This Week in The Journal

● Cellular/Molecular

Complexin Knock-Out Reduces Release Probability in Auditory Neurons

Nicola Strenzke, Soham Chanda, Cornelia Kopp-Scheinpflug, Darina Khimich, Kerstin Reim, Anna V. Bulankina, Andreas Neef, Fred Wolf, Nils Brose, Matthew A. Xu-Friedman, and Tobias Moser

(see pages 7991–8004)

Complexins are hypothesized to clamp synaptic vesicles in a readily releasable state at the plasma membrane until increases in calcium trigger rapid, synchronous release. Strenzke et al. report that knock-out of complexin I impaired hearing in mice. In normal mice, complexin I was present in the synaptic terminals of spiral ganglion neurons (SGNs) in the cochlear nucleus. Knock-out of complexin appeared to reduce release probability at these synapses: miniature EPSC frequency was reduced, paired-pulse depression was absent, spike latency was reduced, and spike timing was more variable. Evoked EPSCs were smaller in cochlear nucleus neurons of knock-outs, and the probability of spiking was reduced at the onset of SGN stimulation. Additionally, asynchronous release was increased, allowing spiking to continue after SGN stimulation ended. These data support the hypothesis that complexins enable precisely timed, reliable spiking, which is required for accurate representation of auditory inputs.

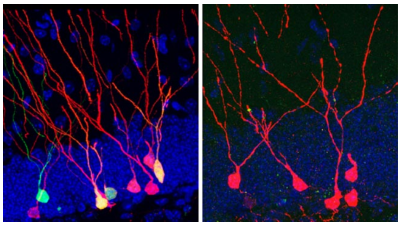
▲ Development/Plasticity/Repair

GABA-Mediated Excitation and CREB Promote Neuron Survival

Ravi Jagasia, Kathrin Steib, Elisabeth Englberger, Sabine Herold, Theresa Faus-Kessler, Michael Saxe, Fred H. Gage, Hongjun Song, and D. Chichung Lie

(see pages 7966–7977)

Adult neurogenesis contributes to learning and memory, and defects are linked to depression in humans. In rodents, most adult-born neurons die, but increased hippocampal activity can increase survival. GABA-mediated excitation promotes survival of adult-born neurons, and Jagasia et al. report that phosphorylation of the cAMP response element-binding protein (CREB) peaks during the developmental stage when GABA is excitatory. To investigate CREB's role in neuron survival, the authors inhibited CREB activity in a subset of adult-born neurons by injecting retroviruses encoding ACREB, a polypeptide that prevents DNA binding by CREB. ACREB reduced neuronal survival and caused abnormal dendritic development. Knocking down the Na^+–K^+–Cl^- cotransporter to make GABA inhibitory in newborn neurons reduced CREB phosphorylation and replicated the effects of ACREB. The effects of knockdown were rescued by coexpressing a highly active CREB mutant, suggesting that GABA-mediated excitation activates CREB to promote survival of adult-born neurons.



Adult-born neurons were transduced with viruses containing red fluorescent protein and either green fluorescent protein (GFP; left) or ACREB GFP (right). Neurons expressing ACREB GFP did not survive. See the article by Jagasia et al. for details.

■ Behavioral/Systems/Cognitive

Period 3 Genotype Affects Brain Activation After Sleep Loss

Gilles Vandewalle, Simon N. Archer, Catherine Wuillaume, Evelyne Balteau, Christian Degueldre, André Luxen, Pierre Maquet, and Derk-Jan Dijk

(see pages 7948–7956)

Sleep deprivation impairs memory, attention, and decision making. Functional magnetic resonance imaging (fMRI) has provided clues about the neural mechanisms responsible for this impairment, but the results can be difficult to interpret because people vary in their response to sleep deprivation. Some of this variability results from differences in the circadian clock gene *Period 3* (*Per3*): individuals homozygous for five repeats of a particular sequence (genotype $Per3^{5/5}$) are more impaired after sleep deprivation than those with four repeats ($Per3^{4/4}$). Vandewalle et al. used fMRI to examine the neural underpinnings of this difference. Subjects performed a memory task in the morning and evening, before and after sleep deprivation. Although the task was kept short to eliminate differences in performance, cortical activation was reduced in $Per3^{5/5}$ subjects in the evening of a normal day and further reduced after sleep deprivation. In contrast, cortical activation was maintained in $Per3^{4/4}$ individuals, and additional areas were activated after sleep deprivation, suggesting recruitment of these areas may help maintain cognitive function.

