (SRE) regulatory site of transcription. In addition to its nuclear localization, Elk-1 is found in the dendrites and soma of neuronal cells and recent evidence implicate a cytoplasmic proapoptotic function of Elk-1, via its association with the mitochondrial permeability transition pore complex. Thus, the nuclear versus cytoplasmic localization of Elk-1 seems to be crucial for its biological function. In this study we show that the excitatory neurotransmitter, glutamate, induces an ERK-dependent Elk-1 activation and nuclear relocalization. We demonstrate that Elk-1 phosphorylation on Ser383/389 has a dual function and triggers both Elk-1 nuclear translocation and SRE-dependent gene expression. Mutating these sites into inactive residues or using a synthetic penetrating peptide (TAT–DEF–Elk-1), which specifically interferes with the DEF docking domain of Elk-1, prevents Elk-1 nuclear translocation without interfering with ERK nor MSK1 (mitogen- and stress-activated protein kinase 1), a CREB kinase downstream from ERK- activation. This results in a differential regulation of glutamate-induced IEG regulation when compared with classical inhibitors of the ERK pathway. Using the TAT–DEF–Elk-1 peptide or the dominant-negative version of Elk-1, we show that Elk-1 phosphorylation controls dendritic elongation, SRF and Actin expression levels as well as cytoskeleton dynamics.

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### DEVELOPMENT/PLASTICITY/REPAIR

## Mosaic Removal of Hedgehog Signaling in the Adult SVZ Reveals That the Residual Wild-Type Stem Cells Have a Limited Capacity for Self-Renewal

Francesca Balordi and Gord Fishell

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The *Smoothed* gene is necessary for cells to transduce hedgehog signaling. Although we and others have previously shown that embryonic removal of *Smoothed* in the neural tube results in a loss of stem cells from the postnatal subventricular zone, it was unclear whether this reflected a requirement for hedgehog signaling in the establishment or maintenance of the adult niche. Here, we have examined the consequences of conditional removal of *Smoothed* gene function within the subventricular zone of the adult neural stem cell niche. We observe that both proliferation and neurogenesis are compromised when hedgehog signaling is removed from subventricular zone stem cells. Moreover, even after a 10 month survival period, the stem cell niche fails to recover. It has been reported that the adult subventricular zone quickly rebounds from an antimitotic insult by increasing proliferation and replenishing the niche. During this recovery, it has been reported that hedgehog signaling appears to be upregulated. When mice in which hedgehog signaling in the subventricular zone has been strongly attenuated are given a similar antimitotic treatment, recovery is limited to the reduced level of proliferation and neurogenesis observed before the mitotic insult. Furthermore, the limited recovery that is observed appears to be largely restricted

to the minority of neural stem cells that escape the conditional inactivation of *Smoothed* gene function. These results demonstrate that ongoing hedgehog signaling is required to maintain adult neural stem cells and that their ability to self-renew is limited.

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## DEVELOPMENT/PLASTICITY/REPAIR

# Conditional Knock-Out of $\beta$ -Catenin in Postnatal-Born Dentate Gyrus Granule Neurons Results in Dendritic Malformation

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Neurons are continuously added to the brain throughout life, and these neurons must develop dendritic arbors and functional connections with existing neurons to be integrated into neuronal circuitry. The molecular mechanisms that regulate dendritic development of newborn neurons in the hippocampal dentate gyrus are still unclear. Here, we show that  $\beta$ -catenin is expressed in newborn granule neurons and in neural progenitor cells in the hippocampal dentate gyrus. Specific knock-out of  $\beta$ -catenin in newborn neurons, without affecting  $\beta$ -catenin expression in neural progenitor cells, led to defects in dendritic morphology of these newborn neurons *in vivo*. Majority of newborn neurons that cannot extend dendrites survive <1 month after they were born. Our results indicate that  $\beta$ -catenin plays an important role in dendritic development of postnatal-born neurons *in vivo*, and is therefore essential for the neurogenesis in the postnatal brain.

