

# This Week in The Journal

## ● Cellular/Molecular

### *Characterization of Cough Receptors*

Stuart B. Mazzone, Sandra M. Reynolds, Nanako Mori, Marian Kollarik, David G. Farmer, et al.

(see pages 13662–13671)

Surprisingly little is known about the neural mechanism of cough. Although slow and fast adapting stretch receptors in the air passages have been hypothesized to trigger cough, stimuli that activate these receptors do not induce cough. Recently, a new receptor type responsive to touch and acid—stimuli that also evoke cough—was identified in guinea pigs. Mazzone et al. have further characterized these receptors. The cough receptors are A $\delta$  afferents that arise from the nodose ganglia and terminate in the extracellular matrix between the smooth muscle and epithelial layers of the trachea and larynx. Unlike other cells in the airways, cough receptors expressed the sodium pump  $\alpha_3$  subunit, and activity of this pump appeared to cause unique labeling of the receptors with the vital dye FM2–10. An  $\alpha_3$ -selective concentration of the sodium pump inhibitor ouabain reduced cough receptor excitability and cough evoked by acid or touch, without noticeably affecting other sodium-pump-dependent responses.



Terminals of cough receptors in guinea pig air passages labeled with FM2–10. See the article by Mazzone et al. for details.

## ▲ Development/Plasticity/Repair

### *Developmental Organization of Zebrafish Motor Networks*

David L. McLean and Joseph R. Fetcho  
(see pages 13566–13577)

As babies develop, their motor control becomes more refined: initially they make large, ballistic movements, but they gradually develop the ability to make smaller, more controlled movements. A similar pattern occurs in zebrafish: embryos make large head and tail movements during swimming, regardless of the speed; larvae produce slower swimming movements by moving only the tail. Previously, McLean et al. showed that spinal neurons controlling fast and slow larval movements are organized such that, as swimming speed increases, more dorsal neurons become active. Dorsal motor neurons are added to an expanding active pool, whereas ventral premotor interneurons are inhibited as more dorsal premotor interneurons become active. McLean and Fetcho now report that this topographical organization emerges gradually during development and reflects the development of behavior. The earliest appearing neurons, which drive fast, strong movements, are displaced dorsally by the subsequent development of more ventral neurons, which control slower, weaker movements.

## ■ Behavioral/Systems/Cognitive

### *Visual Enhancement of Speech Comprehension*

Luc H. Arnal, Benjamin Morillon, Christian A. Kell, and Anne-Lise Giraud  
(see pages 13445–13453)

Speech is easier to understand when the speaker is seen as well as heard. This could be because seeing mouth movements, which begin before sound is produced, allows the listener to anticipate the auditory stimulus. Additionally, because many spoken syllables are recognizable by mouth movements alone, visual inputs help the listener interpret ambiguous auditory inputs.

The first method of enhancement could be achieved by direct connections between visual-motion areas and auditory cortex, whereas the second would likely require comparison between the stimuli, perhaps in the superior temporal sulcus (STS), which responds to both auditory and visual speech. To distinguish these possibilities, Arnal et al. used magnetoencephalography and functional imaging to measure subjects' responses to videos in which the audio and visual components presented the same or different syllables. Their results suggest that the shortest latency visual enhancement of auditory responses does not require comparison, but comparison involving the STS becomes involved secondarily.

## ◆ Neurobiology of Disease

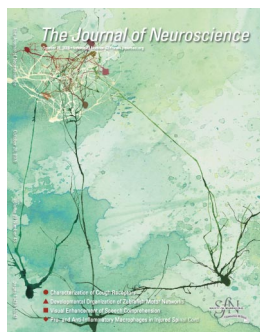
### *Pro- and Anti-Inflammatory Macrophages in Injured Spinal Cord*

Kristina A. Kigerl, John C. Gensel, Daniel P. Ankeny, Jessica K. Alexander, Dustin J. Donnelly, et al.  
(see pages 13435–13444)

Tissue damage causes release of proinflammatory cytokines that attract macrophages to the injured site. After cutaneous injuries, M1 macrophages appear first; they release additional proinflammatory cytokines as well as oxidative metabolites that kill microbes but can also damage healthy tissue. Subsequently, M2 macrophages appear; they limit inflammation and promote wound healing. Kigerl et al. report that M1 macrophages increase rapidly and persist for weeks *in vivo* after spinal cord injury, whereas M2 macrophages are less prevalent and disappear within a few days. Although both types of macrophages promoted neurite growth in cultured neurons, M1 macrophages were also toxic. In contrast, M2 macrophages more potently enhanced growth of long axons—even in the presence of inhibitory molecules—and did not kill neurons. Because much of the functional loss associated with spinal cord injury results from macrophage-associated inflammation, these results suggest that pushing macrophages toward an M2 phenotype could both limit damage and promote recovery.

# The Journal of Neuroscience

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**Cover legend:** An artistic rendition of a glomerulus in the mammalian olfactory bulb, with affiliated excitatory mitral cells (dark green) and external tufted (ET) cells (white) and inhibitory periglomerular (PG) cells (brown, pink, orange). Local dendrodendritic processing involving ET and PG cells appears to control whether the mitral cell output of a glomerulus is entirely 'on' or 'off.' Artwork by Greg Dunn, Neuroscience Graduate Program, University of Pennsylvania. For more information, see the article by Gire and Schoppa in this issue (pages 13454–13464).

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**Correction:** In the article “Suppression of the p75 Neurotrophin Receptor in Uninjured Sensory Neurons Reduces Neuropathic Pain after Nerve Injury” by Koichi Obata, Hirokazu Katsura, Jun Sakurai, Kimiko Kobayashi, Hiroki Yamanaka, Yi Dai, Tetsuo Fukuoka, and Koichi Noguchi, which appeared on pages 11974–11986 of the November 15, 2006 issue, there was an error in the legends for Figs. 1E, 2D, and 4, C and D. These legends described “ $n = 4$ .” However, the quantification of RT-PCR and Western blots was carried out from three, not four, samples in each experiment. All statistically significant values in all figures were obtained from three samples. Therefore, all data were scientifically correct, only the number of samples was incorrect.