◆ Neurobiology of Disease

Aβ Immunization Decreases Abnormal Tau Phosphorylation

Donna M. Wilcock, Nastaran Gharkholonarehe, William E. Van Nostrand, Judianne Davis, Michael P. Vitek, and Carol A. Colton

(see pages 7957–7965)

It is not clear whether neurodegeneration and cognitive decline in Alzheimer's disease (AD) depend more on β-amyloid (Aβ) deposition in plaques or on accumulation of abnormally phosphorylated tau in neurofibrillary tangles, but a prominent hypothesis driving therapy development posits that Aβ aggregation is the primary event that leads to other pathologies. Immunization against Aβ is a promising treatment that reduces Aβ deposition and improves cognitive performance, but its effect on tau hyperphosphorylation and neuronal death have not been tested because no mouse model exhibiting all three AD-associated pathologies has been available. Using two recently developed transgenic mouse lines, Wilcock et al. now demonstrate that immunization against Aβ does indeed reduce tau pathology and neuron loss, as well as improving performance on a memory task. Unfortunately, immunization also induced vascular microhemorrhaging, which might limit the usefulness of immunotherapy for treatment of AD.

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Cover legend: An adult american alligator, *Alligator mississippiensis*. Neurons in the nucleus laminaris of alligators act as coincidence detectors to discriminate interaural time differences using algorithms similar to those used by birds. Photograph copyright Nick Scobel, 2008, used with permission. For more information, see the article by Carr et al. in this issue (pages 7978–7990).

Journal Club

Brief Communications

Articles

CELLULAR/MOLECULAR

NEUROBIOLOGY OF DISEASE

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BRIEF COMMUNICATIONS

Novelty Enhancements in Memory Are Dependent on Lateral Prefrontal Cortex

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Physiological evidence indicates that several brain regions, including the medial temporal lobes and prefrontal cortex (PFC), are involved in processing events that are novel or distinctive in their immediate context. However, behavioral studies that investigate whether these regions are critical for producing stimulus novelty advantages in memory are limited. For example, evidence from an animal lesion study indicated that the PFC is involved in stimulus novelty effects, but this has not been examined in humans. In the current study, we used a von Restorff novelty paradigm to test a large cohort of lateral PFC patients ($n = 16$). We found that patients with lateral PFC damage were impaired in recollection- and familiarity-based recognition, and they did not exhibit a normal memory advantage for novel compared with non-novel items. These results provide neuropsychological evidence supporting a key role for the lateral PFC in producing stimulus novelty advantages in memory.
The Journal of Neuroscience, June 24, 2009 • 29(25):8114 – 8118

Articles

CELLULAR/MOLECULAR

Complexin-I Is Required for High-Fidelity Transmission at the Endbulb of Held Auditory Synapse

Nicola Strenzke,[1,2] Soham Chanda,[3] Cornelia Kopp-Scheinpflug,[4] Darina Khimich,[1] Kerstin Reim,[5] Anna V. Bulankina,[1] Andreas Neef,[6] Fred Wolf,[6,7] Nils Brose,[5] Matthew A. Xu-Friedman,[3] and Tobias Moser[1,6]
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Complexins (CPXs I–IV) presumably act as regulators of the SNARE (soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor) complex, but their function in the intact mammalian nervous system is not well established. Here, we explored the role of CPXs in the mouse auditory system. Hearing was impaired in CPX I knock-out mice but normal in knock-out mice for CPXs II, III, IV, and III/IV as measured by auditory brainstem responses. Complexins were not detectable in cochlear hair cells but CPX I was expressed in spiral ganglion neurons (SGNs) that give rise to the auditory nerve. Ca^{2+}-dependent exocytosis of inner hair cells and sound encoding by SGNs were unaffected in CPX I knock-out mice. In the absence of CPX I, the resting release probability in the endbulb of Held synapses of the auditory nerve fibers with bushy cells in the cochlear nucleus was reduced. As predicted by computational modeling, bushy cells had decreased spike rates at sound onset as well as longer and more variable first spike latencies explaining the abnormal auditory brainstem responses. In addition, we found synaptic transmission to outlast the stimulus at many endbulb of Held synapses *in vitro* and *in vivo*, suggesting impaired synchronization of release to stimulus offset. Although sound encoding in the cochlea proceeds in the absence of complexins, CPX I is required for faithful processing of sound onset and offset in the cochlear nucleus.
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Neuroligin 2 Controls the Maturation of GABAergic Synapses and Information Processing in the Retina

