

This Week in The Journal

● Cellular/Molecular

Cocaine and Its Withdrawal Alter MSN Inhibition and Spiking

Mami Otaka, Masago Ishikawa, Brian R. Lee, Lei Liu, Peter A. Neumann, et al.

(see pages 6753–6758)

Cocaine inhibits the dopamine transporter, thus prolonging activation of dopamine receptors. Elevated dopamine levels produce synaptic and homeostatic plasticity that outlasts the presence of cocaine, and additional plasticity occurs after drug withdrawal and re-exposure. Medium spiny neurons (MSNs) in the nucleus accumbens, which are involved in motivating goal-directed behavior, are important sites of drug-induced plasticity, and modulation of MSN firing is thought to contribute to the development of addiction. How various forms of plasticity are integrated to modify MSN output remains unclear, however. This week, Otaka et al. add a few pieces to the puzzle. In rats allowed to self-administer cocaine for 5 days, the ratio of evoked excitation to evoked inhibition (E/I) in MSNs was reduced, resulting in decreased spiking 1 day after access was denied. The amplitude of miniature (m) IPSCs was reduced after 21 days of withdrawal, but although E/I increased, MSN spiking remained low. Re-exposure to cocaine increased mIPSC frequency, returned evoked E/I to control levels, and increased spiking.

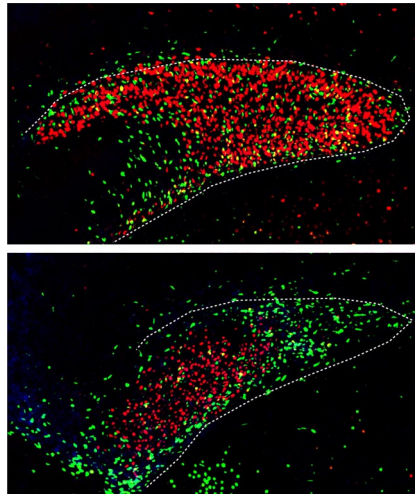
● Development/Plasticity/Repair

Bmp7 Promotes Subgranular Zone Expansion by Inducing Lef1

Youngshik Choe, Anastasiia Kozlova, Daniel Graf, and Samuel J. Pleasure

(see pages 6766–6775)

The subgranular zone between the hilus and granule cell layer of the dentate gyrus is one of two sites that produce neurons in adult mammals. This zone is formed by mitotic precursor cells that migrate from the subventricular zone at the earliest stages of dentate development. These precursors produce the neurons that form the inner granule cell layers of the dentate, and they continue to generate neurons throughout life. Two critical players in



Inhibiting Bmp7-induced signaling in dentate precursor cells on postnatal day 1 (bottom) reduces the number of cells expressing Lef1 (green) and a marker of dentate granule cells (red) compared to controls (top). See the article by Choe et al. for details.

dentate development are the secreted protein Wnt3a and its downstream transcription factor Lef1: Wnt3a-null mice lack hippocampi, and Lef1-null mice have few granule cells. Choe et al. now report that bone morphogenic protein 7 (Bmp7) feeds into this pathway by inducing Lef1 expression. Ectopic expression of Bmp7 in the medial cortical wall increased the production of dentate granule cells during embryogenesis, whereas decreasing meningeal expression of Bmp7 reduced numbers of Lef1-positive cells, proliferating precursors, and postmitotic granule cells in the developing dentate gyrus.

● Behavioral/Cognitive

Rats Localize Objects by Sensing Whisker Bending and Pushing

Lorenz Pammer, Daniel H. O'Connor, S. Andrew Hires, Nathan G. Clack, Daniel Huber, et al.

(see pages 6726–6741)

As a rodent's whisker presses against an object, the whisker bends, pushes laterally against the side of the whisker follicle, and pushes axially into the follicle. Because whiskers are tapered, the stresses produced in the follicle change at different rates depending on where the object con-

tacts the whisker. Stresses within follicles activate mechanoreceptors, and rodents use differential activation of these receptors to discern object shape and distance. Pammer et al. found that head-fixed mice could discriminate object positions differing by as little as 1 mm with a single whisker. To determine which mechanical variables are important for discriminating radial distance, they analyzed high-speed video recordings to estimate the bending moment, lateral force, and axial force produced at the base of whiskers by rigid and compliant objects placed at different positions. Their results suggest that mice use multiple variables—in particular, relative rates of change in bending moment and axial force—to determine object distance.

● Neurobiology of Disease

SorCS1 Mutations Disrupt APP Trafficking

Rachel F. Lane, John W. Steele, Dongming Cai, Michelle E. Ehrlich, Alan D. Attie, et al.

(see pages 7099–7107)

Amyloid precursor protein (APP) and the secretases that cleave it are transmembrane proteins that are processed, sorted, and trafficked through membranous organelles. Sequential cleavage of APP to generate A β is likely to occur in the endocytic pathway, and accumulating evidence suggests that defects in membrane trafficking in this pathway promote formation of A β 42, the oligomerization-prone peptide implicated in Alzheimer's disease (AD). Several proteins involved in membrane trafficking have been linked to AD, including SorCS1, which associates with APP and influences A β production. SorCS1 has been proposed to regulate either internalization of APP from the plasma membrane or trafficking of APP from endosomes to the trans-Golgi network (TGN). Lane et al. present data supporting the latter hypothesis. A mutation in the cytoplasmic tail of SorCS1c increased its plasma membrane levels without affecting those of APP. And another SorCS1c mutation increased levels of APP cleavage products in enlarged endosome-like compartments, reduced levels of these fragments in the TGN, but did not alter plasma membrane levels.

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Cover legend: Confocal projections showing ventral zebrafish olfactory bulbs at 11, 21, and 35 days after fertilization. The magnification and image settings are consistent among the three specimens shown. Olfactory glomeruli (red) were visualized with an antibody directed against synaptic vesicle protein 2 and axonal inputs from the olfactory epithelium (white) were visualized with an antibody against keyhole limpet hemocyanin. Some regions of the olfactory bulb remain virtually unchanged during this period of dramatic growth and reorganization, while alterations in other regions are influenced by olfactory experience. For more information, see the article by Braubach et al. (6905–6916).

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Exposure to Cocaine Regulates Inhibitory Synaptic Transmission in the Nucleus Accumbens

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Medium spiny neurons (MSNs) within the nucleus accumbens shell (NAc) function to gate and prioritize emotional/motivational arousals for behavioral output. The neuronal output of NAc MSNs is mainly determined by the integration of membrane excitability and excitatory/inhibitory synaptic inputs. Whereas cocaine-induced alterations at excitatory synapses and membrane excitability have been extensively examined, the overall functional output of NAc MSNs following cocaine exposure is still poorly defined because little is known about whether inhibitory synaptic input to these neurons is affected by cocaine. Here, our results demonstrate multidimensional alterations at inhibitory synapses in NAc neurons following cocaine self-administration in rats. Specifically, the amplitude of miniature IPSCs (mIPSCs) was decreased after 21 d withdrawal from 5 d cocaine self-administration. Upon re-exposure to cocaine after 21 d withdrawal, whereas the amplitude of mIPSCs remained downregulated, the frequency became significantly higher. Furthermore, the reversal potential of IPSCs, which was not significantly altered during withdrawal, became more hyperpolarized upon cocaine re-exposure. Moreover, the relative weight of excitatory and inhibitory inputs to NAc MSNs was significantly decreased after 1 d cocaine withdrawal, increased after 21 d withdrawal, and returned to the basal level upon cocaine re-exposure after 21 d withdrawal. These results, together with previous results showing cocaine-induced adaptations at excitatory synapses and intrinsic membrane excitability of NAc MSNs, may provide a relatively thorough picture of the functional state of NAc MSNs following cocaine exposure.