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## Articles

### CELLULAR/MOLECULAR

## Control of On/Off Glomerular Signaling by a Local GABAergic Microcircuit in the Olfactory Bulb

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Odors are coded at the input level of the olfactory bulb by a spatial map of activated glomeruli, reflecting different odorant receptors (ORs) stimulated in the nose. Here we examined the function of local synaptic processing within glomeruli in transforming these input patterns into an output for the bulb, using patch-clamp recordings and calcium imaging in rat bulb slices. Two types of transformations were observed at glomeruli, the first of which produced a bimodal, “on/off” glomerular signal that varied probabilistically depending on olfactory receptor neuron (ORN) input levels. The bimodal response behavior was seen in glomerular synaptic responses, as well as in action potential (“spike”) firing, wherein all mitral cells affiliated with a glomerulus either engaged in prolonged spike bursts or did not spike at all. In addition, evidence was obtained that GABAergic periglomerular (PG) cells that surround a glomerulus can prevent activation of a glomerulus through inhibitory inputs targeted onto excitatory external tufted cells. The path of PG cell activation appeared to be confined to one glomerulus, such that ORNs at one glomerulus initiated inhibition of the same glomerulus. The observed glomerular “self-inhibition” provides a mechanism of filtering odor signals that would be an alternative to commonly proposed mechanisms of lateral inhibition between OR-specific glomeruli. In this case, selective suppression of weak odor signals could be achieved based on the difference in the input resistance of PG cells versus excitatory neurons at a glomerulus.

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## A Key Role for gp130 Expressed on Peripheral Sensory Nerves in Pathological Pain

Manfred Andratsch,<sup>1</sup> Norbert Mair,<sup>1</sup> Cristina E. Constantin,<sup>1</sup> Nadja Scherbakov,<sup>1</sup> Camilla Benetti,<sup>1</sup> Serena Quarta,<sup>1</sup> Christian Vogl,<sup>1</sup> Claudia A. Sailer,<sup>1</sup> Nurcan Üceyler,<sup>2</sup> Johannes Brockhaus,<sup>3</sup> Rudolf Martini,<sup>2</sup> Claudia Sommer,<sup>2</sup> Hanns Ulrich Zeilhofer,<sup>3</sup> Werner Müller,<sup>4</sup> Rohini Kuner,<sup>5</sup> John B. Davis,<sup>6</sup> Stefan Rose-John,<sup>7</sup> and Michaela Kress<sup>1</sup>

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Interleukin-6 (IL-6) is a key mediator of inflammation. Inhibitors of IL-6 or of its signal transducing receptor gp130 constitute a novel class of anti-inflammatory drugs, which raise great hopes for improved treatments of painful inflammatory diseases such as rheumatoid arthritis. IL-6 and gp130 may enhance pain not only indirectly through their proinflammatory actions but also through a direct action on nociceptors (i.e., on neurons activated by painful stimuli). We found indeed that the IL-6/gp130 ligand-receptor complex induced heat hypersensitivity both *in vitro* and *in vivo*. This process was mediated by activation of PKC- $\delta$  via Gab1/2/PI<sub>3</sub>K and subsequent regulation of TRPV1, a member of the transient receptor potential (TRP) family of ion channels. To assess the relevance of this direct pain promoting effect of IL-6, we generated conditional knock-out mice, which lack *gp130* specifically in nociceptors, and tested them in models of inflammatory and tumor-induced pain. These mice showed significantly reduced levels of inflammatory and tumor-induced pain but no changes in immune reactions or tumor growth. Our results uncover the significance of gp130 expressed in peripheral pain sensing neurons in the pathophysiology of major clinical pain disorders and suggest their use as novel pain relieving agents in inflammatory and tumor pain.

The Journal of Neuroscience, October 28, 2009 • 29(43):13473–13483

## Molecular Reconstruction of mGluR5a-Mediated Endocannabinoid Signaling Cascade in Single Rat Sympathetic Neurons

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Endocannabinoids (eCB) such as 2-arachidonylglycerol (2-AG) are lipid metabolites that are synthesized in a postsynaptic neurons and act upon CB<sub>1</sub> cannabinoid receptors (CB<sub>1</sub>R) in presynaptic nerve terminals. This retrograde transmission underlies several forms of short and long term synaptic plasticity within the CNS. Here, we constructed a model system based on isolated rat sympathetic neurons, in which an eCB signaling cascade could be studied in a reduced, spatially compact, and genetically malleable system. We constructed a complete eCB production/mobilization pathway by sequential addition of molecular components. Heterologous expression of four components was required for eCB production and detection: metabotropic glutamate receptor 5a (mGluR5a), Homer 2b, diacylglycerol lipase  $\alpha$ , and CB<sub>1</sub>R. In these neurons, application of L-glutamate produced voltage-dependent modulation of N-type Ca<sup>2+</sup> channels mediated by activation of CB<sub>1</sub>R. Using both molecular dissection and pharmacological agents, we provide evidence that activation of mGluR5a results in rapid enzymatic production of 2-AG followed by activation of CB<sub>1</sub>R. These experiments define the critical

elements required to recapitulate retrograde eCB production and signaling in a single peripheral neuron. Moreover, production/mobilization of eCB can be detected on a physiologically relevant time scale using electrophysiological techniques. The system provides a platform for testing candidate molecules underlying facilitation of eCB transport across the plasma membrane.

The Journal of Neuroscience, October 28, 2009 • 29(43):13603–13612

## Cytoplasmic Polyadenylation Element-Binding Protein Regulates Neurotrophin-3-Dependent $\beta$ -Catenin mRNA Translation in Developing Hippocampal Neurons

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Neuronal morphogenesis, the growth and arborization of neuronal processes, is an essential component of brain development. Two important but seemingly disparate components regulating neuronal morphology have previously been described. In the hippocampus, neurotrophins, particularly brain-derived neurotrophic factor (BDNF) and neurotrophin-3 (NT3), act to enhance cell growth and branching, while activity-induced branching was shown to be dependent upon intracellular  $\beta$ -catenin. We now describe a molecular link between NT3 stimulation and  $\beta$ -catenin increase in developing neurons and demonstrate that this process is required for the NT3-mediated increase in process branching. Here, we show that  $\beta$ -catenin is rapidly increased specifically in growth cones following NT3 stimulation. This increase in  $\beta$ -catenin is protein synthesis dependent and requires the activity of cytoplasmic polyadenylation element-binding protein-1 (CPEB1), an mRNA-binding protein that regulates mRNA translation. We find that CPEB1 protein binds  $\beta$ -catenin mRNA in a CPE-dependent manner and that both localize to growth cones of developing hippocampal neurons. Both the NT3-mediated rapid increase in  $\beta$ -catenin and process branching are abolished when CPEB1 function is inhibited. In addition, the NT3-mediated increase in  $\beta$ -catenin in growth cones is dependent upon internal calcium and the activity of CaMKII (calcium/calmodulin-dependent kinase II). Together, these results suggest that CPEB1 regulates  $\beta$ -catenin synthesis in neurons and may contribute to neuronal morphogenesis.