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In the present study, we investigated the role of Neuroligin 2 (NL2) in synaptic transmission and network function using the mouse retina as a model circuit. We show that NL2 is preferentially located at GABAergic rather than glycinergic or glutamatergic postsynapses. The absence of NL2 from the retina resulted in a severe reduction of $GABA_A$ receptor clustering, and in subtle alterations of the retinal circuitry. Light processing was impaired accordingly, and retinal ganglion cells, the output neurons of the

retina, showed increased basal activity and altered coding of visual information. Together, our data indicate that NL2 is essential for the functional integrity of GABAergic signaling and as a consequence, for information processing in the retina.
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Visualization of Chemokine Receptor Activation in Transgenic Mice Reveals Peripheral Activation of CCR2 Receptors in States of Neuropathic Pain

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CCR2 chemokine receptor signaling has been implicated in the generation of diverse types of neuropathology, including neuropathic pain. For example, *ccr2* knock-out mice are resistant to the establishment of neuropathic pain, and mice overexpressing its ligand, monocyte chemoattractant protein-1 (MCP1; also known as CCL2), show enhanced pain sensitivity. However, whether CCR2 receptor activation occurs in the central or peripheral nervous system in states of neuropathic pain has not been clear. We developed a novel method for visualizing CCR2 receptor activation *in vivo* by generating bitransgenic reporter mice in which the chemokine receptor CCR2 and its ligand MCP1 were labeled by the fluorescent proteins enhanced green fluorescent protein and monomeric red fluorescent protein-1, respectively. CCR2 receptor activation under conditions such as acute inflammation and experimental autoimmune encephalomyelitis could be faithfully visualized by using these mice. We examined the status of CCR2 receptor activation in a demyelination injury model of neuropathic pain and found that MCP1-induced CCR2 receptor activation mainly occurred in the peripheral nervous system, including the injured peripheral nerve and dorsal root ganglia. These data explain the rapid antinociceptive effects of peripherally administered CCR2 antagonists under these circumstances, suggesting that CCR2 antagonists may ameliorate pain by inhibiting CCR2 receptor activation in the periphery. The method developed here for visualizing CCR2 receptor activation *in vivo* may be extended to G-protein-coupled receptors (GPCRs) in general and will be valuable for studying intercellular GPCR-mediated communication *in vivo*.
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Ca^{2+} Regulation of Dynamin-Independent Endocytosis in Cortical Astrocytes

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Astrocytes release ATP and glutamate through vesicular exocytosis to mediate neuron–glial interactions. In contrast to exocytosis, the endocytic pathways in astroglial cells are poorly understood. Here, we identify a constitutive endocytic pathway in cultured astrocytes that is dependent on neither clathrin nor dynamin. This dynamin-independent endocytic pathway is regulated by Rab5, an early endosome protein. The endocytosed vesicles show fast transition from early endosomes to late endosomes and lysosomes within a few minutes. Interestingly, this clathrin- and dynamin-independent endocytosis in astrocytes is potently regulated by intracellular Ca^{2+}. ATP and glutamate greatly enhance the dynamin-independent endocytosis through elevating the intracellular Ca^{2+}. In addition, amyloid-β peptide (Aβ) also enhances the dynamin-independent endocytosis by inducing Ca^{2+} transients in astrocytes. These results demonstrate a novel endocytic pathway in glial cells that is dynamin independent but tightly regulated by intracellular Ca^{2+}. The regulation by ATP, glutamate, and Aβ suggests an important role of the dynamin-independent endocytosis in both physiological and pathological conditions.
The Journal of Neuroscience, June 24, 2009 • 29(25):8063–8074

Glutamate Transporter Coupling to Na,K-ATPase

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Deactivation of glutamatergic signaling in the brain is mediated by glutamate uptake into glia and neurons by glutamate transporters. Glutamate transporters are sodium-dependent proteins that putatively rely indirectly on Na,K-ATPases to generate ion gradients that drive transmitter uptake. Based on anatomical colocalization, mutual sodium dependency, and the inhibitory effects of the Na,K-ATPase inhibitor ouabain on glutamate transporter activity, we postulated that glutamate transporters are directly coupled to Na,K-ATPase and that Na,K-ATPase is an essential modulator of glutamate uptake.