The Journal of Neuroscience, December 26, 2007 • 27(52):14260–14264

# Impaired Migration in the Rostral Migratory Stream But Spared Olfactory Function after the Elimination of Programmed Cell Death in Bax Knock-Out Mice

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Rats and mice exhibit neurogenesis of olfactory bulb (OB) interneurons throughout adulthood. To homeostatically maintain stable neuron numbers, it is necessary to continuously remove a subset of OB neurons by programmed cell death (PCD). Here we demonstrate that Bax is critical for the elimination of OB neurons by showing that Bax-KO mice exhibit greatly reduced PCD in the OB. Despite the reduction of PCD, however, proliferation of progenitors and the size of the OB were virtually unaffected in Bax-knock-out (KO) mice. However, reducing PCD by Bax deletion affected the migration of a subset of adult-produced neurons by the disruption of glial tube formation as well as by premature detachment of neuroblasts from the migratory chain. Rescued cells aberrantly remained in the subventricular zone (SVZ)-rostral migratory stream (RMS), in which they differentiated into calretinin<sup>+</sup> or GABA-expressing interneurons. Because of the migratory deficit, OB cell homeostasis involving new cell entry and PCD (neuronal turnover) was virtually absent in adult Bax-KO mice. Despite this, Bax-KO mice exhibited normal olfactory behaviors such as odor discrimination and olfactory memory which are thought to be influenced by adult neurogenesis. These results demonstrate that PCD is involved in the regulation of RMS migration and differentiation after OB neurogenesis, but that animals maintain normal olfactory function in the absence of PCD.

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# Analyzing Somatosensory Axon Projections with the Sensory Neuron-Specific *Advillin* Gene

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Peripheral sensory neurons detect diverse physical stimuli and transmit the information into the CNS. At present, the genetic tools for specifically studying the development, plasticity, and regeneration of the sensory axon projections are limited. We found that the gene encoding Advillin, an actin binding protein that belongs to the gelsolin superfamily, is expressed almost exclusively in peripheral sensory neurons. We next generated a line of knock-in mice in which the start codon of the *Advillin* is replaced by the gene encoding human placenta alkaline phosphatase (Avil-hPLAP mice). In heterozygous Avil-hPLAP mice, sensory axons, the exquisite sensory endings, as well as the fine central axonal collaterals can be clearly visualized with a simple alkaline phosphatase staining. Using this mouse line, we found that the development of peripheral target innervation and sensory ending formation is an ordered process with specific timing depending on sensory modalities. This is also true for the in-growth of central axonal collaterals into the brainstem and the spinal cord. Our results demonstrate that Avil-hPLAP mouse is a valuable tool for specifically studying peripheral sensory neurons. Functionally, we found that the regenerative axon growth of *Advillin*-null sensory neurons is significantly shortened and that deletion of *Advillin* reduces the plasticity of whisker-related barrelettes patterns in the hindbrain.

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## A Critical Function for $\beta$ -Amyloid Precursor Protein in Neuronal Migration Revealed by *In Utero* RNA Interference

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Physiological processing of the  $\beta$ -amyloid precursor protein (APP) generates amyloid  $\beta$ -protein, which can assemble into oligomers that mediate synaptic failure in Alzheimer's disease. Two decades of research have led to human trials of compounds that chronically target this processing, and yet the normal function of APP *in vivo* remains unclear. We used the method of *in utero* electroporation of shRNA constructs into the developing cortex to acutely knock down APP in rodents. This approach revealed that neuronal precursor cells in embryonic cortex require APP to migrate correctly into the nascent cortical plate. cDNAs encoding human APP or its homologues, amyloid precursor-like protein 1 (APLP1) or APLP2, fully rescued the shRNA-mediated migration defect. Analysis of an array of mutations and deletions in APP revealed that both the extracellular and cytoplasmic domains of APP are required for efficient rescue. Whereas knock-down of APP inhibited cortical plate entry, overexpression of APP caused accelerated migration of cells past the cortical plate boundary, confirming that normal APP levels are required for correct neuronal migration. In addition, we found that Disabled-1 (Dab1), an adaptor protein with a well established role in cortical cell migration, acts downstream of APP for this function in cortical plate entry. We conclude that full-length APP functions as an important factor for proper migration of neuronal precursors into the cortical plate during the development of the mammalian brain.

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## Selective Targeting of Different Neural Cell Adhesion Molecule Isoforms during Motoneuron–Myotube Synapse Formation in Culture and the Switch from an Immature to Mature Form of Synaptic Vesicle Cycling