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## Progressive Postnatal Motoneuron Loss in Mice Lacking GDF-15

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Growth/differentiation factor-15 (GDF-15) is a widely expressed distant member of the TGF- $\beta$  superfamily with prominent neurotrophic effects on midbrain dopaminergic neurons. We show here that GDF-15-deficient mice exhibit progressive postnatal losses of spinal, facial, and trigeminal motoneurons. This deficit reaches a  $\sim$ 20% maximum at 6 months and is accompanied by losses of motor axons and significant impairment of rotarod skills. Similarly, sensory neurons in dorsal root ganglia (L4, L5) are reduced by 20%, whereas sympathetic neurons are not affected. GDF-15 is expressed and secreted by Schwann cells, retrogradely transported along adult sciatic nerve axons, and promotes survival of axotomized facial neurons as well as cultured motor, sensory, and sympathetic neurons. Despite striking similarities in the GDF-15 and CNTF knock-out phenotypes, expression levels of CNTF and other neurotrophic factors in the sciatic nerve were unaltered suggesting that GDF-15 is a genuine novel trophic factor for motor and sensory neurons.

The Journal of Neuroscience, October 28, 2009 • 29(43):13640–13648

## Dendritic Compartment and Neuronal Output Mode Determine Pathway-Specific Long-Term Potentiation in the Piriform Cortex

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The apical dendrite of layer 2/3 pyramidal cells in the piriform cortex receives two spatially distinct inputs: one projecting onto the distal apical dendrite in sensory layer 1a, the other targeting the proximal apical dendrite in layer 1b. We observe an expression gradient of A-type K<sup>+</sup> channels that weakens the backpropagating action potential-mediated depolarization in layer 1a compared with layer 1b. We find that the pairing of presynaptic and postsynaptic firing leads to significantly smaller Ca<sup>2+</sup> signals in the distal dendritic spines in layer 1a compared with the proximal spines in layer 1b. The consequence is a selective failure to induce long-term potentiation (LTP) in layer 1a, which can be rescued by pharmacological enhancement of action potential backpropagation. In contrast, LTP induction by pairing presynaptic and postsynaptic firing is possible in layer 1b but requires bursting of the postsynaptic cell. This output mode strongly depends on the balance of excitation and inhibition in the piriform cortex. We show, on the single-spine level, how the plasticity of functionally distinct synapses is gated by the intrinsic electrical properties of piriform cortex layer 2 pyramidal cell dendrites and the cellular output mode.

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# Selective Expression of a Sodium Pump Isozyme by Cough Receptors and Evidence for Its Essential Role in Regulating Cough

Stuart B. Mazzone,<sup>1</sup> Sandra M. Reynolds,<sup>2</sup> Nanako Mori,<sup>2</sup> Marian Kollarik,<sup>2</sup> David G. Farmer,<sup>2</sup> Allen C. Myers,<sup>2</sup> and Brendan J. Canning<sup>2</sup>

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We have identified a distinct subtype of airway vagal afferent nerve that plays an essential role in regulating the cough reflex. These afferents are exquisitely sensitive to punctate mechanical stimuli, acid, and decreases in extracellular chloride concentrations, but are insensitive to capsaicin, bradykinin, histamine, adenosine, serotonin, or changes in airway intraluminal pressures. In this study we used intravital imaging, retrograde neuronal tracing, and electrophysiological analyses to characterize the structural basis for their peculiar mechanical sensitivity and to further characterize the regulation of their excitability. In completing these experiments, we uncovered evidence for an essential role of an isozyme of Na<sup>+</sup>-K<sup>+</sup> ATPase in regulating cough. These vagal sensory neurons arise bilaterally from the nodose ganglia and are selectively and brilliantly stained intravitaly with the styryl dye FM2-10. Cough receptor terminations are confined and adherent to the extracellular matrix separating the airway epithelium and smooth muscle layers, a site of extensive remodeling in asthma and chronic obstructive pulmonary disease. The cough receptor terminals uniquely express the  $\alpha_3$  subunit of Na<sup>+</sup>-K<sup>+</sup> ATPase. Intravital staining of cough receptors by FM2-10, cough receptor excitability *in vitro*, and coughing *in vivo* are potently and selectively inhibited by the sodium pump inhibitor ouabain. These data provide the first detailed morphological description of the peripheral terminals of the sensory nerves regulating cough and identify a selective molecular target for their modulation.

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## Proopiomelanocortin Expression in both GABA and Glutamate Neurons

Shane T. Hentges,<sup>1</sup> Veronica Otero-Corchon,<sup>2</sup> Reagan L. Pennock,<sup>1</sup> Connie M. King,<sup>1</sup> and Malcolm J. Low<sup>2,3</sup>

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Proopiomelanocortin (POMC) neurons have been intensively studied because of their essential role in regulating energy balance and body weight. Many effects of POMC neurons can be attributed to their release of cognate neuropeptides from secretory granules in axon terminals. However, these neurons also synaptically release non-peptide neurotransmitters. The aim of this study was to settle the controversy whether there are separate populations of POMC neurons that release GABA or glutamate. Transgenic mice expressing a red fluorescent protein [Discosoma red (DsRed)] driven by *Pomc* neuronal regulatory elements (POMC–DsRed) were crossed to mice that expressed green fluorescent protein (gfp) in GABAergic neurons (GAD67–gfp). Approximately 40% of POMC neurons in the arcuate nucleus of the double-transgenic mice expressed the GAD67–gfp transgene. *In vitro* neurotransmitter release was detected using whole-cell electrophysiologic recordings in cultured GAD67–gfp-positive and GAD67–gfp-negative POMC neurons that had formed recurrent synapses (autapses). Autapses from GAD67–gfp-positive neurons were uniformly GABAergic. In contrast, autapses from the GAD67–gfp-negative POMC neurons exclusively exhibited postsynaptic currents mediated by glutamate. Together, these results indicate that there are two subpopulations of POMC neurons in the arcuate nucleus differentiated by their amino acid neurotransmitter phenotype. Whole-cell voltage-clamp recordings from POMC neurons in live brain slices indicated that GABAergic and glutamatergic POMC neurons are under similar presynaptic and postsynaptic regulation, although the GABAergic POMC neurons are smaller and have higher input resistance. GABAergic and glutamatergic POMC neurons may mediate distinct aspects of POMC neuron function, including the regulation of energy homeostasis.