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Dopamine Triggers Heterosynaptic Plasticity

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As a classic neuromodulator, dopamine has long been thought to modulate, rather than trigger, synaptic plasticity. In contrast, our present results demonstrate that within the parallel projections of dopaminergic and GABAergic terminals from the ventral tegmental area to the nucleus accumbens core (NAcCo), action-potential-activated release of dopamine heterosynaptically triggers LTD at GABAergic synapses, which is likely mediated by activating presynaptically located dopamine D1 class receptors and expressed by inhibiting presynaptic release of GABA. Moreover, this dopamine-mediated heterosynaptic LTD is abolished after withdrawal from cocaine exposure. These results suggest that action-potential-dependent dopamine release triggers very different cellular consequences from those induced by volume release or pharmacological manipulation. Activation of the ventral tegmental area to NAcCo projections is essential for emotional and motivational responses. This dopamine-mediated LTD allows a flexible output of NAcCo neurons, whereas disruption of this LTD may contribute to the rigid emotional and motivational state observed in addicts during cocaine withdrawal.

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Tunnel Vision: Sharper Gradient of Spatial Attention in Autism

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Enhanced perception of detail has long been regarded a hallmark of autism spectrum conditions (ASC), but its origins are unknown. Normal sensitivity on all fundamental perceptual measures—visual acuity, contrast discrimination, and flicker detection—is strongly established in the literature. If individuals with ASC do not have superior low-level vision, how is perception of detail enhanced? We argue that this apparent paradox can be resolved by considering visual attention, which is known to enhance basic visual sensitivity, resulting in greater acuity and lower contrast thresholds. Here, we demonstrate that the focus of attention and concomitant enhancement of perception are sharper in human individuals with ASC than in matched controls. Using a simple visual acuity task embedded in a standard cueing paradigm, we mapped the spatial and temporal gradients of attentional enhancement by varying the distance and onset time of visual targets relative to an exogenous cue, which obligatorily captures attention. Individuals with ASC demonstrated a greater fall-off in performance with distance from the cue than controls, indicating a sharper spatial gradient of attention. Further, this sharpness was highly correlated with the severity of autistic symptoms in ASC, as well as autistic traits across both ASC and control groups. These findings establish the presence of a form of “tunnel vision” in ASC, with far-reaching implications for our understanding of the social and neurobiological aspects of autism.

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MicroRNAs Regulate Human Brain Endothelial Cell-Barrier Function in Inflammation: Implications for Multiple Sclerosis

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Blood–brain barrier (BBB) dysfunction is a major hallmark of many neurological diseases, including multiple sclerosis (MS). Using a genomics approach, we defined a microRNA signature that is diminished at the BBB of MS patients. In particular, miR-125a-5p is a key regulator of brain endothelial tightness and immune cell efflux. Our findings suggest that repair of a disturbed BBB through microRNAs may represent a novel avenue for effective treatment of MS.

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Deficit in Long-Term Synaptic Plasticity Is Rescued by a Computationally Predicted Stimulus Protocol

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Mutations in the gene encoding CREB-binding protein (CBP) cause deficits in long-term plasticity, learning, and memory. Here, long-term synaptic facilitation (LTF) at *Aplysia* sensorimotor synapses in cell culture was used as a model system to investigate methods for overcoming deficits in LTF produced by a CBP knockdown. Injecting CBP–siRNA into individual sensory neurons reduced CBP levels and impaired LTF produced by a standard protocol of five 5-min pulses of serotonin (5-HT) delivered at 20 min interstimulus intervals. A computational model, which simulated molecular processes underlying LTF induction, predicted a rescue protocol of five pulses of 5-HT at non-uniform interstimulus intervals that overcame the consequences of reduced CBP and restored LTF. These results suggest that complementary empirical and computational studies can identify methods for ameliorating impairments of learning attributable to molecular lesions.

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Articles

CELLULAR/MOLECULAR

Drosophila TRPA1 Functions in Temperature Control of Circadian Rhythm in Pacemaker Neurons

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Most animals from flies to humans count on circadian clocks to synchronize their physiology and behaviors. Daily light cycles are well known environmental cues for setting circadian rhythms. Warmer and cooler temperatures that mimic day and night are also effective in entraining circadian activity in most animals. Even vertebrate organisms can be induced to show circadian responses through exposure to temperature cycles. In poikilothermic animals such as *Drosophila*, temperature differences of only 2–3°C are sufficient to synchronize locomotor rhythms. However, the molecular sensors that participate in temperature regulation of circadian activity in fruit flies or other animals are enigmatic. It is also unclear whether such detectors are limited to the periphery or may be in the central brain. Here, we showed that *Drosophila* TRPA1 (transient receptor potential cation channel A1) was necessary for normal activity patterns during temperature cycles. The *trpA1* gene was expressed in a subset of pacemaker neurons in the central brain. In response to temperature entrainment, loss of *trpA1* impaired activity, and altered expression of the circadian clock protein period (Per) in a subset of pacemaker neurons. These findings underscore a role for a thermoTRP in temperature regulation that extends beyond avoidance of noxious or suboptimal temperatures.

The Journal of Neuroscience, April 17, 2013 • 33(16):6716–6725

Integrin $\alpha 3$ Is Required for Late Postnatal Stability of Dendrite Arbors, Dendritic Spines and Synapses, and Mouse Behavior

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Most dendrite branches and a large fraction of dendritic spines in the adult rodent forebrain are stable for extended periods of time. Destabilization of these structures compromises brain function and is a major contributing factor to psychiatric and neurodegenerative diseases. Integrins are a class of transmembrane extracellular matrix receptors that function as $\alpha\beta$ heterodimers and activate signaling cascades regulating the actin cytoskeleton. Here we identify integrin $\alpha 3$ as a key mediator of neuronal stability. Dendrites, dendritic spines, and synapses develop normally in mice with selective loss of integrin $\alpha 3$ in excitatory forebrain neurons, reaching their mature sizes and densities through postnatal day 21 (P21). However, by P42, integrin $\alpha 3$ mutant mice exhibit significant reductions in hippocampal dendrite arbor size and complexity, loss of dendritic spine and synapse densities, and impairments in hippocampal-dependent behavior. Furthermore, gene-dosage experiments demonstrate that integrin $\alpha 3$ interacts functionally with the Arg nonreceptor tyrosine kinase to activate p190RhoGAP, which inhibits RhoA GTPase and regulates hippocampal dendrite and synapse stability and mouse behavior. Together, our data support a fundamental role for integrin $\alpha 3$ in regulating dendrite arbor stability, synapse maintenance, and proper hippocampal function. In addition, these results provide a biochemical and structural explanation for the defects in long-term potentiation, learning, and memory reported previously in mice lacking integrin $\alpha 3$.