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Characterization of neuromuscular junction formation and function in mice lacking all neural cell adhesion molecule (NCAM) isoforms or only the 180 isoform demonstrated that the 180 isoform was required at adult synapses to maintain effective transmission with repetitive stimulation whereas the 140 and/or 120 isoform(s) were sufficient to mediate the downregulation of synaptic vesicle cycling along the axon after synapse formation. However, the expression and targeting of each isoform and its relationship to distinct forms of synaptic vesicle cycling before and after synapse formation was previously unknown. By transfecting chick motoneurons with fluorescently tagged mouse 180, 140 and 120 isoforms, we show that before myotube contact the 180 and 140 isoforms are expressed in distinct puncta along the axon which are sites of an immature form (Brefeldin A sensitive, L-type  $\text{Ca}^{2+}$  channel mediated) of vesicle cycling. After myotube contact the 140 and 180 isoforms are downregulated from the axon and selectively targeted to the presynaptic terminal. This coincided with the downregulation of vesicle cycling along the axon and the expression of the mature form (BFA insensitive, P/Q type  $\text{Ca}^{2+}$  channel mediated) of vesicle cycling at the terminal. The synaptic targeting of exogenously expressed 180 and 140 isoforms also occurred when chick motoneurons contacted  $+/+$  mouse myotubes; however only the 180 but not the 140 isoform was targeted on contact with NCAM<sup>-/-</sup> myotubes. These observations indicate that postsynaptic NCAM is required for the synaptic targeting of presynaptic 140 NCAM but that the localization of presynaptic 180 NCAM occurs via a different mechanism.

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## Inhibiting Glycosaminoglycan Chain Polymerization Decreases the Inhibitory Activity of Astrocyte-Derived Chondroitin Sulfate Proteoglycans

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Chondroitin sulfate proteoglycans (CSPGs) are upregulated in the CNS after injury and participate in the inhibition of axon regeneration mainly through their glycosaminoglycan (GAG) side chains. In the present study, we have identified a new way to alleviate the inhibition of axonal regeneration by CSPG GAGs. We have successfully decreased the amount of CSPG GAG produced by astrocytes by targeting chondroitin polymerizing factor (ChPF), a key enzyme in the CSPG biosynthetic pathway. Using short interfering RNA (siRNA), we reduced ChPF mRNA levels by 70% in both the Neu7 astrocyte cell line and primary rat astrocytes. This reduction leads to a decrease in ChPF protein levels and a reduced amount of CSPG GAG chains in the conditioned media (CM) of these cells. Secretion of neurocan by primary astrocytes and NG2 core protein by Neu7 cells transfected with ChPF siRNA is not decreased, suggesting that inhibiting GAG chain synthesis does not affect core protein trafficking from these cells. CM from siRNA-treated Neu7 cells is a less repulsive substrate for axons than CM from control cells. In addition, axonal outgrowth from cerebellar granule neurons is increased on or in CM from ChPF siRNA-treated Neu7 cells. These data indicate that targeting the biosynthesis of CSPG GAG is a potentially new therapeutic avenue for decreasing CSPG GAG produced by astrocytes after CNS injury.

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## Systemic and Nasal Delivery of Orexin-A (Hypocretin-1) Reduces the Effects of Sleep Deprivation on Cognitive Performance in Nonhuman Primates

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Hypocretin-1 (orexin-A) was administered to sleep-deprived (30–36 h) rhesus monkeys immediately preceding testing on a multi-image delayed match-to-sample (DMS) short-term memory task. The DMS task used multiple delays and stimulus images and effectively measures cognitive deficits produced by sleep deprivation (Porrino et al., 2005). Two methods of administration of orexin-A were tested, intravenous injections (2.5–10.0  $\mu\text{g}/\text{kg}$ , i.v.) and a novel method developed for nasal delivery via an atomizer spray mist to the nostrils (dose estimated 1.0  $\mu\text{g}/\text{kg}$ ). Results showed that orexin-A delivered via the intravenous and nasal routes significantly improved performance in sleep-deprived monkeys; however, the nasal delivery method was significantly more effective than the highest dose (10  $\mu\text{g}/\text{kg}$ ) of intravenous orexin-A tested. The improvement in performance by orexin-A was specific to trials classified as high versus low cognitive load as determined by performance difficulty under normal testing conditions. Except for the maximum intravenous dose (10  $\mu\text{g}/\text{kg}$ ), neither delivery method affected task performance in alert non-sleep-deprived animals. The improved performance in sleep-deprived animals was accompanied by orexin-A related alterations in local cerebral glucose metabolism (CMRglc) in specific brain regions shown previously to be engaged by the task and impaired by sleep deprivation (Porrino et al., 2005). Consistent with the differential effects on performance, nasal delivered orexin-A produced a more pronounced reversal of sleep deprivation induced changes in brain metabolic activity (CMRglc) than intravenous orexin-A. These findings provide strong evidence for the effectiveness of intranasal orexin-A in alleviating cognitive deficits produced by loss of sleep.