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## Control of Cortical Axon Elongation by a GABA-Driven Ca<sup>2+</sup>/Calmodulin-Dependent Protein Kinase Cascade

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Ca<sup>2+</sup> signaling plays important roles during both axonal and dendritic growth. Yet whether and how Ca<sup>2+</sup> rises may trigger and contribute to the development of long-range cortical connections remains mostly unknown. Here, we demonstrate that two separate limbs of the Ca<sup>2+</sup>/calmodulin-dependent protein kinase cascade (CaMKK)–CaMKI cascades, CaMKK–CaMKI $\alpha$  and CaMKK–CaMKI $\gamma$ , critically coordinate axonal and dendritic morphogenesis of cortical neurons, respectively. The axon-specific morphological phenotype required a diffuse cytoplasmic localization and a strikingly  $\alpha$ -isoform-specific kinase activity of CaMKI. Unexpectedly, treatment with muscimol, a GABA<sub>A</sub> receptor agonist, selectively stimulated elongation of axons but not of dendrites, and the CaMKK–CaMKI $\alpha$  cascade critically mediated this axonogenic effect. Consistent with these findings, during early brain development, *in vivo* knockdown of CaMKI $\alpha$  significantly impaired the terminal axonal extension and thereby perturbed the refinement of the interhemispheric callosal projections into the contralateral cortices. Our findings thus indicate a novel role for the GABA-driven

CaMKK–CaMKI $\alpha$  cascade as a mechanism critical for accurate cortical axon pathfinding, an essential process that may contribute to fine-tuning the formation of interhemispheric connectivity during the perinatal development of the CNS.

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## DEVELOPMENT/PLASTICITY/REPAIR

# Classical Major Histocompatibility Complex Class I Molecules in Motoneurons: New Actors at the Neuromuscular Junction

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Major histocompatibility complex (MHC) class I molecules have fundamental functions in the immune system. Recent studies have suggested that these molecules may also have non-immune functions in the nervous system, in particular related to synaptic function and plasticity. Because adult motoneurons express mRNAs for MHC class I molecules, we have examined their subcellular expression pattern *in vivo* and their role for the synaptic connectivity of these neurons. We observed immunoreactivity for classical MHC class I (Ia) protein in motoneuron somata, but the predominant expression was found in axons and presynaptically at neuromuscular junctions (NMJs). Peripheral nerve lesion induced a strong increase of motoneuron MHC class Ia (H2-K<sup>b</sup>/D<sup>b</sup>) mRNA, indicating a role for MHC class Ia molecules during regeneration. Accordingly, there was an accumulation of MHC class Ia proteins at the cut ends and in growth cones of motor axons after lesion. In  $K^{b-/-}D^{b-/-}$  mice (lacking MHC class Ia molecules), the time course for recovery of grip ability in reinnervated muscles was significantly delayed. Muscles from  $K^{b-/-}D^{b-/-}$  mice displayed an increased density and a disturbed distribution of NMJs and fewer terminal Schwann cells/NMJ compared with wild-type mice. A population of Schwann cells in sciatic nerves expressed the paired Ig receptor B, which binds to MHC class I molecules. These results provide the first evidence that neuronal MHC class Ia molecules are present in motor axons, that they are important for organization of NMJs and motor recovery after nerve lesion, and that their actions may be mediated via Schwann cells.

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## Structural Changes between Seasons in the Songbird Auditory Forebrain

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The song control system (SCS) of seasonal songbirds shows remarkable seasonal plasticity. Male starlings (*Sturnus vulgaris*) sing throughout the year, but in the breeding season, when concentrations of testosterone are elevated, the song is highly sexually motivated. The main goal of this study was to investigate structural seasonal changes in regions involved in auditory processing and in socio-sexual behavior. Using *in vivo* Diffusion Tensor Imaging (DTI), we measured in breeding and nonbreeding seasons volume and tissue characteristics of several brain regions of nine adult male starlings. We demonstrate that the songbird brain exhibits an extreme seasonal plasticity not merely limited to the SCS. Volumetric analysis showed seasonal telencephalon volume changes and more importantly also a volumetric change in the caudal region of the nidopallium (NCM), a region analogous to the mammalian secondary auditory cortex. Analysis of the DTI data allowed detection of seasonal changes in cellular attributes in NCM and regions involved in social behavior. This study extends our view on a seasonally dynamic avian brain which not only hones its song control system but also auditory and social systems to be prepared for the breeding season.

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## Spinal Interneurons Differentiate Sequentially from Those Driving the Fastest Swimming Movements in Larval Zebrafish to Those Driving the Slowest Ones

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Studies of neuronal networks have revealed few general principles that link patterns of development with later functional roles. While investigating the neural control of movements, we recently discovered a topographic map in the spinal cord of larval zebrafish that relates the position of motoneurons and interneurons to their order of recruitment during swimming. Here, we show that the map reflects an orderly pattern of differentiation of neurons driving different movements. First, we use high-speed filming to show that large-amplitude swimming movements with bending along much of the body appear first, with smaller, regional swimming movements emerging later. Next, using whole-cell patch recordings, we demonstrate that the excitatory circuits that drive large-amplitude, fast swimming movements at larval stages are present and functional early on in embryos. Finally, we systematically assess the orderly emergence of spinal circuits according to swimming speed using transgenic fish expressing the photoconvertible protein Kaede to track neuronal differentiation *in vivo*. We conclude that a simple principle governs the development of spinal networks in which the neurons driving the fastest, most powerful swimming in larvae develop first with ones that drive increasingly weaker and slower larval movements layered on over time. Because the neurons are arranged by time of differentiation in the spinal cord, the result is a topographic map that represents the speed/strength of movements at which

neurons are recruited and the temporal emergence of networks. This pattern may represent a general feature of neuronal network development throughout the brain and spinal cord.