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The Adhesion-GPCR BAI1 Regulates Synaptogenesis by Controlling the Recruitment of the Par3/Tiam1 Polarity Complex to Synaptic Sites

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Excitatory synapses are polarized structures that primarily reside on dendritic spines in the brain. The small GTPase Rac1 regulates the development and plasticity of synapses and spines by modulating actin dynamics. By restricting the Rac1-guanine nucleotide exchange factor Tiam1 to spines, the polarity protein Par3 promotes synapse development by spatially controlling Rac1 activation. However, the mechanism for recruiting Par3 to spines is unknown. Here, we identify brain-specific angiogenesis inhibitor 1 (BAI1) as a synaptic adhesion GPCR that is required for synaptogenesis in mice and rats. We show that BAI1 interacts with Par3/Tiam1 and recruits these proteins to synaptic sites. BAI1 knockdown results in Par3/Tiam1 mislocalization and loss of activated Rac1 and filamentous actin from spines. Interestingly, BAI1 also mediates Rac-dependent engulfment in professional phagocytes through its interaction with a different Rac1-guanine nucleotide exchange factor module, ELMO/DOCK180. However, this interaction is dispensable for BAI1's role in synapse development because a BAI1 mutant that cannot interact with ELMO/DOCK180 rescues spine defects in BAI1-knockdown neurons, whereas a mutant that cannot interact with Par3/Tiam1 rescues neither spine defects nor Par3 localization. Further, overexpression of Tiam1 rescues BAI1 knockdown spine phenotypes. These results indicate that BAI1 plays an important role in synaptogenesis that is mechanistically distinct from its role in phagocytosis. Furthermore, our results provide the first example of a cell surface receptor that targets members of the PAR polarity complex to synapses.

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Acute Suppression of Spontaneous Neurotransmission Drives Synaptic Potentiation

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The impact of spontaneous neurotransmission on neuronal plasticity remains poorly understood. Here, we show that acute suppression of spontaneous NMDA receptor-mediated (NMDAR-mediated) neurotransmission potentiates synaptic responses in the CA1 regions of rat and mouse hippocampus. This potentiation requires protein synthesis, brain-derived neurotrophic factor expression, eukaryotic elongation factor-2 kinase function, and increased surface expression of AMPA receptors. Our behavioral studies link this same synaptic signaling pathway to the fast-acting antidepressant responses elicited by ketamine. We also show that selective neurotransmitter depletion from spontaneously recycling vesicles triggers synaptic potentiation via the same pathway as NMDAR blockade, demonstrating that presynaptic impairment of spontaneous release, without manipulation of evoked neurotransmission, is sufficient to elicit postsynaptic plasticity. These findings uncover an unexpectedly dynamic impact of spontaneous glutamate release on synaptic efficacy and provide new insight into a key synaptic substrate for rapid antidepressant action.

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Molecular Mechanism of Constitutive Endocytosis of Acid-Sensing Ion Channel 1a and Its Protective Function in Acidosis-Induced Neuronal Death

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Acid-sensing ion channels (ASICs) are proton-gated cation channels widely expressed in the peripheral and CNSs, which critically contribute to a variety of pathophysiological conditions that involve tissue acidosis, such as ischemic stroke and epileptic seizures. However, the trafficking mechanisms of ASICs and the related proteins remain largely unknown. Here, we demonstrate that ASIC1a, the main ASIC subunit in the brain, undergoes constitutive endocytosis in a clathrin- and dynamin-dependent manner in both mouse cortical neurons and heterologous cell cultures. The endocytosis of ASIC1a was inhibited by either the small molecular inhibitor tyrphostin A23 or knockdown of the core subunit of adaptor protein 2 (AP2) $\mu 2$ using RNA interference, supporting a clathrin-dependent endocytosis of ASIC1a. In addition, the internalization of ASIC1a was blocked by dominant-negative dynamin1 mutation K44A and the small molecular inhibitor dynasore, suggesting that it is also dynamin-dependent. We show that the membrane-proximal residues ⁴⁶⁵LCRRG⁴⁶⁹ at the cytoplasmic C terminus of ASIC1a are critical for interaction with the endogenous adaptor protein complex and inhibition of ASIC1a internalization strongly exacerbated acidosis-induced death of cortical neurons from wild-type but not ASIC1a knock-out mice. Together, these results reveal the molecular mechanism of ASIC1a internalization and suggest the importance of endocytic pathway in functional regulation of ASIC1a channels as well as neuronal damages mediated by these channels during neurodegeneration.

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DEVELOPMENT/PLASTICITY/REPAIR

Bone Morphogenic Protein Signaling Is a Major Determinant of Dentate Development

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To understand life-long neurogenesis in the dentate gyrus (DG), characterizing dentate neural stem cells and the signals controlling their development are crucial. In the present study, we show that bone morphogenic protein (Bmp) signaling is a critical regulator of embryonic dentate development, required for initiating neurogenesis in embryonic DG progenitors and required for the establishment of dentate neural stem cells postnatally. We tested the hypothesis that Bmp signaling regulates dentate development in part by controlling the expression of Lef1, a Wnt responsive transcription factor expressed in dentate stem cells and absolutely required for dentate granule cell production. Bmp activation through the Acvr1 receptor induced Lef1 expression and neurogenesis in the embryonic DG. Ectopic expression of Bmp7 in the embryonic midline increased DG neurogenesis and inhibition of local Bmp signaling decreased embryonic DG neurogenesis. Mice with selective loss of Bmp expression due to defective meningeal development or with selective conditional deletion of meningeal Bmp7 also have dentate developmental defects. Conditional deletion of Activin receptor type I (Acvr1) or Smad4 (a downstream target nuclear effector of Bmp signaling) in DG neural stem cells resulted in defects in the postnatal subgranular zone and reduced neurogenesis. These results suggest that Acvr1-mediated meningeal Bmp signaling regulates Lef1 expression in the dentate, regulating embryonic DG neurogenesis, DG neural stem cell niche formation, and maintenance.

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In Vivo Synaptic Scaling Is Mediated by GluA2-Lacking AMPA Receptors in the Embryonic Spinal Cord

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When spiking activity within a network is perturbed for hours to days, compensatory changes in synaptic strength are triggered that are thought to be important for the homeostatic maintenance of network or cellular spiking activity. In one form of this homeostatic plasticity, called synaptic scaling, all of a cell's AMPAergic miniature postsynaptic currents (mEPSCs) are increased or decreased by some scaling factor. Although synaptic scaling has been observed in a variety of systems, the mechanisms that underlie AMPAergic scaling have been controversial. Certain studies find that synaptic scaling is mediated by GluA2-lacking calcium receptors (CP-AMPA receptors), whereas others have found that scaling is mediated by GluA2-containing calcium-impermeable receptors (CI-AMPA receptors). Spontaneous network activity is observed in most developing circuits, and in the spinal cord this activity drives embryonic movements. Blocking spontaneous network activity in the chick embryo by infusing lidocaine *in vivo* triggers synaptic scaling in spinal motoneurons; here we show that AMPAergic scaling occurs through increases in mEPSC conductance that appear to be mediated by the insertion of GluA2-lacking AMPA receptors at the expense of GluA2-containing receptors. We have previously reported that *in vivo* blockade of GABA_A transmission, at a

developmental stage when GABA is excitatory, also triggered AMPAergic synaptic scaling. Here, we show that this form of AMPAergic scaling is also mediated by CP-AMPARs. These findings suggest that AMPAergic scaling triggered by blocking spiking activity or GABA_A receptor transmission represents similar phenomena, supporting the idea that activity blockade triggers scaling by reducing GABA_A transmission.

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Restoration of Retinal Structure and Function after Selective Photocoagulation

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CNS neurons change their connectivity to accommodate a changing environment, form memories, or respond to injury. Plasticity in the adult mammalian retina after injury or disease was thought to be limited to restructuring resulting in abnormal retinal anatomy and function. Here we report that neurons in the mammalian retina change their connectivity and restore normal retinal anatomy and function after injury. Patches of photoreceptors in the rabbit retina were destroyed by selective laser photocoagulation, leaving retinal inner neurons (bipolar, amacrine, horizontal, ganglion cells) intact. Photoreceptors located outside of the damaged zone migrated to make new functional connections with deafferented bipolar cells located inside the lesion. The new connections restored ON and OFF responses in deafferented ganglion cells. This finding extends the previously perceived limits of restorative plasticity in the adult retina and allows for new approaches to retinal laser therapy free of current detrimental side effects such as scotomata and scarring.