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## Selective Deletion of *Bdnf* in the Ventromedial and Dorsomedial Hypothalamus of Adult Mice Results in Hyperphagic Behavior and Obesity

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Brain-derived neurotrophic factor (BDNF) and its receptor TrkB are expressed in several hypothalamic and hindbrain nuclei involved in regulating energy homeostasis, developmentally and in the adult animal. Their depletion during the fetal or early postnatal periods when developmental processes are still ongoing elicits hyperphagic behavior and obesity in mice. Whether BDNF is a chief element in appetite control in the mature brain remains controversial. The required sources of this neurotrophin are also unknown. We show that glucose administration rapidly induced BDNF mRNA expression, mediated by *Bdnf* promoter 1, and TrkB transcription in the ventromedial hypothalamus (VMH) of adult mice, consistent with a role of this pathway in satiety. Using viral-mediated selective knock-down of BDNF in the VMH and dorsomedial hypothalamus (DMH) of adult mice, we were able to elucidate the physiological relevance of BDNF in energy balance regulation. Site-specific mutants exhibited hyperphagic behavior and obesity but normal energy expenditure. Furthermore, intracerebroventricular administration of BDNF triggered an immediate neuronal response in multiple hypothalamic nuclei in wild-type mice, suggesting that its anorexigenic actions involve short-term mechanisms. Locomotor, aggressive, and depressive-like behaviors, all of which are associated with neural circuits involving the VMH, were not altered in VMH/DMH-specific BDNF mutants. These findings demonstrate that BDNF is an integral component of central mechanisms mediating satiety in the adult mouse and, moreover, that its synthesis in the VMH and/or DMH is required for the suppression of appetite.

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## Mechanosensory Gating of Proprioceptor Input to Modulatory Projection Neurons

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Sensorimotor gating commonly occurs at sensory neuron synapses onto motor circuit neurons and motor neurons. Here, using the crab stomatogastric nervous system, we show that sensorimotor gating also occurs at the level of the projection neurons that activate motor circuits. We compared the influence of the gastro-pyloric receptor (GPR) muscle stretch-sensitive neuron on two projection neurons, modulatory commissural neuron 1 (MCN1) and commissural projection neuron 2 (CPN2), with and without a preceding activation of the mechanosensory ventral cardiac neurons (VCNs). MCN1 and CPN2 project from the paired commissural ganglia (CoGs) to the stomatogastric ganglion (STG), where they activate the gastric mill (chewing) motor circuit. When stimulated separately, the GPR and VCN neurons each elicit the gastric mill rhythm by coactivating MCN1 and CPN2. When GPR is instead stimulated during the VCN-gastric mill rhythm, it slows this rhythm. This effect results from a second GPR synapse onto MCN1 that presynaptically inhibits its STG terminals. Here, we show that, during the VCN-triggered rhythm, the GPR excitation of MCN1 and CPN2 in the CoGs is gated out, leaving only its influence in the STG. This gating effect appears to occur within the CoG and does not result from a ceiling effect on projection neuron firing frequency. Additionally, this gating action enables GPR to either activate rhythmic motor activity or act as a phasic sensorimotor feedback system. These results also indicate that the site of sensorimotor gating can occur at the level of the projection neurons that activate a motor circuit.

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# Dimensions of Impulsivity Are Associated with Poor Spatial Working Memory Performance in Monkeys

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Impulsive behavior and novelty seeking are dimensions of temperament that are behavioral determinants of risk for attention deficit/hyperactivity disorder and its neurocognitive endophenotypes, and variation in the dopamine D<sub>4</sub> receptor gene (DRD4) explains at least a portion of the variance in the traits. To further characterize the dimensional phenotype associated with impulsiveness, adolescent male monkeys were evaluated using ecologically valid tests of impulsive approach and aggression in response to social or nonsocial stimuli; subsequently, a delayed response task was implemented to assess spatial working memory performance. Subjects were selected into this study based on their response to the social challenge task or by DRD4 genotype, resulting in three groups: low-impulsivity/common DRD4 allele, high-impulsivity/common DRD4 allele, or rare DRD4 allele. All animals acquired the delayed response task and could perform at near ceiling levels when a ~0 s delay version was imposed, but as delays were lengthened, high-impulsive animals, regardless of DRD4 genotype, made fewer correct responses than did low-impulsive subjects; an inverse relationship existed for working memory and impulsivity. Notably, impulsive behavior evoked by social and nonsocial stimuli explained overlapping and independent portions of the variance in working memory performance. CSF levels of monoamine metabolites did not significantly differentiate the high- and low-impulsive animals, although monkeys carrying the DRD4 rare allele tended to exhibit higher monoamine turnover. These data indicate that dimensions of impulsivity may impact on working memory performance in qualitatively similar ways but through different mechanisms.