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## Differential Gene Expression in the Developing Lateral Geniculate Nucleus and Medial Geniculate Nucleus Reveals Novel Roles for *Zic4* and *Foxp2* in Visual and Auditory Pathway Development

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Primary sensory nuclei of the thalamus process and relay parallel channels of sensory input into the cortex. The developmental processes by which these nuclei acquire distinct functional roles are not well understood. To identify novel groups of genes with a potential role in differentiating two adjacent sensory nuclei, we performed a microarray screen comparing perinatal gene expression in the principal auditory relay nucleus, the medial geniculate nucleus (MGN), and principal visual relay nucleus, the lateral geniculate nucleus (LGN). We discovered and confirmed groups of highly ranked, differentially expressed genes with qRT-PCR and *in situ* hybridization. A functional role for *Zic4*, a transcription factor highly enriched in the LGN, was investigated using *Zic4*-null mice, which were found to have changes in topographic patterning of retinogeniculate projections. *Foxp2*, a transcriptional repressor expressed strongly in the MGN, was found to be positively regulated by activity in the MGN. These findings identify roles for two differentially expressed genes, *Zic4* and *Foxp2*, in visual and auditory pathway development. Finally, to test whether modality-specific patterns of gene expression are influenced by extrinsic patterns of input, we performed an additional microarray screen comparing the normal MGN to “rewired” MGN, in which normal auditory afferents are ablated and novel retinal inputs innervate the MGN. Data from this screen indicate that rewired MGN acquires some patterns of gene expression that are present in the developing LGN, including an upregulation of *Zic4* expression, as well as novel patterns of expression which may represent unique processes of cross-modal plasticity.

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## Permanent Functional Reorganization of Retinal Circuits Induced by Early Long-Term Visual Deprivation

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Early sensory experience shapes the functional and anatomical connectivity of neuronal networks. Light deprivation alters synaptic transmission and modifies light response properties in the visual system, from retinal circuits to higher visual centers. These effects are more pronounced during a critical period in juvenile life and are mostly reversed by restoring normal light conditions. Here we show that complete light deprivation, from birth to periods beyond the critical period, permanently modifies the receptive field properties of retinal ganglion cells. Visual deprivation reduced both the strength of light responses in ganglion cells and their receptive field size. Light deprivation produced an imbalance in the ratio of inhibitory to excitatory inputs, with a shift toward larger inhibitory conductances. Ganglion cell receptive fields in visually deprived animals showed a spatial mismatch of inhibitory and excitatory inputs and inhibitory inputs were highly scattered over the receptive field. These results indicate that visual experience early in life is critical for the refinement of retinal circuits and for appropriate signaling of the spatiotemporal properties of visual stimuli, thus influencing the response properties of neurons in higher visual centers and their processing of visual information.

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## $\beta$ -Catenin Signaling Levels in Progenitors Influence the Laminal Cell Fates of Projection Neurons

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The mechanisms underlying the timing of the laminar fate decisions during cortical neurogenesis remain poorly understood. Here we show that  $\beta$ -catenin signaling in cortical neural precursors can regulate the laminar fate of their daughters. In ventricular zone neural precursors,  $\beta$ -catenin signaling is higher when deep-layer neurons are being generated and lower when upper-layer neurons are being generated. Overactivation of  $\beta$ -catenin in cortical precursors midway through corticogenesis increased the relative production of deep-layer neurons, while inhibition of signaling increased the relative production of upper-layer neurons. Furthermore, in late-gestation upper-layer precursors, overactive  $\beta$ -catenin signaling was able to partially restore production of deep-layer neurons. These observations suggest that increased  $\beta$ -catenin signaling can reset the timing of cortical precursors to promote the production of deep-layer neurons, while inhibition of  $\beta$ -catenin signaling advances the timing to promote upper-layer production.

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## Dual Neural Routing of Visual Facilitation in Speech Processing

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Viewing our interlocutor facilitates speech perception, unlike for instance when we telephone. Several neural routes and mechanisms could account for this phenomenon. Using magnetoencephalography, we show that when seeing the interlocutor, latencies of auditory responses (M100) are the shorter the more predictable speech is from visual input, whether the auditory signal was congruent or not. Incongruence of auditory and visual input affected auditory responses ~20 ms after latency shortening was detected, indicating that initial content-dependent auditory facilitation by vision is followed by a feedback signal that reflects the error between expected and received auditory input (prediction error). We then used functional magnetic resonance imaging and confirmed that distinct routes of visual information to auditory processing underlie these two functional mechanisms. Functional connectivity between visual motion and auditory areas depended on the degree of visual predictability, whereas connectivity between the superior temporal sulcus and both auditory and visual motion areas was driven by audiovisual (AV) incongruence. These results establish two distinct mechanisms by which the brain uses potentially predictive visual information to improve auditory perception. A fast direct corticocortical pathway conveys visual motion parameters to auditory cortex, and a slower and indirect feedback pathway signals the error between visual prediction and auditory input.

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## Brain Hemispheres Selectively Track the Expected Value of Contralateral Options

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A main focus in economics is on binary choice situations, in which human agents have to choose between two alternative options. The classical view is that decision making consists of valuating each option, comparing the two expected values, and selecting the higher one. Some neural correlates of option values have been described in animals, but little is known about how they are represented in the human brain: are they integrated into a single center or distributed over different areas? To address this issue, we examined whether the expected values of two options, which were cued by visual symbols and chosen with either the left or right hand, could be distinguished using functional magnetic resonance imaging. The two options were linked to monetary rewards through probabilistic contingencies that subjects had to learn so as to maximize payoff. Learning curves were fitted with a standard computational model that updates, on a trial-by-trial basis, the value of the chosen option in proportion to a reward prediction error. Results show that during learning, left and right option values were specifically expressed in the contralateral ventral prefrontal cortex, regardless of the upcoming choice. We therefore suggest that expected values are represented in a distributed manner that respects the topography of the brain systems elicited by the available options.