Na,K-ATPase was purified from rat cerebellum by tandem anion exchange and ouabain affinity chromatography, and the cohort of associated proteins was characterized by mass spectrometry. The $\alpha1$–$\alpha3$ subunits of Na,K-ATPase were detected, as were the glutamate transporters GLAST and GLT-1, demonstrating that glutamate transporters copurify with Na,K-ATPases. The link between glutamate transporters and Na,K-ATPase was further established by coimmunoprecipitation and colocalization. Analysis of the regulation of glutamate transporter and Na,K-ATPase activities was assessed using [^{3}H]D-aspartate, [^{3}H]L-glutamate, and rubidium-86 uptake into synaptosomes and cultured astrocytes. In synaptosomes, ouabain produced a dose-dependent inhibition of glutamate transporter and Na,K-ATPase activities, whereas in astrocytes, ouabain showed a bimodal effect whereby glutamate transporter activity was stimulated at 1 μM ouabain and inhibited at higher concentrations. The effects of protein kinase inhibitors on [^{3}H]D-aspartate uptake indicated the selective involvement of Src kinases, which are probably a component of the Na,K-ATPase/glutamate transporter complex. These findings demonstrate that glutamate transporters and Na,K-ATPases are part of the same macromolecular complexes and operate as a functional unit to regulate glutamatergic neurotransmission.
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Subcellular Dynamics of Somatostatin Receptor Subtype 1 in the Rat Arcuate Nucleus: Receptor Localization and Synaptic Connectivity Vary in Parallel with the Ultradian Rhythm of Growth Hormone Secretion

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Growth hormone (GH) secretion in male rats exhibits a 3.3 h ultradian rhythm generated by the reciprocal interaction of GH-releasing hormone (GHRH) and somatostatin (SRIF). SRIF receptor subtypes sst_1 and sst_2 are highly expressed in GHRH neurons of the hypothalamic arcuate nucleus (ARC). We previously demonstrated an ultradian oscillation in binding of SRIF analogs to the ARC in relation to GH peaks and troughs. Here we tested the hypothesis that these ultradian changes in SRIF binding are due to differential plasma membrane targeting of sst_1 receptors in ARC neurons using immunocytochemistry and electron microscopy. We found that 87% of sst_1-positive ARC neurons also synthesized GHRH. Subcellularly, 80% of sst_1 receptors were located intracellularly and 20% at the plasma membrane regardless of GH status. However, whereas 30% of the cell-surface sst_1 receptors were located perisynaptically or subsynaptically following exposure to high GH secretion, this fraction was increased to 42% following a GH trough period ($p = 0.05$). Furthermore, the relative abundance of symmetric and asymmetric synapses on sst_1-positive dendrites also varied significantly, depending on the GH cycle, from approximately equal numbers following GH troughs to 70:30 in favor of symmetric, i.e., inhibitory, inputs after GH peaks ($p < 0.02$). These findings suggest that postsynaptic localization of sst_1 receptors and synaptic connectivity in the ARC undergo pronounced remodeling in parallel with the GH rhythm. Such synaptic plasticity may be an important mechanism by which sst_1 mediates SRIF's cyclical effects on ARC GHRH neurons to generate the ultradian rhythm of GH secretion.