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# Using Imagination to Understand the Neural Basis of Episodic Memory

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Functional MRI (fMRI) studies investigating the neural basis of episodic memory recall, and the related task of thinking about plausible personal future events, have revealed a consistent network of associated brain regions. Surprisingly little, however, is understood about the contributions individual brain areas make to the overall recollective experience. To examine this, we used a novel fMRI paradigm in which subjects had to imagine fictitious experiences. In contrast to future thinking, this results in experiences that are not explicitly temporal in nature or as reliant on self-processing. By using previously imagined fictitious experiences as a comparison for episodic memories, we identified the neural basis of a key process engaged in common, namely scene construction, involving the generation, maintenance and visualization of complex spatial contexts. This was associated with activations in a distributed network, including hippocampus, parahippocampal gyrus, and retrosplenial cortex. Importantly, we disambiguated these common effects from episodic memory-specific responses in anterior medial prefrontal cortex, posterior cingulate cortex and precuneus. These latter regions may support self-schema and familiarity processes, and contribute to the brain's ability to distinguish real from imaginary memories. We conclude that scene construction constitutes a common process underlying episodic memory and imagination of fictitious experiences, and suggest it may partially account for the similar brain networks implicated in navigation, episodic future thinking, and the default mode. We suggest that additional brain regions are co-opted into this core network in a task-specific manner to support functions such as episodic memory that may have additional requirements.

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# Immediate Reward Bias in Humans: Fronto-Parietal Networks and a Role for the Catechol-O-Methyltransferase 158<sup>Val/Val</sup> Genotype

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The tendency to choose lesser immediate benefits over greater long-term benefits characterizes alcoholism and other addictive disorders. However, despite its medical and socioeconomic importance, little is known about its neurobiological mechanisms. Brain regions that are activated when deciding between immediate or delayed rewards have been identified (McClure et al., 2004, 2007), as have areas in which responses to reward stimuli predict a paper-and-pencil measure of temporal discounting (Hariri et al., 2006). These studies assume “hot” and “cool” response selection systems, with the hot system proposed to generate impulsive choices in the presence of a proximate reward. However, to date, brain regions in which the magnitude of activity during decision making reliably predicts intertemporal choice behavior have not been identified. Here we address this question in sober alcoholics and non-substance-abusing control subjects and show that immediate reward bias directly scales with the magnitude of functional magnetic resonance imaging bold oxygen level-dependent (BOLD) signal during decision making at sites within the posterior parietal cortex (PPC), dorsal prefrontal cortex (dPFC), and rostral parahippocampal gyrus regions. Conversely, the tendency of an individual to wait for a larger, delayed reward correlates directly with BOLD signal in the lateral orbitofrontal cortex. In addition, genotype at the Val158Met polymorphism of the catechol-O-methyltransferase gene predicts both impulsive choice behavior and activity levels in the dPFC and PPC during decision making. These genotype effects remained significant after controlling for alcohol abuse history. These results shed new light on the neurobiological underpinnings of temporal discounting behavior and identify novel behavioral and neural consequences of genetic variation in dopamine metabolism.

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# Parietal Lobe and Episodic Memory: Bilateral Damage Causes Impaired Free Recall of Autobiographical Memory

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Does the parietal lobe have a critical role in memory? The neuroimaging literature indicates that it has an important role, especially in episodic memory. However, the neuropsychological literature suggests that its role is more limited to attentional, spatial, or imagery aspects of memory. Here, we present data to adjudicate this disagreement. Two patients with bilateral parietal lobe damage received detailed assessments of their autobiographical memories. The results show that although both patients easily recalled various memories, their freely recalled memories were relatively impoverished, lacking in detail. This deficit was ubiquitous, and not limited to spatial or perceptual aspects of memory. The memory deficit disappeared when memory was specifically probed by asking pointed questions. Additional tests show that it is unlikely that their free recall deficit can be explained by general mental imagery problems. In sum, the parietal lobe appears to have a critical role in recollection aspects of episodic memory.

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# Asymmetry of Anticipatory Activity in Visual Cortex Predicts the Locus of Attention and Perception

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Humans can use advance information to direct spatial attention before stimulus presentation and respond more accurately to stimuli at the attended location compared with unattended locations. Likewise, spatially directed attention is associated with anticipatory activity in the portion of visual cortex representing the attended location. It is unknown, however, whether and how anticipatory signals predict the locus of spatial attention and perception. Here, we show that prestimulus, preparatory activity is highly correlated across regions representing attended and unattended locations. Comparing activity representing attended versus unattended locations, rather than measuring activity for only one location, dramatically improves the accuracy with which preparatory signals predict the locus of attention, largely by removing this positive correlation common across locations. In V3A, moreover, only the difference in activity between attended and unattended locations predicts whether upcoming visual stimuli will be accurately perceived. These results suggest that the locus of attention is coded in visual cortex by an asymmetry of anticipatory activity between attended and unattended locations and that this asymmetry predicts the accuracy of perception. This coding strategy may bias activity in downstream brain regions to represent the stimulus at the attended location.