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LHX2 Is Necessary for the Maintenance of Optic Identity and for the Progression of Optic Morphogenesis

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Eye formation is regulated by a complex network of eye field transcription factors (EFTFs), including LIM-homeodomain gene LHX2. We disrupted LHX2 function at different stages during this process using a conditional knock-out strategy in mice. We find that LHX2 function is required in an ongoing fashion to maintain optic identity across multiple stages, from the formation of the optic vesicle to the differentiation of the neuroretina. At each stage, loss of *Lhx2* led to upregulation of a set of molecular markers that are normally expressed in the thalamic eminence and in the anterodorsal hypothalamus in a portion of the optic vesicle or retina. Furthermore, the longer LHX2 function was maintained, the further optic morphogenesis progressed. Early loss of function caused profound mispatterning of the entire telencephalic-optic-hypothalamic field, such that the optic vesicle became mispositioned and appeared to arise from the diencephalic-telencephalic boundary. At subsequent stages, loss of *Lhx2* did not affect optic vesicle position but caused arrest of optic cup formation. If *Lhx2* was selectively disrupted in the neuroretina from E11.5, the neuroretina showed gross dysmorphology along with aberrant expression of markers specific to the thalamic eminence and anterodorsal hypothalamus. Our findings indicate a continual requirement for LHX2 throughout the early stages of optic development, not only to maintain optic identity by suppressing alternative fates but also to mediate multiple steps of optic morphogenesis. These findings provide new insight into the anophthalmic phenotype of the *Lhx2* mutant and reveal novel roles for this transcription factor in eye development.

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The MicroRNA-17–92 Cluster Enhances Axonal Outgrowth in Embryonic Cortical Neurons

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MicroRNAs (miRNAs) regulate dendritogenesis and plasticity. However, the biological function of miRNAs in axons has not been extensively investigated. Here, using rat primary cortical neurons cultured in a microfluidic chamber, we found that the distal axons of the neurons expressed the miR-17–92 cluster, and proteins that regulate production and activity of mature miRNAs, Dicer and Argonaute 2, respectively, were present in the distal axons. Overexpression of the miR-17–92 cluster in cortical neurons substantially increased axonal outgrowth, whereas distal axonal attenuation of endogenous miR-19a, a key miRNA of the miR-17–92 cluster, with the miRNA hairpin inhibitor suppressed axonal outgrowth. Moreover, overexpression of the miR-17–92 cluster reduced phosphatase and tensin homolog (PTEN) proteins and elevated phosphorylated mammalian target of rapamycin (mTOR) in the distal axons. In contrast, distal axonal attenuation of miR-19a increased PTEN proteins and inactivated mTOR in the axons, but did not affect these protein levels in the cell bodies. Overexpression of PTEN and attenuation of endogenous PTEN prevailed over the enhancement and inhibitory effects of the miR-19a on axonal outgrowth, respectively. Axonal application of LY294002, a phosphoinositide3-kinase inhibitor, or rapamycin, an mTOR inhibitor, abolished axonal outgrowth enhanced by overexpression of the miR-17–92 cluster. Collectively, these findings demonstrate that axonal alteration of miR-17–92 cluster expression regulates axonal outgrowth and that local modulation of PTEN protein levels by miR-19a likely contributes to the axonal outgrowth.

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Experience-Dependent versus Experience-Independent Postembryonic Development of Distinct Groups of Zebrafish Olfactory Glomeruli

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Olfactory glomeruli are innervated with great precision by the axons of different olfactory sensory neuron types and act as functional units in odor information processing. Approximately 140 glomeruli are present in each olfactory bulb of adult zebrafish; these units consist of either highly stereotypic large glomeruli or smaller anatomically indistinguishable glomeruli. In the present study, we investigated developmental differences among these types of glomeruli. We observed that 10 large and individually identifiable glomeruli already developed before hatching, at 72 h after fertilization, in configurations that resembled their mature organization. However, the cross-sectional area of these glomeruli increased throughout larval development, and they eventually comprised the largest units in postlarval olfactory bulbs. In contrast, small and anatomically indistinguishable glomeruli formed only after hatching, apparently by segregating from five larger precursors that were identifiable during embryonic development. The differentiation of these small glomeruli proceeded with conspicuous variation in number and arrangement, both among larvae and between olfactory bulbs of the same individuals. To determine factors that might contribute to this variability, we investigated the effects of olfactory enrichment on the development of amino acid-responsive lateral glomeruli, which include both large and small units. Larvae reared in an amino acid-enriched environment had normal large lateral glomeruli, but the small lateral glomeruli were more numerous and displayed reduced cross-sectional areas compared with glomeruli in control animals. Our results suggest that large and small glomeruli mature via distinct developmental processes that may be differentially influenced by sensory experience.

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Calcineurin Signaling Mediates Activity-Dependent Relocation of the Axon Initial Segment

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The axon initial segment (AIS) is a specialized neuronal subcompartment located at the beginning of the axon that is crucially involved in both the generation of action potentials and the regulation of neuronal polarity. We recently showed that prolonged neuronal depolarization produces a distal shift of the entire AIS structure away from the cell body, a change associated with a decrease in neuronal excitability. Here, we used dissociated rat hippocampal cultures, with a major focus on the dentate granule cell (DGC) population, to explore the signaling pathways underlying activity-dependent relocation of the AIS. First, a pharmacological screen of voltage-gated calcium channels (VGCCs) showed that AIS relocation is triggered by activation of L-type Ca_v1 VGCCs with negligible contribution from any other VGCC subtypes. Additional pharmacological analysis revealed that downstream signaling events are mediated by the calcium-sensitive phosphatase calcineurin; inhibition of calcineurin with either FK506 or cyclosporin A totally abolished both depolarization- and optogenetically-induced activity-dependent AIS relocation. Furthermore, calcineurin activation is sufficient for AIS plasticity, because expression of a constitutively active form of the phosphatase resulted in relocation of the AIS of DGCs without a depolarizing stimulus. Finally, we assessed the role of calcineurin in other forms of depolarization-induced plasticity. Neither membrane resistance changes nor spine density changes were affected by FK506 treatment, suggesting that calcineurin acts via a separate pathway to modulate AIS plasticity. Together, these results emphasize calcineurin as a vital player in the regulation of intrinsic plasticity as governed by the AIS.

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SYSTEMS/CIRCUITS

A Brain Area for Visual Numerals

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Is there a distinct area within the human visual system that has a preferential response to numerals, as there is for faces, words, or scenes? We addressed this question using intracranial electrophysiological recordings and observed a significantly higher response in the high-frequency broadband range (high γ , 65–150 Hz) to visually presented numerals, compared with morphologically similar (i.e., letters and false fonts) or semantically and phonologically similar stimuli (i.e., number words and non-number words). Anatomically, this preferential response was consistently localized in the inferior temporal gyrus and anterior to the temporo-occipital incisure. This region lies within or close to the fMRI signal-dropout zone produced by the nearby auditory canal and venous sinus artifacts, an observation that may account for negative findings in previous fMRI studies of preferential response to numerals. Because visual numerals are culturally dependent symbols that are only learned through education, our novel finding of anatomically localized preferential response to such symbols provides a new example of acquired category-specific responses in the human visual system.