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## Oscillations, Phase-of-Firing Coding, and Spike Timing-Dependent Plasticity: An Efficient Learning Scheme

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Recent experiments have established that information can be encoded in the spike times of neurons relative to the phase of a background oscillation in the local field potential—a phenomenon referred to as “phase-of-firing coding” (PoFC). These firing phase preferences could result from combining an oscillation in the input current with a stimulus-dependent static component that would produce the variations in preferred phase, but it remains unclear whether these phases are an epiphenomenon or really affect neuronal interactions—only then could they have a functional role. Here we show that PoFC has a major impact on downstream learning and decoding with the now well established spike timing-dependent plasticity (STDP). To be precise, we demonstrate with simulations how a single neuron equipped with STDP robustly detects a pattern of input currents automatically encoded in the phases of a subset of its afferents, and repeating at random intervals. Remarkably, learning is possible even when only a small fraction of the afferents (~10%) exhibits PoFC. The ability of STDP to detect repeating patterns had been noted before in continuous activity, but it turns out that oscillations greatly facilitate learning. A benchmark with more conventional rate-based codes demonstrates the superiority of oscillations and PoFC for both STDP-based learning and the speed of decoding: the oscillation partially formats the input spike times, so that they mainly depend on the current input currents, and can be efficiently learned by STDP and then recognized in just one oscillation cycle. This suggests a major functional role for oscillatory brain activity that has been widely reported experimentally.

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## Endogenous BDNF in the Dorsolateral Striatum Gates Alcohol Drinking

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We previously found that brain-derived neurotrophic factor (BDNF)-haplodeficient mice exhibit greater ethanol-induced place preference and psychomotor sensitization, and greater ethanol consumption after deprivation, than control mice. We further observed that, in mice, voluntary ethanol intake increases *BDNF* expression in the dorsal striatum (DS). Here, we determined whether BDNF within the DS regulates ethanol self-administration in Long-Evans rats trained to self-administer a 10% ethanol solution. We observed a greater increase in *BDNF* expression after ethanol self-administration in the dorsolateral striatum (DLS) than in the dorsomedial striatum (DMS). We further found that downregulation of endogenous BDNF using viral-mediated siRNA in the DLS, but not in the DMS, significantly increased ethanol self-administration. Infusion of exogenous BDNF (0.25  $\mu\text{g}/\mu\text{l}$ /side into the DMS; 0.25 and 0.75  $\mu\text{g}/\mu\text{l}$ /side into the DLS) attenuated responding for ethanol when infused 3 h before the beginning of the self-administration session. Although the decrease in ethanol intake was similar in the DLS and DMS, BDNF infused in the DLS, but not in the DMS, induced an early termination of the drinking episode. Furthermore, the action of BDNF in the DLS was specific for ethanol, as infusion of the neurotrophic factor in the DMS, but not DLS, resulted in a reduction of sucrose intake. Together, these findings demonstrate that the BDNF pathway within the DLS controls the level of ethanol self-administration. Importantly, our results suggest that an endogenous signaling pathway within the same brain region that mediates drug-taking behavior also plays a critical role in gating the level of ethanol intake.

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## Predicting Language Lateralization from Gray Matter

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It has long been predicted that the degree to which language is lateralized to the left or right hemisphere might be reflected in the underlying brain anatomy. We investigated this relationship on a voxel-by-voxel basis across the whole brain using structural and functional magnetic resonance images from 86 healthy participants. Structural images were converted to gray matter probability images, and language activation was assessed during naming and semantic decision. All images were spatially normalized to the same symmetrical template, and lateralization images were generated by subtracting right from left hemisphere signal at each voxel. We show that the degree to which language was left or right lateralized was positively correlated with the degree to which gray matter density was lateralized. *Post hoc* analyses revealed a general relationship between gray matter probability and blood oxygenation level-dependent signal. This is the first demonstration that structural brain scans can be used to predict language lateralization on a voxel-by-voxel basis in the normal healthy brain.

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## Human Reinforcement Learning Subdivides Structured Action Spaces by Learning Effector-Specific Values

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Humans and animals are endowed with a large number of effectors. Although this enables great behavioral flexibility, it presents an equally formidable reinforcement learning problem of discovering which actions are most valuable because of the high dimensionality of the action space. An unresolved question is how neural systems for reinforcement learning—such as prediction error signals for action valuation associated with dopamine and the striatum—can cope with this “curse of dimensionality.” We propose a reinforcement learning framework that allows for learned action valuations to be decomposed into effector-specific components when appropriate to a task, and test it by studying to what extent human behavior and blood oxygen level-dependent (BOLD) activity can exploit such a decomposition in a multieffector choice task. Subjects made simultaneous decisions with their left and right hands and received separate reward feedback for each hand movement. We found that choice behavior was better described by a learning model that decomposed the values of bimanual movements into separate values for each effector, rather than a traditional model that treated the bimanual actions as unitary with a single value. A decomposition of value into effector-specific components was also observed in value-related BOLD signaling, in the form of lateralized biases in striatal correlates of prediction error and anticipatory value correlates in the intraparietal sulcus. These results suggest that the human brain can use decomposed value representations to “divide and conquer” reinforcement learning over high-dimensional action spaces.

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## Adult-Born Hippocampal Dentate Granule Cells Undergoing Maturation Modulate Learning and Memory in the Brain

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Adult-born dentate granule cells (DGCs) contribute to learning and memory, yet it remains unknown when adult-born DGCs become involved in the cognitive processes. During neurogenesis, immature DGCs display distinctive physiological characteristics while undergoing morphological maturation before final integration into the neural circuits. The survival and activity of the adult-born DGCs can be influenced by the experience of the animal during a critical period when newborn DGCs are still immature.

To assess the temporal importance of adult neurogenesis, we developed a transgenic mouse model that allowed us to transiently reduce the numbers of adult-born DGCs in a temporally regulatable manner. We found that mice with a reduced population of adult-born DGCs at the immature stage were deficient in forming robust, long-term spatial memory and displayed impaired performance in extinction tasks. These results suggest that immature DGCs that undergo maturation make important contributions to learning and memory.