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NOS1AP Regulates Dendrite Patterning of Hippocampal Neurons through a Carboxypeptidase E-Mediated Pathway

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During neuronal development, neurons form elaborate dendritic arbors that receive signals from axons. Additional studies are needed to elucidate the factors regulating the establishment of dendritic patterns. Our work explored possible roles played by nitric oxide synthase 1 adaptor protein (NOS1AP; also known as C-terminal PDZ ligand of neuronal nitric oxide synthase or CAPON) in dendritic patterning of cultured hippocampal neurons. Here we report that the long isoform of NOS1AP (NOS1AP-L) plays a novel role in regulating dendrite outgrowth and branching. NOS1AP-L decreases dendrite number when overexpressed at any interval between day *in vitro* (DIV) 0 and DIV 12, and knockdown of NOS1AP-L results in increased dendrite number. In contrast, the short isoform of NOS1AP (NOS1AP-S) decreases dendrite number only when overexpressed during DIV 5–7. Using mutants of NOS1AP-L, we show that neither the PDZ-binding domain nor the PTB domain is necessary for the effects of NOS1AP-L. We have functionally narrowed the region of NOS1AP-L that mediates this effect to the middle amino acids 181–307, a region that is not present in NOS1AP-S. Furthermore, we performed a yeast two-hybrid screen and identified carboxypeptidase E (CPE) as a binding partner for the middle region of NOS1AP-L. Biochemical and cellular studies reveal that CPE mediates the effects of NOS1AP on dendrite morphology. Together, our results suggest that NOS1AP-L plays an important role in the initiation, outgrowth, and maintenance of dendrites during development.

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Histone Deacetylases 1 and 2 Form a Developmental Switch That Controls Excitatory Synapse Maturation and Function

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The structural assembly of synapses can be accomplished in a rapid time frame, although most nascent synapses formed during early development are not fully functional and respond poorly to presynaptic action potentials. The mechanisms that are responsible for this delay in synapse maturation are unknown. Histone deacetylases (HDACs) regulate the activity state of chromatin and repress gene expression through the removal of acetyl groups from histones. Class I HDACs, which include HDAC1 and HDAC2, are expressed in the CNS, although their specific role in neuronal function has not been studied. To delineate the contribution of HDAC1 and HDAC2 in the brain, we have used pharmacological inhibitors of HDACs and mice with conditional alleles to HDAC1 and HDAC2. We found that a decrease in the activities of both HDAC1 and HDAC2 during early synaptic development causes a robust facilitation of excitatory synapse maturation and a modest increase in synapse numbers. In contrast, in mature neurons a decrease in HDAC2 levels alone was sufficient to attenuate basal excitatory neurotransmission without a significant change in the numbers of detectable nerve terminals. Therefore, we propose that HDAC1 and HDAC2 form a developmental switch that controls synapse maturation and function acting in a manner dependent on the maturational states of neuronal networks.

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GABA-cAMP Response Element-Binding Protein Signaling Regulates Maturation and Survival of Newly Generated Neurons in the Adult Hippocampus

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Survival and integration of new neurons in the hippocampal circuit are rate-limiting steps in adult hippocampal neurogenesis. Neuronal network activity is a major regulator of these processes, yet little is known about the respective downstream signaling pathways. Here, we investigate the role of cAMP response element-binding protein (CREB) signaling in adult hippocampal neurogenesis. CREB is activated in new granule neurons during a distinct developmental period. Loss of CREB function in a cell-autonomous manner impairs dendritic development, decreases the expression of the neurogenic transcription factor NeuroD and of the neuronal microtubule-associated protein, doublecortin (DCX), and compromises the survival of newborn neurons. In addition, GABA-mediated excitation regulates CREB activation at early developmental stages. Importantly, developmental defects after loss of GABA-mediated excitation can be compensated by enhanced CREB signaling. These results indicate that CREB signaling is a central pathway in adult hippocampal neurogenesis, regulating the development and survival of new hippocampal neurons downstream of GABA-mediated excitation.

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Phosphodiesterase 5 Inhibition Improves Synaptic Function, Memory, and Amyloid-β Load in an Alzheimer's Disease Mouse Model

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Memory loss, synaptic dysfunction, and accumulation of amyloid β-peptides (Aβ) are major hallmarks of Alzheimer's disease (AD). Downregulation of the nitric oxide/cGMP/cGMP-dependent protein kinase/c-AMP responsive element-binding protein (CREB) cascade has been linked to the synaptic deficits after Aβ elevation. Here, we report that the phosphodiesterase 5 inhibitor (PDE5) sildenafil (Viagra), a molecule that enhances phosphorylation of CREB, a molecule involved in memory, through elevation of cGMP levels, is beneficial against the AD phenotype in a mouse model of amyloid deposition. We demonstrate that the inhibitor produces an immediate and long-lasting amelioration of synaptic function, CREB phosphorylation, and memory. This effect is also associated with a long-lasting reduction of Aβ levels. Given that side effects of PDE5 inhibitors are widely known and do not preclude their administration to a senile population, these drugs have potential for the treatment of AD and other diseases associated with elevated Aβ levels.