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Distinct Dendritic Arborization and *In Vivo* Firing Patterns of Parvalbumin-Expressing Basket Cells in the Hippocampal Area CA3

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Hippocampal CA3 area generates temporally structured network activity such as sharp waves and gamma and theta oscillations. Parvalbumin-expressing basket cells, making GABAergic synapses onto cell bodies and proximal dendrites of pyramidal cells, control pyramidal cell activity and participate in network oscillations in slice preparations, but their roles *in vivo* remain to be tested. We have recorded the spike timing of parvalbumin-expressing basket cells in areas CA2/3 of anesthetized rats in relation to CA3 putative pyramidal cell firing and activity locally and in area CA1. During theta oscillations, CA2/3 basket cells fired on the same phase as putative pyramidal cells, but, surprisingly, significantly later than downstream CA1 basket cells. This indicates a distinct modulation of CA3 and CA1 pyramidal cells by basket cells, which receive different inputs. We observed unexpectedly large dendritic arborization of CA2/3 basket cells in stratum lacunosum moleculare (33% of length, 29% surface, and 24% synaptic input from a total of ~35,000), different from the dendritic arborizations of CA1 basket cells. Area CA2/3 basket cells fired phase locked to both CA2/3 and CA1 gamma oscillations, and increased firing during CA1 sharp waves, thus supporting the role of CA3 networks in the generation of gamma oscillations and sharp waves. However, during ripples associated with sharp waves, firing of CA2/3 basket cells was phase locked only to local but not CA1 ripples, suggesting the independent generation of fast oscillations by basket cells in CA1 and CA2/3. The distinct spike timing of basket cells during oscillations in CA1 and CA2/3 suggests differences in synaptic inputs paralleled by differences in dendritic arborizations.

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Restricted Neural Plasticity in Vestibulospinal Pathways after Unilateral Labyrinthectomy as the Origin for Scoliotic Deformations

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Adolescent idiopathic scoliosis in humans is often associated with vestibulomotor deficits. Compatible with a vestibular origin, scoliotic deformations were provoked in adult *Xenopus* frogs by unilateral labyrinthectomy (UL) at larval stages. The aquatic ecophysiology and absence of body-weight-supporting limb proprioceptive signals in amphibian tadpoles as a potential sensory substitute after UL might be the cause for a persistent asymmetric descending vestibulospinal activity. Therefore, peripheral vestibular lesions in larval *Xenopus* were used to reveal the morphophysiological alterations at the cellular and network levels. As a result, spinal motor nerves that were modulated by the previously intact side before UL remained permanently silent during natural vestibular stimulation after the lesion. In addition, retrograde tracing of descending pathways revealed a loss of vestibular neurons on the ipsilesional side with crossed vestibulospinal projections. This loss facilitated a general mass imbalance in descending premotor activity and a permanent asymmetric motor drive to the axial musculature. Therefore, we propose that the persistent asymmetric contraction of trunk muscles exerts a constant, uncompensated differential mechanical pull on bilateral skeletal elements that enforces a distortion of the soft cartilaginous skeletal elements and bone shapes. This ultimately provokes severe scoliotic deformations during ontogenetic development similar to the human syndrome.

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Cortical-Like Receptive Fields in the Lateral Geniculate Nucleus of Marmoset Monkeys

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Most neurons in primary visual cortex (V1) exhibit high selectivity for the orientation of visual stimuli. In contrast, neurons in the main thalamic input to V1, the lateral geniculate nucleus (LGN), are considered to be only weakly orientation selective. Here we characterize a sparse population of cells in marmoset LGN that show orientation and spatial frequency selectivity as great as that of cells in V1. The recording position in LGN and histological reconstruction of these cells shows that they are part of the koniocellular (K) pathways. Accordingly we have named them K-o (“koniocellular-orientation”) cells. Most K-o cells prefer vertically oriented gratings; their contrast sensitivity and TF tuning are similar to those of parvocellular cells, and they receive negligible functional input from short wavelength-sensitive (“blue”) cone photoreceptors. Four K-o cells tested displayed binocular responses. Our results provide further evidence that in primates as in nonprimate mammals the cortical input streams include a diversity of visual representations. The presence of K-o cells increases functional homologies between K pathways in primates and “sluggish/W” pathways in nonprimate visual systems.

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Reach and Gaze Representations in Macaque Parietal and Premotor Grasp Areas

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Voluntary movements are frequently composed of several actions that are combined to achieve a specific behavior. For example, prehension involves reaching and grasping actions to transport the hand to a target to grasp or manipulate it. For controlling these actions, separate parietofrontal networks have been described for generating reaching and grasping actions. However, this separation has been challenged recently for the dorsomedial part of this network (area V6A). Here we report that the anterior intraparietal (AIP) and the rostral ventral premotor area (F5) in the macaque, which are both part of the dorsolateral parietofrontal network and causally linked to hand grasping movements, also represent spatial information during the execution of a reach-to-grasp task. In addition to grip type information, gaze and target positions were represented in AIP and F5 and could be readily decoded from single unit activity in these areas. Whereas the fraction of grip type tuned units increased toward movement execution, the number of cells with spatial representations stayed relatively constant throughout the task, although more prominently in AIP than in F5. Furthermore, the recorded target position signals were substantially encoded in retinotopic coordinates. In conclusion, the simultaneous presence of grasp-related and spatial information in AIP and F5 suggests at least a supportive role of these spatial signals for the planning of grasp actions. Whether these spatial signals in AIP and F5 also play a causal role for the planning of reach actions would need to be the subject of further investigations.

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Application of High-Frequency Repetitive Transcranial Magnetic Stimulation to the DLPFC Alters Human Prefrontal–Hippocampal Functional Interaction

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Neural plasticity is crucial for understanding the experience-dependent reorganization of brain regulatory circuits and the pathophysiology of schizophrenia. An important circuit-level feature derived from functional magnetic resonance imaging (fMRI) is prefrontal–hippocampal seeded connectivity during working memory, the best established intermediate connectivity phenotype of schizophrenia risk to date. The phenotype is a promising marker for the effects of plasticity-enhancing interventions, such as high-frequency repetitive transcranial magnetic stimulation (rTMS), and can be studied in healthy volunteers in the absence of illness-related confounds, but the relationship to brain plasticity is unexplored. We recruited 39 healthy volunteers to investigate the effects of 5 Hz rTMS on prefrontal–hippocampal coupling during working memory and rest. In a randomized and sham-controlled experiment, neuronavigation-guided rTMS was applied to the right dorsolateral prefrontal cortex (DLPFC), and fMRI and functional connectivity analyses [seeded connectivity and psychophysiological interaction (PPI)] were used as readouts. Moreover, the test–retest reliability of working-memory related connectivity markers was evaluated. rTMS provoked a significant decrease in seeded functional connectivity of the right DLPFC and left hippocampus during working memory that proved to be relatively time-invariant and robust. PPI analyses provided evidence for a nominal effect of rTMS and poor test–retest reliability. No effects on *n*-back-related activation and DLPFC–hippocampus resting-state connectivity were observed. These data provide the first *in vivo* evidence for the effects of plasticity induction on human prefrontal–hippocampal network dynamics, offer insights into the biological mechanisms of a well established intermediate phenotype linked to schizophrenia, and underscores the importance of the choice of outcome measures in test–retest designs.