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# Task-Related Interaction between Basal Ganglia and Cortical Dopamine Release

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Dopamine (DA) is a powerful neuromodulator for a wide variety of behaviors. Considerable evidence accumulated from rodent and monkey experiments over the last two decades suggests that DA activity in the frontal cortex is reciprocally linked to that in functionally related basal ganglia (BG) structures. However, the functional importance of this in humans is still unknown. To address this issue, we measured endogenous DA release using positron emission tomography in 15 healthy subjects as they practiced the first training session of a finger sequence learning task. Significant results were observed not only in striatal areas but also in extrastriatal “motor” regions, bilaterally. Faster learning was specifically coupled to lower DA release in the sensorimotor part of the globus pallidus pars interna (GPi) contralateral to the moving hand, which was paralleled by a higher increase in DA levels in the pre-supplementary motor area (pre-SMA). This finding provides original evidence supporting a motor-learning-related interaction between DA release in left GPi and pre-SMA, a mechanism that may also apply to other anatomically and functionally interconnected BG and frontal cortical areas as a function of behavior.

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# Focusing Effect of Acetylcholine on Neuroplasticity in the Human Motor Cortex

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Cholinergic neuromodulation is pivotal for arousal, attention, and cognitive processes. Loss or dysregulation of cholinergic inputs leads to cognitive impairments like those manifested in Alzheimer’s disease. Such dysfunction can be at least partially restored by an increase of acetylcholine (ACh). In animal studies, ACh selectively facilitates long-term excitability changes induced by feed-forward afferent input. Consequently, it has been hypothesized that ACh enhances the signal-to-noise ratio of input

processing. However, the neurophysiological foundation for its ability to enhance cognition in humans is not well documented. In this study we explore the effects of rivastigmine, a cholinesterase inhibitor, on global and synapse-specific forms of cortical plasticity induced by transcranial direct current stimulation (tDCS) and paired associative stimulation (PAS) on 10–12 healthy subjects, respectively. Rivastigmine essentially blocked the induction of the global excitability enhancement elicited by anodal tDCS and revealed a tendency to first reduce and then stabilize cathodal tDCS-induced inhibitory aftereffects. However, ACh enhanced the synapse-specific excitability enhancement produced by facilitatory PAS and consolidated the inhibitory PAS-induced excitability diminution. These findings are in line with a cholinergic focusing effect that optimizes the detection of relevant signals during information processing in humans.

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## Action and Outcome Encoding in the Primate Caudate Nucleus

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The basal ganglia appear to have a central role in reinforcement learning. Previous experiments, focusing on activity preceding movement execution, support the idea that dorsal striatal neurons bias action selection according to the expected values of actions. However, many phasically active striatal neurons respond at a time too late to initiate or select movements. Given the data suggesting a role for the basal ganglia in reinforcement learning, postmovement activity may therefore reflect evaluative processing important for learning the values of actions. To better understand these postmovement neurons, we determined whether individual striatal neurons encode information about saccade direction, whether a reward had been received, or both. We recorded from phasically active neurons in the caudate nucleus while monkeys performed a probabilistically rewarded delayed saccade task. Many neurons exhibited peak responses after saccade execution (77 of 149) that were often tuned for the direction of the preceding saccade (61 of 77). Of those neurons responding during the reward epoch, one subset showed direction tuning for the immediately preceding saccade (43 of 60), whereas another subset responded differentially on rewarded versus unrewarded trials (35 of 60). We found that there was relatively little overlap of these properties in individual neurons. The encoding of action and outcome was performed by largely separate populations of caudate neurons that were active after movement execution. Thus, striatal neurons active primarily after a movement appear to be segregated into two distinct groups that provide complimentary information about the outcomes of actions.

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## NEUROBIOLOGY OF DISEASE

## Dopamine Alters AMPA Receptor Synaptic Expression and Subunit Composition in Dopamine Neurons of the Ventral Tegmental Area Cultured with Prefrontal Cortex Neurons