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Focal Adhesion Kinase Acts Downstream of EphB Receptors to Maintain Mature Dendritic Spines by Regulating Cofilin Activity

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Dendritic spines are the postsynaptic sites of most excitatory synapses in the brain and are highly enriched in polymerized F-actin, which drives the formation and maintenance of mature dendritic spines and synapses. We propose that suppressing the activity of the actin-severing protein cofilin plays an important role in the stabilization of mature dendritic spines, and is accomplished through an EphB receptor–focal adhesion kinase (FAK) pathway. Our studies revealed that Cre-mediated knock-out of *loxP*-flanked *fak* prompted the reversion of mature dendritic spines to an immature filopodial-like phenotype in primary hippocampal cultures. The effects of FAK depletion on dendritic spine number, length, and morphology were rescued by the overexpression of the constitutively active FAK ^{Y397E}, but not FAK ^{Y397F}, indicating the significance of FAK activation by phosphorylation on tyrosine 397. Our studies demonstrate that FAK acts downstream of EphB receptors in hippocampal neurons and EphB2–FAK signaling controls the stability of mature dendritic spines by promoting cofilin phosphorylation, thereby inhibiting cofilin activity. While constitutively active nonphosphorylatable cofilin ^{S3A} induced an immature spine profile, phosphomimetic cofilin ^{S3D} restored mature spine morphology in neurons with disrupted EphB activity or lacking FAK. Further, we found that EphB-mediated regulation of cofilin activity at least partially depends on the activation of Rho-associated kinase (ROCK) and LIMK-1. These findings indicate that EphB2-mediated dendritic spine stabilization relies, in part, on the ability of FAK to activate the RhoA–ROCK–LIMK-1 pathway, which functions to suppress cofilin activity and inhibit cofilin-mediated dendritic spine remodeling.

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Inosine Alters Gene Expression and Axonal Projections in Neurons Contralateral to a Cortical Infarct and Improves Skilled Use of the Impaired Limb

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Recovery after stroke and other types of brain injury is restricted in part by the limited ability of undamaged neurons to form compensatory connections. Inosine, a naturally occurring purine nucleoside, stimulates neurons to extend axons in culture and, *in vivo*, enhances the ability of undamaged neurons to form axon collaterals after brain damage. The molecular changes induced by inosine are unknown, as is the ability of inosine to restore complex functions associated with a specific cortical area. Using a unilateral injury model limited to the sensorimotor cortex, we show that inosine triples the number of corticospinal tract axons that project from the unaffected hemisphere and form synaptic bouton-like structures in the denervated half of the spinal cord. These changes correlate with improved recovery in animals' ability to grasp and consume food pellets with the affected forepaw. Studies using laser-capture microdissection and microarray analysis show that inosine profoundly affects gene expression in corticospinal neurons contralateral to the injury. Inosine attenuates transcriptional changes caused by the stroke, while upregulating the expression of genes associated with axon growth and the complement cascade. Thus, inosine alters gene expression in neurons contralateral to a stroke, enhances the ability of these neurons to form connections on the denervated side of the spinal cord, and improves performance with the impaired limb.

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Inhibition of the Mammalian Target of Rapamycin Signaling Pathway Suppresses Dentate Granule Cell Axon Sprouting in a Rodent Model of Temporal Lobe Epilepsy