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Neuronal Avalanches in the Resting MEG of the Human Brain

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What constitutes normal cortical dynamics in healthy human subjects is a major question in systems neuroscience. Numerous *in vitro* and *in vivo* animal studies have shown that ongoing or resting cortical dynamics are characterized by cascades of activity across many spatial scales, termed neuronal avalanches. In experiment and theory, avalanche dynamics are identified by two measures: (1) a power law in the size distribution of activity cascades with an exponent of $-3/2$ and (2) a branching parameter of the critical value of 1, reflecting balanced propagation of activity at the border of premature termination and potential blowup. Here we analyzed resting-state brain activity recorded using noninvasive magnetoencephalography (MEG) from 124 healthy human subjects and two different MEG facilities using different sensor technologies. We identified large deflections at single MEG sensors and combined them into spatiotemporal cascades on the sensor array using multiple timescales. Cascade size distributions obeyed power laws. For the timescale at which the branching parameter was close to 1, the power law exponent was $-3/2$. This relationship was robust to scaling and coarse graining of the sensor array. It was absent in phase-shuffled controls with the same power spectrum or empty scanner data. Our results demonstrate that normal cortical activity in healthy human subjects at rest organizes as neuronal avalanches and is well described by a critical branching process. Theory and experiment have shown that such critical, scale-free dynamics optimize information processing. Therefore, our findings imply that the human brain attains an optimal dynamical regime for information processing.

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The Mechanical Variables Underlying Object Localization along the Axis of the Whisker

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Rodents move their whiskers to locate objects in space. Here we used psychophysical methods to show that head-fixed mice can localize objects along the axis of a single whisker, the radial dimension, with one-millimeter precision. High-speed videography allowed us to estimate the forces and bending moments at the base of the whisker, which underlie radial distance measurement. Mice judged radial object location based on multiple touches. Both the number of touches (1–17) and the forces exerted by the pole on the whisker (up to 573 μN ; typical peak amplitude, 100 μN) varied greatly across trials. We manipulated the bending moment and lateral force pressing the whisker against the sides of the follicle and the axial force pushing the whisker into the follicle by varying the compliance of the object during behavior. The behavioral responses suggest that mice use multiple variables (bending moment, axial force, lateral force) to extract radial object localization. Characterization of whisker mechanics revealed that whisker bending stiffness decreases gradually with distance from the face over five orders of magnitude. As a result, the relative amplitudes of different stress variables change dramatically with radial object distance. Our data suggest that mice use distance-dependent whisker mechanics to estimate radial object location using an algorithm that does not rely on precise control of whisking, is robust to variability in whisker forces, and is independent of object compliance and object movement. More generally, our data imply that mice can measure the amplitudes of forces in the sensory follicles for tactile sensation.

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Connectivity-Based Parcellation of the Human Frontal Pole with Diffusion Tensor Imaging

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The human frontal pole (FP) approximately corresponds to Brodmann's area 10 and is a highly differentiated cortical area with unique cytoarchitectonic characteristics. However, its functional diversity is highly suggestive of the existence of functional subregions. Based on anatomical connection patterns derived from diffusion tensor imaging data, we applied a spectral clustering algorithm to parcellate the human right FP into orbital (FPo), lateral (FPl), and medial (FPM) subregions. This parcellation scheme was validated by corresponding analyses of the left FP and right FP in another independent dataset. Both visual observation and quantitative comparison of the anatomical connection patterns of the three FP subregions revealed that the FPo showed greater connection probabilities to brain regions of the social emotion network (SEN), including the orbitofrontal cortex, temporal pole, and amygdala, the FPl showed stronger connections to the dorsolateral prefrontal cortex of the cognitive processing network (CPN), and the FPM showed stronger connections to brain areas of the default mode network (DMN), including the anterior cingulate cortex and medial prefrontal cortex. We further analyzed the resting-state functional connectivity patterns of the three FP subregions. Consistent with the findings of anatomical connection analyses, the FPo was functionally correlated with the SEN, the FPl was correlated with the CPN, and the FPM was correlated with the DMN. These findings suggest that the human FP includes three separable subregions with different anatomical and functional connectivity patterns and that these subregions are involved in different brain functional networks and serve different functions.

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Acute Stress Contributes to Individual Differences in Pain and Pain-Related Brain Activity in Healthy and Chronic Pain Patients

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Individual differences in pain sensitivity and reactivity are well recognized but the underlying mechanisms are likely to be diverse. The phenomenon of stress-induced analgesia is well documented in animal research and individual variability in the stress response in humans may produce corresponding changes in pain. We assessed the magnitude of the acute stress response of 16 chronic back pain (CBP) patients and 18 healthy individuals exposed to noxious thermal stimulations administered in a functional magnetic resonance imaging experiment and tested its possible contribution to individual differences in pain perception. The temperature of the noxious stimulations was determined individually to control for differences in pain sensitivity. The two groups showed similar significant increases in reactive cortisol across the scanning session when compared with their basal levels collected over 7 consecutive days, suggesting normal hypothalamic–pituitary–adrenal axis reactivity to painful stressors in CBP patients. Critically, after controlling for any effect of group and stimulus temperature, individuals with stronger cortisol responses reported less pain

unpleasantness and showed reduced blood oxygenation level-dependent activation in nucleus accumbens at the stimulus onset and in the anterior mid-cingulate cortex (aMCC), the primary somatosensory cortex, and the posterior insula. Mediation analyses indicated that pain-related activity in the aMCC mediated the relationship between the reactive cortisol response and the pain unpleasantness. Psychophysiological interaction analysis further revealed that higher stress reactivity was associated with reduced functional connectivity between the aMCC and the brainstem. These findings suggest that acute stress modulates pain in humans and contributes to individual variability in pain affect and pain-related brain activity.

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Modulation of Beta Oscillations in the Subthalamic Nucleus with Prosaccades and Antisaccades in Parkinson's Disease

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Increased oscillations in the beta band are thought to be related to motor symptoms of Parkinson's disease (PD). Previous studies have shown that beta-band desynchronization in the subthalamic nucleus (STN) is reduced just before and during limb movements. While the STN is part of the basal ganglia (BG)-thalamocortical circuit controlling limb movements, it is also part of the BG-brainstem projection controlling saccadic eye movements. Late-stage PD patients have deficits in saccades in addition to difficulties with limb movements arising from impaired functions of the BG. We investigated saccade-related changes in beta-band (15–30 Hz) oscillatory activities in the human STN while PD patients performed visually guided prosaccades and antisaccades, the latter requiring suppression of reflexive responses and volitional initiation of saccades. We recorded local field potentials from deep brain stimulation electrodes implanted in the STN in human PD patients 1–5 d after surgery and compared prosaccades and antisaccades with these and with limb movements. Saccade-related beta-band desynchronizations were observed just before and during saccades in all subjects, suggesting that reduction of beta-band oscillatory activity in the STN is related to preparation and execution of saccades. Furthermore, beta-band desynchronizations for antisaccades started earlier, were sustained for longer periods, were of greater magnitude, and were observed more often than prosaccades. Beta-band desynchronization in the STN may reflect the additional processes associated with suppression of reflexive responses and volitional execution of saccades in the opposite direction.