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## Broadband Shifts in Local Field Potential Power Spectra Are Correlated with Single-Neuron Spiking in Humans

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A fundamental question in neuroscience concerns the relation between the spiking of individual neurons and the aggregate electrical activity of neuronal ensembles as seen in local field potentials (LFPs). Because LFPs reflect both spiking activity and subthreshold events, this question is not simply one of data aggregation. Recording from 20 neurosurgical patients, we directly examined the relation between LFPs and neuronal spiking. Examining 2030 neurons in widespread brain regions, we found that firing rates were positively correlated with broadband (2–150 Hz) shifts in the LFP power spectrum. In contrast, narrowband oscillations correlated both positively and negatively with firing rates at different recording sites. Broadband power shifts were a more reliable predictor of neuronal spiking than narrowband power shifts. These findings suggest that broadband LFP power provides valuable information concerning neuronal activity beyond that contained in narrowband oscillations.

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## Perceptual Learning of Object Shape

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Recognition of objects is accomplished through the use of cues that depend on internal representations of familiar shapes. We used a paradigm of perceptual learning during visual search to explore what features human observers use to identify objects. Human subjects were trained to search for a target object embedded in an array of distractors, until their performance improved from near-chance levels to over 80% of trials in an object-specific manner. We determined the role of specific object components in the recognition of the object as a whole by measuring the transfer of learning from the trained object to other objects sharing components with it. Depending on the geometric relationship of the trained object with untrained objects, transfer to untrained objects was observed. Novel objects that shared a component with the trained object were identified at much higher levels than those that did not, and this could be used as an indicator of which features of the object were important for recognition. Training on an object also transferred to the components of the object when these components were embedded in an array of distractors of similar complexity. These results suggest that objects are not represented in a holistic manner during learning but that their individual components are encoded. Transfer between objects was not complete and occurred for more than one component, regardless of how well they distinguish the object from distractors. This suggests that a joint involvement of multiple components was necessary for full performance.

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## Pattern Motion Selectivity of Spiking Outputs and Local Field Potentials in Macaque Visual Cortex

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The dorsal pathway of the primate visual cortex is involved in the processing of motion signals that are useful for perception and behavior. Along this pathway, motion information is first measured by the primary visual cortex (V1), which sends specialized projections to extrastriate regions such as the middle temporal area (MT). Previous work with plaid stimuli has shown that most V1 neurons respond to the individual components of moving stimuli, whereas some MT neurons are capable of estimating the global motion of the pattern. In this work, we show that the majority of neurons in the medial superior temporal area (MST), which receives input from MT, have this pattern-selective property. Interestingly, the local field potentials (LFPs) measured simultaneously with the spikes often exhibit properties similar to that of the presumptive feedforward input to each area: in the high-gamma frequency band, the LFPs in MST are as component selective as the spiking outputs of MT, and MT LFPs have plaid responses that are similar to the spiking outputs of V1. In the lower LFP frequency bands (beta and low gamma), component selectivity is very common, and pattern selectivity is almost entirely absent in both MT and MST. Together, these results suggest a surprisingly strong link between the sensory tuning of cortical LFPs and afferent inputs, with important implications for the interpretation of imaging studies and for models of cortical function.

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# Effects of the Antipsychotic Risperidone on Dopamine Synthesis in Human Brain Measured by Positron Emission Tomography with L- $[\beta\text{-}^{11}\text{C}]\text{DOPA}$ : A Stabilizing Effect for Dopaminergic Neurotransmission?

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Effects of antipsychotic drugs have widely been considered to be mediated by blockade of postsynaptic dopamine  $D_2$  receptors. Effects of antipsychotics on presynaptic functions of dopaminergic neurotransmission might also be related to therapeutic effects of antipsychotics. To investigate the effects of antipsychotics on presynaptic functions of dopaminergic neurotransmission in relation with occupancy of dopamine  $D_2$  receptors, changes in dopamine synthesis capacity by antipsychotics and occupancy of dopamine  $D_2$  receptors were measured by positron emission tomography (PET) in healthy men. PET studies using  $[\text{}^{11}\text{C}]\text{raclopride}$  and L- $[\beta\text{-}^{11}\text{C}]\text{DOPA}$  were performed under resting condition and oral administration of single dose of the antipsychotic drug risperidone on separate days. Although occupancy of dopamine  $D_2$  receptors corresponding dose of risperidone was observed, the changes in dopamine synthesis capacity by the administration of risperidone were not significant, nor was the relation between the occupancy of dopamine  $D_2$  receptors and these changes. A significant negative correlation was observed between the baseline dopamine synthesis capacity and the changes in dopamine synthesis capacity by risperidone, indicating that this antipsychotic can be assumed to stabilize the dopamine synthesis capacity. The therapeutic effects of risperidone in schizophrenia might be related to such stabilizing effects on dopaminergic neurotransmission responsiveness.

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# What “Works” in Working Memory? Separate Systems for Selection and Updating of Critical Information

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Cognition depends critically on working memory, the active representation of a limited number of items over short periods of time. In addition to the maintenance of information during the course of cognitive processing, many tasks require that some of the items in working memory become transiently more important than others. Based on cognitive models of working memory, we hypothesized two complementary essential cognitive operations to achieve this: a selection operation that retrieves the most relevant item, and an updating operation that changes the focus of attention onto it. Using functional magnetic resonance imaging, high-resolution oculometry, and behavioral analysis, we demonstrate that these two operations are functionally and neuroanatomically dissociated. Updating the attentional focus elicited transient activation in the caudal superior frontal sulcus and posterior parietal cortex. In contrast, increasing demands on selection selectively modulated activation in rostral superior frontal sulcus and posterior cingulate/precuneus. We conclude that prioritizing one memory item over others invokes independent mechanisms of mnemonic retrieval and attentional focusing, each with its distinct neuroanatomical basis within frontal and parietal regions. These support the developing understanding of working memory as emerging from the interaction between memory and attentional systems.

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## NEUROBIOLOGY OF DISEASE

# Identification of Two Distinct Macrophage Subsets with Divergent Effects Causing either Neurotoxicity or Regeneration in the Injured Mouse Spinal Cord

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Macrophages dominate sites of CNS injury in which they promote both injury and repair. These divergent effects may be caused by distinct macrophage subsets, i.e., “classically activated” proinflammatory (M1) or “alternatively activated” anti-inflammatory (M2) cells. Here, we show that an M1 macrophage response is rapidly induced and then maintained at sites of traumatic spinal cord injury and that this response overwhelms a comparatively smaller and transient M2 macrophage response. The high M1/M2 macrophage ratio has significant implications for CNS repair. Indeed, we present novel data showing that only M1 macrophages are neurotoxic and M2 macrophages promote a regenerative growth response in adult sensory axons, even in the context of inhibitory substrates that dominate sites of CNS injury (e.g., proteoglycans and myelin). Together, these data suggest that polarizing the differentiation of resident microglia and infiltrating blood monocytes toward an M2 or “alternatively” activated macrophage phenotype could promote CNS repair while limiting secondary inflammatory-mediated injury.