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Excitatory synapses onto dopamine (DA) neurons of the ventral tegmental area (VTA) represent a critical site of psychostimulant-induced synaptic plasticity. This plasticity involves alterations in synaptic strength through AMPA receptor (AMPA) redistribution. Here, we report an *in vitro* model for studying regulation of AMPAR trafficking in DA neurons under control conditions and after elevation of DA levels, mimicking cocaine exposure. We used cocultures containing rat VTA neurons and prefrontal cortex (PFC) neurons from enhanced cyan fluorescent protein-expressing mice. In VTA-PFC cocultures, D<sub>1</sub> receptor activation (10 min) increased synaptic and nonsynaptic glutamate receptor subunit 1 (GluR1) and GluR2 surface expression on DA neurons. NMDA or AMPA receptor antagonists blocked this effect, and it was not observed in pure VTA cultures, suggesting that DA agonists acted on D<sub>1</sub> receptors on PFC neurons, altering their excitatory transmission onto VTA DA neurons and, thus, influencing AMPARs. To mimic the longer elevation in extracellular DA levels produced by systemic cocaine, cocultures were incubated with DA for 1 h. Synaptic GluR1 was increased 24 h later, reminiscent of the increased AMPA/NMDA ratio at excitatory synapses onto VTA DA neurons 24 h after cocaine injection (Ungless et al., 2001). In contrast, GluR2 was unchanged. Analysis of colocalization of surface GluR1–3 labeling suggested that control DA neurons express a substantial number of GluR1/2, GluR2/3, and homomeric GluR1 receptors and that the increase in surface AMPARs 24 h after DA exposure may in part reflect increased GluR1/3-containing receptors. These results help define the cellular basis for plasticity underlying the development of behavioral sensitization.

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## Omega-3 Fatty Acid Docosahexaenoic Acid Increases SorLA/LR11, a Sorting Protein with Reduced Expression in Sporadic Alzheimer's Disease (AD): Relevance to AD Prevention

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Environmental and genetic factors, notably ApoE4, contribute to the etiology of late-onset Alzheimer's disease (LOAD). Reduced mRNA and protein for an apolipoprotein E (ApoE) receptor family member, SorLA (LR11) has been found in LOAD but not early-onset AD, suggesting that LR11 loss is not secondary to pathology. LR11 is a neuronal sorting protein that reduces amyloid precursor protein (APP) trafficking to secretases that generate  $\beta$ -amyloid (A $\beta$ ). Genetic polymorphisms that reduce LR11 expression are associated with increased AD risk. However these polymorphisms account for only a fraction of cases with LR11 deficits, suggesting involvement of

environmental factors. Because lipoprotein receptors are typically lipid-regulated, we postulated that LR11 is regulated by docosahexaenoic acid (DHA), an essential  $\omega$ -3 fatty acid related to reduced AD risk and reduced A $\beta$  accumulation. In this study, we report that DHA significantly increases LR11 in multiple systems, including primary rat neurons, aged non-Tg mice and an aged DHA-depleted APPsw AD mouse model. DHA also increased LR11 in a human neuronal line. *In vivo* elevation of LR11 was also observed with dietary fish oil in young rats with insulin resistance, a model for type II diabetes, another AD risk factor. These data argue that DHA induction of LR11 does not require DHA-depleting diets and is not age dependent. Because reduced LR11 is known to increase A $\beta$  production and may be a significant genetic cause of LOAD, our results indicate that DHA increases in SorLA/LR11 levels may play an important role in preventing LOAD.

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## RGS9–2 Negatively Modulates L-3,4-Dihydroxyphenylalanine-Induced Dyskinesia in Experimental Parkinson's Disease

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Chronic L-dopa treatment of Parkinson's disease (PD) often leads to debilitating involuntary movements, termed L-dopa-induced dyskinesia (LID), mediated by dopamine (DA) receptors. RGS9–2 is a GTPase accelerating protein that inhibits DA D2 receptor-activated G proteins. Herein, we assess the functional role of RGS9–2 on LID. In monkeys, Western blot analysis of striatal extracts shows that RGS9–2 levels are not altered by MPTP-induced DA denervation and/or chronic L-dopa administration. In MPTP monkeys with LID, striatal RGS9–2 overexpression – achieved by viral vector injection into the striatum – diminishes the involuntary movement intensity without lessening the anti-parkinsonian effects of the D1/D2 receptor agonist L-dopa. In contrast, in these animals, striatal RGS9–2 overexpression diminishes both the involuntary movement intensity and the anti-parkinsonian effects of the D2/D3 receptor agonist ropinirole. In unilaterally 6-OHDA-lesioned rats with LID, we show that the time course of viral vector-mediated striatal RGS9–2 overexpression parallels the time course of improvement of L-dopa-induced involuntary movements. We also find that unilateral 6-OHDA-lesioned RGS9<sup>–/–</sup> mice are more susceptible to L-dopa-induced involuntary movements than unilateral 6-OHDA-lesioned RGS9<sup>+/+</sup> mice, albeit the rotational behavior – taken as an index of the anti-parkinsonian response – is similar between the two groups of mice. Together, these findings suggest that RGS9–2 plays a pivotal role in LID pathophysiology. However, the findings also suggest that increasing RGS9–2 expression and/or function in PD patients may only be a suitable therapeutic strategy to control involuntary movements induced by nonselective DA agonist such as L-dopa.