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A Dynamic Deep Sleep Stage in *Drosophila*

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How might one determine whether simple animals such as flies sleep in stages? Sleep in mammals is a dynamic process involving different stages of sleep intensity, and these are typically associated with measurable changes in brain activity (Blake and Gerard, 1937; Rechtschaffen and Kales, 1968; Webb and Agnew, 1971). Evidence for different sleep stages in invertebrates remains elusive, even though it has been well established that many invertebrate species require sleep (Campbell and Tobler, 1984; Hendricks et al., 2000; Shaw et al., 2000; Sauer et al., 2003). Here we used electrophysiology and arousal-testing paradigms to show that the fruit fly, *Drosophila melanogaster*, transitions between deeper and lighter sleep within extended bouts of inactivity, with deeper sleep intensities after ~15 and ~30 min of inactivity. As in mammals, the timing and intensity of these dynamic sleep processes in flies is homeostatically regulated and modulated by behavioral experience. Two molecules linked to synaptic plasticity regulate the intensity of the first deep sleep stage. Optogenetic upregulation of cyclic adenosine monophosphate during the day increases sleep intensity at night, whereas loss of function of a molecule involved in synaptic pruning, the fragile-X mental retardation protein, increases sleep intensity during the day. Our results show that sleep is not homogenous in insects, and suggest that waking behavior and the associated synaptic plasticity mechanisms determine the timing and intensity of deep sleep stages in *Drosophila*.

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The Postsubiculum and Spatial Learning: The Role of Postsubicular Synaptic Activity and Synaptic Plasticity in Hippocampal Place Cell, Object, and Object-Location Memory

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Visual landmarks exert stimulus control over spatial behavior and the spatially tuned firing of place, head-direction, and grid cells in the rodent. However, the neural site of convergence for representations of landmarks and representations of space has yet to be identified. A potential site of plasticity underlying associations with landmarks is the postsubiculum. To test this, we blocked glutamatergic transmission in the rat postsubiculum with CNQX, or NMDA receptor-dependent plasticity with D-AP5. These infusions were sufficient to block evoked potentials from the lateral dorsal thalamus and long-term depression following tetanization of this input to the postsubiculum, respectively. In a second experiment, CNQX disrupted the stability of rat hippocampal place cell fields in a familiar environment. In a novel environment, blockade of plasticity with D-AP5 in the postsubiculum did not block the formation of a stable place field map following a 6 h delay. In a final behavioral experiment, postsubicular infusions of both compounds blocked object-location memory in the rat, but did not affect object recognition memory. These results suggest that the postsubiculum is

necessary for the recognition of familiar environments, and that NMDA receptor-dependent plasticity in the postsubiculum is required for the formation of new object-place associations that support recognition memory. However, plasticity in the postsubiculum is not necessary for the formation of new spatial maps.
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Attention Selectively Modifies the Representation of Individual Faces in the Human Brain

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Attention modifies neural tuning for low-level features, but it is unclear how attention influences tuning for complex stimuli. We investigated this question in humans using fMRI and face stimuli. Participants were shown six faces (F1–F6) along a morph continuum, and selectivity was quantified by constructing tuning curves for individual voxels. Face-selective voxels exhibited greater responses to their preferred face than to nonpreferred faces, particularly in posterior face areas. Anterior face areas instead displayed tuning for face categories: voxels in these areas preferred either the first (F1–F3) or second (F4–F6) half of the morph continuum. Next, we examined the effects of attention on voxel tuning by having subjects direct attention to one of the superimposed images of F1 and F6. We found that attention selectively enhanced responses in voxels preferring the attended face. Together, our results demonstrate that single voxels carry information about individual faces and that the nature of this information varies across cortical face areas. Additionally, we found that attention selectively enhances these representations. Our findings suggest that attention may act via a unitary principle of selective enhancement of responses to both simple and complex stimuli across multiple stages of the visual hierarchy.

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A Causal Role for the Extrastriate Body Area in Detecting People in Real-World Scenes

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People are extremely efficient at detecting relevant objects in complex natural scenes. In three experiments, we used functional magnetic resonance imaging-guided transcranial magnetic stimulation (TMS) to investigate the role of the extrastriate body area (EBA) in the detection of people in scenes. In Experiment 1, participants reported, in different blocks, whether people or cars were present in a briefly presented scene. Detection (d-prime) of people, but not of cars, was impaired after TMS over right EBA (rEBA; five pulses at –200, –100, 0, 100, 200 ms) compared with sham stimulation. In Experiment 2, we applied TMS either before (–200, –100 ms) or after (+100, +200) the scene onset. Poststimulus EBA stimulation impaired people detection relative to prestimulus EBA stimulation, while timing had no effect during sham stimulation. In Experiment 3, we examined anatomical specificity by comparing TMS over EBA with TMS over scene-selective transverse occipital sulcus (TOS). Two scenes were presented side by side, and response times to detect which scene contained people (or cars) were measured. For people detection, but not for car detection, response times during EBA stimulation were significantly slower than during TOS stimulation. Furthermore, rEBA stimulation led to an equivalent slowing of response times to left and right lateralized targets. These findings are the first to demonstrate the causal involvement of a category-selective human brain region in detecting its preferred stimulus category in natural scenes. They shed light on the nature of such regions, and help us understand how we efficiently extract socially relevant information from a complex input.

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Rapid Brain Responses Independently Predict Gain Maximization and Loss Minimization during Economic Decision Making

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Success in many decision-making scenarios depends on the ability to maximize gains and minimize losses. Even if an agent knows which cues lead to gains and which lead to losses, that agent could still make choices yielding suboptimal rewards. Here, by analyzing event-related potentials (ERPs) recorded in humans during a probabilistic gambling task, we show that individuals' behavioral tendencies to maximize gains and to minimize losses are associated with their ERP responses to the receipt of those gains and losses, respectively. We focused our analyses on ERP signals that predict behavioral adjustment: the frontocentral feedback-related negativity (FRN) and two P300 (P3) subcomponents, the frontocentral P3a and the parietal P3b. We found that, across participants, gain maximization was predicted by differences in amplitude of the P3b for suboptimal versus optimal gains (i.e., P3b amplitude difference between the least good and the best gains). Conversely, loss minimization was predicted by differences in the P3b amplitude to suboptimal versus optimal losses (i.e., difference between the worst and the least bad losses). Finally, we observed that the P3a and P3b, but not the FRN, predicted behavioral adjustment on subsequent trials, suggesting a specific adaptive mechanism by which prior experience may alter ensuing behavior. These findings indicate that individual differences in gain maximization and loss minimization are linked to individual differences in rapid neural responses to monetary outcomes.

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Depletion of Perineuronal Nets Enhances Recognition Memory and Long-Term Depression in the Perirhinal Cortex

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Perineuronal nets (PNNs) are extracellular matrix structures surrounding cortical neuronal cell bodies and proximal dendrites and are involved in the control of brain plasticity and the closure of critical periods. Expression of the link protein Crtl1/Hapln1 in neurons has recently been identified as the key event triggering the formation of PNNs. Here we show that the genetic attenuation of PNNs in adult brain Crtl1 knock-out mice enhances long-term object recognition memory and facilitates long-term depression in the perirhinal cortex, a neural correlate of object recognition memory. Identical prolongation of memory follows localized digestion of PNNs with chondroitinase ABC, an enzyme that degrades the chondroitin sulfate proteoglycan components of PNNs. The memory-enhancing effect of chondroitinase ABC treatment attenuated over time, suggesting that the regeneration of PNNs gradually restored control plasticity levels. Our findings indicate that PNNs regulate both memory and experience-driven synaptic plasticity in adulthood.