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## Simvastatin Inhibits the Activation of p21<sup>ras</sup> and Prevents the Loss of Dopaminergic Neurons in a Mouse Model of Parkinson's Disease

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Parkinson's disease (PD) is second only to Alzheimer's disease as the most common devastating human neurodegenerative disorder. Despite intense investigation, no interdictive therapy is available for PD. We investigated whether simvastatin, a Food and Drug Administration-approved cholesterol-lowering drug, could protect against nigrostriatal degeneration after 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) intoxication to model PD in mice. First, MPP<sup>+</sup> induced the activation of p21<sup>ras</sup> and nuclear factor- $\kappa$ B (NF- $\kappa$ B) in mouse microglial cells. Inhibition of MPP<sup>+</sup>-induced activation of NF- $\kappa$ B by  $\Delta$ p21<sup>ras</sup>, a dominant-negative mutant of p21<sup>ras</sup>, supported the involvement of p21<sup>ras</sup> in MPP<sup>+</sup>-induced microglial activation of NF- $\kappa$ B. Interestingly, simvastatin attenuated activation of both p21<sup>ras</sup> and NF- $\kappa$ B in MPP<sup>+</sup>-stimulated microglial cells. Consistently, we found a very rapid activation of p21<sup>ras</sup> *in vivo* in the substantia nigra pars compacta of MPTP-intoxicated mice. However, after oral administration, simvastatin entered into the nigra, reduced nigral activation of p21<sup>ras</sup>, attenuated nigral activation of NF- $\kappa$ B, inhibited nigral expression of proinflammatory molecules, and suppressed nigral activation of glial cells. These findings paralleled dopaminergic neuronal protection, normalized striatal neurotransmitters, and improved motor functions in MPTP-intoxicated mice. Similarly, pravastatin, another cholesterol-lowering drug, suppressed microglial inflammatory responses and protected dopaminergic neurons in MPTP-intoxicated mice, but at levels less than simvastatin. Furthermore, both the statins administered 2 d after initiation of the disease were still capable of inhibiting the demise of dopaminergic neurons and concomitant loss of neurotransmitters, suggesting that statins are capable of slowing down the progression of neuronal loss in the MPTP mouse model. Therefore, we conclude that statins may be of therapeutic benefit for PD patients.

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## Beclin 1 Gene Transfer Activates Autophagy and Ameliorates the Neurodegenerative Pathology in $\alpha$ -Synuclein Models of Parkinson's and Lewy Body Diseases

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Accumulation of the synaptic protein  $\alpha$ -synuclein ( $\alpha$ -syn) is a hallmark of Parkinson's disease (PD) and Lewy body disease (LBD), a heterogeneous group of disorders with dementia and parkinsonism, where Alzheimer's disease and PD interact. Accumulation of  $\alpha$ -syn in these patients might be associated with alterations in the autophagy pathway. Therefore, we postulate that delivery of beclin 1, a regulator of the autophagy pathway, might constitute a strategy toward developing a therapy for LBD/PD. Overexpression of  $\alpha$ -syn from lentivirus transduction in a neuronal cell line resulted in lysosomal accumulation and alterations in autophagy. Coexpression of beclin 1 activated autophagy, reduced accumulation of  $\alpha$ -syn, and ameliorated associated neuritic alterations. The effects of beclin 1 overexpression on LC3 and  $\alpha$ -syn accumulation were partially blocked by 3-MA and completely blocked by bafilomycin A1. In contrast, rapamycin enhanced the effects of beclin 1. To evaluate the potential effects of activating autophagy *in vivo*, a lentivirus expressing beclin 1 was delivered to the brain of a  $\alpha$ -syn transgenic mouse. Neuropathological analysis demonstrated that beclin 1 injections ameliorated the synaptic and dendritic pathology in the tg mice and reduced the accumulation of  $\alpha$ -syn in the limbic system without any significant deleterious effects. This was accompanied by enhanced lysosomal activation and reduced alterations in the autophagy pathway. Thus, beclin 1 plays an important role in the intracellular degradation of  $\alpha$ -syn either directly or indirectly through the autophagy pathway and may present a novel therapeutic target for LBD/PD.

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## Intrabody Gene Therapy Ameliorates Motor, Cognitive, and Neuropathological Symptoms in Multiple Mouse Models of Huntington's Disease

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Huntington's disease (HD) is an autosomal dominant neurodegenerative disease resulting from the expansion of a glutamine repeat in the huntingtin (Htt) protein. Current therapies are directed at managing symptoms such as chorea and psychiatric disturbances. In an effort to develop a therapy directed at disease prevention we investigated the utility of highly specific, anti-Htt intracellular antibodies (intrabodies). We previously showed that V<sub>1</sub>12.3, an intrabody recognizing the N terminus of Htt, and Happ1, an intrabody recognizing the proline-rich domain of Htt, both reduce mHtt-induced toxicity and aggregation in cell culture and brain slice models of HD. Due to the different mechanisms of action of these two intrabodies, we then tested both in the brains of five mouse models of HD using a chimeric adeno-associated virus 2/1 (AAV2/1) vector with a modified CMV enhancer/chicken  $\beta$ -actin promoter. V<sub>1</sub>12.3 treatment, while beneficial in a lentiviral model of HD, has no effect on the YAC128 HD model and actually increases severity of phenotype and mortality in the R6/2 HD model. In contrast, Happ1 treatment confers significant beneficial effects in a variety of assays of motor and cognitive deficits. Happ1 also strongly ameliorates the neuropathology found in the lentiviral, R6/2, N171-82Q, YAC128, and BACHD models of HD. Moreover, Happ1 significantly prolongs the life span of N171-82Q mice. These results indicate that increasing the turnover of mHtt using AAV-Happ1 gene therapy represents a highly specific and effective treatment in diverse mouse models of HD.

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