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## FMRP Phosphorylation Reveals an Immediate-Early Signaling Pathway Triggered by Group I mGluR and Mediated by PP2A

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Fragile X syndrome is a common form of inherited mental retardation and is caused by loss of fragile X mental retardation protein (FMRP), a selective RNA-binding protein that influences the translation of target messages. Here, we identify protein phosphatase 2A (PP2A) as an FMRP phosphatase and report rapid FMRP dephosphorylation after immediate group I metabotropic glutamate receptor (mGluR) stimulation (<1 min) in neurons caused by enhanced PP2A enzymatic activity. In contrast, extended mGluR activation (1–5 min) resulted in mammalian target of rapamycin (mTOR)-mediated PP2A suppression and FMRP rephosphorylation. These activity-dependent changes in FMRP phosphorylation were also observed in dendrites and showed a temporal correlation with the translational profile of select FMRP target transcripts. Collectively, these data reveal an immediate-early signaling pathway linking group I mGluR activity to rapid FMRP phosphorylation dynamics mediated by mTOR and PP2A.

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## Liver X Receptor Activation Enhances Cholesterol Loss from the Brain, Decreases Neuroinflammation, and Increases Survival of the NPC1 Mouse

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Although cholesterol is a major component of the CNS, there is little information on how or whether a change in sterol flux across the blood–brain barrier might alter neurodegeneration. In Niemann-Pick type C (NPC) disease, a mutation in NPC1 protein causes unesterified cholesterol to accumulate in the lysosomal compartment of every cell, including neurons and glia. Using the murine model of this disease, we used genetic and pharmacologic approaches in an attempt to alter cholesterol homeostasis

across the CNS. Genetic deletion of the sterol transporters ATP-binding cassette transporter A1 (ABCA1) and low-density lipoprotein receptor in the NPC1 mouse did not affect sterol balance or longevity. However, deletion of the nuclear receptor, liver X receptor  $\beta$  (LXR $\beta$ ), had an adverse effect on progression of the disease. We therefore tested the effects of increasing LXR activity by oral administration of a synthetic ligand for this transcription factor. Treatment with this LXR agonist increased cholesterol excretion out of brain from 17 to 49  $\mu\text{g}$  per day, slowed neurodegeneration, and prolonged life. This agonist did not alter synthesis of cholesterol or expression of genes associated with the formation of 24(S)-hydroxycholesterol or neurosteroids such as CYP46A1, 3 $\alpha$ HSD, and CYP11A1. However, levels of the sterol transporters ABCA1 and ATP-binding cassette transporter G1 were increased. Concomitantly, markers of neuroinflammation, CD14, MAC1, CD11c, and inducible nitric oxide synthase, were reduced, and microglia reverted from their amoeboid, active form to a ramified, resting configuration. Thus, LXR activation resulted in increased cholesterol excretion from the brain, decreased neuroinflammation, and deactivation of microglia to slow neurodegeneration and extend the lifespan of the NPC1 mouse.

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## Proprioceptive Sensory Neuropathy in Mice with a Mutation in the Cytoplasmic Dynein Heavy Chain 1 Gene

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Mice heterozygous for the radiation-induced Sprawling (*Swl*) mutation display an early-onset sensory neuropathy with muscle spindle deficiency. The lack of an H reflex despite normal motor nerve function in the hindlimbs of these mutants strongly suggests defective proprioception. Immunohistochemical analyses reveal that proprioceptive sensory neurons are severely compromised in the lumbar dorsal root ganglia of newborn *Swl*<sup>+</sup> mice, whereas motor neuron numbers remain unaltered even in aged animals. We have used positional cloning to identify a nine base-pair deletion in the cytoplasmic dynein heavy chain 1 gene (*Dync1h1*) in this mutant. Furthermore, we demonstrate that *Loa*<sup>+</sup> mice, which have previously been shown to carry a missense point mutation in *Dync1h1* that results in late-onset motor neuron loss, also present with a severe, early-onset proprioceptive sensory neuropathy. Interestingly, in contrast to the *Loa* mutation, the *Swl* mutation does not delay disease progression in a motor neuron disease mouse model overexpressing a human mutant superoxide dismutase (SOD1<sup>G93A</sup>) transgene. Together, we provide *in vivo* evidence that distinct mutations in cytoplasmic dynein can either result in a pure sensory neuropathy or in a sensory neuropathy with motor neuron involvement.

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