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Cognitive Control and the Salience Network: An Investigation of Error Processing and Effective Connectivity

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The Salience Network (SN) consists of the dorsal anterior cingulate cortex (dACC) and bilateral insulae. The network responds to behaviorally salient events, and an important question is how its nodes interact. One theory is that the dACC provides the earliest cortical signal of behaviorally salient events, such as errors. Alternatively, the anterior right insula (aRI) has been proposed to provide an early cognitive control signal. As these regions frequently coactivate, it has been difficult to disentangle their roles using conventional methods. Here we use dynamic causal modeling and a Bayesian model evidence technique to investigate the causal relationships between nodes in the SN after errors. Thirty-five human subjects performed the Simon task. The task has two conditions (congruent and incongruent) producing two distinct error types. Neural activity associated with errors was investigated using fMRI. Subjects made a total of 1319 congruent and 1617 incongruent errors. Errors resulted in robust activation of the SN. Dynamic causal modeling analyses demonstrated that input into the SN was most likely via the aRI for both error types and that the aRI was the only region intrinsically connected to both other nodes. Only incongruent errors produced behavioral adaptation, and the strength of the connection between the dACC and the left insulae correlated with the extent of this behavioral change. We conclude that the aRI, not the dACC, drives the SN after errors on an attentionally demanding task, and that a change in the effective connectivity of the dACC is associated with behavioral adaptation after errors.

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NEUROBIOLOGY OF DISEASE

WDR81 Is Necessary for Purkinje and Photoreceptor Cell Survival

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The gene encoding the WD repeat-containing protein 81 (WDR81) has recently been described as the disease locus in a consanguineous family that suffers from cerebellar ataxia, mental retardation, and quadrupedal locomotion syndrome (CAMRQ2). Adult mice from the *N*-ethyl-*N*-nitrosourea-induced mutant mouse line *nur5* display tremor and an abnormal gait, as well as Purkinje cell degeneration and photoreceptor cell loss. We have used polymorphic marker mapping to demonstrate that affected *nur5* mice carry a missense mutation, L1349P, in the *Wdr81* gene. Moreover, homozygous *nur5* mice that carry a wild-type *Wdr81* transgene are rescued from the abnormal phenotype, indicating that *Wdr81* is the causative gene in *nur5*. WDR81 is expressed in Purkinje cells and photoreceptor cells, among other CNS neurons, and like the human mutation, the *nur5* modification lies in the predicted major facilitator superfamily domain of the WDR81 protein. Electron microscopy analysis revealed that a subset of mitochondria in Purkinje cell dendrites of the mutant animals displayed an aberrant, large spheroid-like structure. Moreover, immunoelectron microscopy and analysis of

mitochondrial-enriched cerebellum fractions indicate that WDR81 is localized in mitochondria of Purkinje cell neurons. Because the *nur5* mouse mutant demonstrates phenotypic similarities to the human disease, it provides a valuable genetic model for elucidating the pathogenic mechanism of the *WDR81* mutation in CAMRQ2. The Journal of Neuroscience, April 17, 2013 • 33(16):6834–6844

Sodium Channel Cleavage Is Associated with Aberrant Neuronal Activity and Cognitive Deficits in a Mouse Model of Alzheimer's Disease

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BACE1 is the rate-limiting enzyme that cleaves amyloid precursor protein (APP) to produce the amyloid β peptides that accumulate in Alzheimer's disease (AD). BACE1, which is elevated in AD patients and APP transgenic mice, also cleaves the β 2-subunit of voltage-gated sodium channels (Nav β 2). Although increased BACE1 levels are associated with Nav β 2 cleavage in AD patients, whether Nav β 2 cleavage occurs in APP mice had not yet been examined. Such a finding would be of interest because of its potential impact on neuronal activity: previous studies demonstrated that BACE1-overexpressing mice exhibit excessive cleavage of Nav β 2 and reduced sodium current density, but the phenotype associated with loss of function mutations in either Nav β -subunits or pore-forming α -subunits is epilepsy. Because mounting evidence suggests that epileptiform activity may play an important role in the development of AD-related cognitive deficits, we examined whether enhanced cleavage of Nav β 2 occurs in APP transgenic mice, and whether it is associated with aberrant neuronal activity and cognitive deficits. We found increased levels of BACE1 expression and Nav β 2 cleavage fragments in cortical lysates from APP transgenic mice, as well as associated alterations in Nav1.1 α expression and localization. Both pyramidal neurons and inhibitory interneurons exhibited evidence of increased Nav β 2 cleavage. Moreover, the magnitude of alterations in sodium channel subunits was associated with aberrant EEG activity and impairments in the Morris water maze. Together, these results suggest that altered processing of voltage-gated sodium channels may contribute to aberrant neuronal activity and cognitive deficits in AD.

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MER5101, a Novel A β 1-15:DT Conjugate Vaccine, Generates a Robust Anti-A β Antibody Response and Attenuates A β Pathology and Cognitive Deficits in APPswe/PS1 Δ E9 Transgenic Mice

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Active amyloid- β (A β) immunotherapy is under investigation to prevent or treat early Alzheimer's disease (AD). In 2002, a Phase II clinical trial (AN1792) was halted due to meningoencephalitis in ~6% of the AD patients, possibly caused by a T-cell-mediated immunological response. Thus, generating a vaccine that safely generates high anti-A β antibody levels in the elderly is required. In this study, MER5101, a novel conjugate of A β 1-15 peptide (a B-cell epitope fragment) conjugated to an immunogenic carrier protein, diphtheria toxoid (DT), and formulated in a nanoparticulate emulsion-based adjuvant, was administered to 10-month-old APPswe/PS1 Δ E9 transgenic (Tg) and wild-type (Wt) mice. High anti-A β antibody levels were observed in both vaccinated APPswe/PS1 Δ E9 Tg and Wt mice. Antibody isotypes were mainly IgG1 and IgG2b, suggesting a Th2-biased response. Restimulation of splenocytes with the A β 1-15:DT conjugate resulted in a strong proliferative response, whereas proliferation was absent after restimulation with A β 1-15 or A β 1-40/42 peptides, indicating a cellular immune response against DT while avoiding an A β -specific T-cell response. Moreover, significant reductions in cerebral A β plaque burden, accompanied by attenuated microglial activation and increased synaptic density, were observed in MER5101-vaccinated APPswe/PS1 Δ E9 Tg mice compared with Tg adjuvant controls. Last, MER5101-immunized APPswe/PS1 Δ E9 Tg mice showed improvement of cognitive deficits in both contextual fear conditioning and the Morris water maze. Our novel, highly immunogenic A β conjugate vaccine, MER5101, shows promise for improving A β vaccine safety and efficacy and therefore, may be useful for preventing and/or treating early AD.

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Protein Sorting Motifs in the Cytoplasmic Tail of SorCS1 Control Generation of Alzheimer's Amyloid- β Peptide

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Endosomal sorting of the Alzheimer amyloid precursor protein (APP) plays a key role in the biogenesis of the amyloid- β (A β) peptide. Genetic lesions underlying Alzheimer's disease (AD) can act by interfering with this physiological process. Specifically, proteins involved in trafficking between endosomal compartments and the *trans*-Golgi network (TGN) [including the retromer complex (Vps35, Vps26) and its putative receptors (sortilin, SorL1, SorCS1)] have been implicated in the molecular pathology of late-onset AD. Previously, we demonstrated a role for SorCS1 in APP metabolism and A β production and, while we implicated a role for the retromer in this

regulation, the underlying mechanism remained poorly understood. Here, we provide evidence for a motif within the SorCS1c cytoplasmic tail that, when manipulated, results in perturbed sorting of APP and/or its fragments to endosomal compartments, decreased retrograde TGN trafficking, and increased A β production in H4 neuroglioma cells. These perturbations apparently do not involve turnover of the cell surface APP pool, but rather they involve intracellular APP and/or its fragments, downstream of APP endocytosis.

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