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Dentate granule cell axon (mossy fiber) sprouting is a common abnormality in patients with temporal lobe epilepsy. Mossy fiber sprouting creates an aberrant positive-feedback network among granule cells that does not normally exist. Its role in epileptogenesis is unclear and controversial. If it were possible to block mossy fiber sprouting from developing after epileptogenic treatments, its potential role in the pathogenesis of epilepsy could be tested. Previous attempts to block mossy fiber sprouting have been unsuccessful. The present study targeted the mammalian target of rapamycin (mTOR) signaling pathway, which regulates cell growth and is blocked by rapamycin. Rapamycin was focally, continuously, and unilaterally infused into the dorsal hippocampus for prolonged periods beginning within hours after rats sustained pilocarpine-induced status epilepticus. Infusion for 1 month reduced aberrant Timm staining (a marker of mossy fibers) in the granule cell layer and molecular layer. Infusion for 2 months inhibited mossy fiber sprouting more. However, after rapamycin infusion ceased, aberrant Timm staining developed and approached untreated levels. When onset of infusion began after mossy fiber sprouting had developed for 2 months, rapamycin did not reverse aberrant Timm staining. These findings suggest that inhibition of the mTOR signaling pathway suppressed development of mossy fiber sprouting. However, suppression required continual treatment, and rapamycin treatment did not reverse already established axon reorganization.

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BEHAVIORAL/SYSTEMS/COGNITIVE

Functional Magnetic Resonance Imaging-Assessed Brain Responses during an Executive Task Depend on Interaction of Sleep Homeostasis, Circadian Phase, and *PER3* Genotype

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Cognition is regulated across the 24 h sleep-wake cycle by circadian rhythmicity and sleep homeostasis through unknown brain mechanisms. We investigated these mechanisms in a functional magnetic resonance imaging study of executive function using a working memory 3-back task during a normal sleep-wake cycle and during sleep loss. The study population was stratified according to homozygosity for a variable-number (*4* or *5*) tandem-repeat polymorphism in the coding region of the clock gene *PERIOD3*. This polymorphism confers vulnerability to sleep loss and circadian misalignment through its effects on sleep homeostasis. In the less-vulnerable genotype, no changes were observed in brain responses during the normal-sleep wake cycle. During sleep loss, these individuals recruited supplemental anterior frontal, temporal and subcortical regions, while executive function was maintained. In contrast, in the vulnerable genotype, activation in a posterior prefrontal area was already reduced when comparing the evening to the morning during a normal sleep-wake cycle. Furthermore, in the morning after a night of sleep loss, widespread reductions in activation in prefrontal, temporal, parietal and occipital areas were observed in this genotype. These differences occurred in the absence of genotype-dependent differences in circadian phase. The data show that dynamic changes in brain responses to an executive task evolve across the sleep-wake and circadian cycles in a regionally specific manner that is

determined by a polymorphism which affects sleep homeostasis. The findings support a model of individual differences in executive control, in which the allocation of prefrontal resources is constrained by sleep pressure and circadian phase.
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Detection of Interaural Time Differences in the Alligator

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The auditory systems of birds and mammals use timing information from each ear to detect interaural time difference (ITD). To determine whether the Jeffress-type algorithms that underlie sensitivity to ITD in birds are an evolutionarily stable strategy, we recorded from the auditory nuclei of crocodilians, who are the sister group to the birds. In alligators, precisely timed spikes in the first-order nucleus magnocellularis (NM) encode the timing of sounds, and NM neurons project to neurons in the nucleus laminaris (NL) that detect interaural time differences. *In vivo* recordings from NL neurons show that the arrival time of phase-locked spikes differs between the ipsilateral and contralateral inputs. When this disparity is nullified by their best ITD, the neurons respond maximally. Thus NL neurons act as coincidence detectors. A biologically detailed model of NL with alligator parameters discriminated ITDs up to 1 kHz. The range of best ITDs represented in NL was much larger than in birds, however, and extended from 0 to 1000 μs contralateral, with a median ITD of 450 μs. Thus, crocodilians and birds employ similar algorithms for ITD detection, although crocodilians have larger heads.
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Spatial Pattern Coding of Sensory Information by Climbing Fiber-Evoked Calcium Signals in Networks of Neighboring Cerebellar Purkinje Cells

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Climbing fiber input produces complex spike synchrony across populations of cerebellar Purkinje cells oriented in the parasagittal axis. Elucidating the fine spatial structure of this synchrony is crucial for understanding its role in the encoding and processing of sensory information within the olivocerebellar cortical circuit. We investigated these issues using *in vivo* multineuron two-photon calcium imaging in combination with information theoretic analysis. Spontaneous dendritic calcium transients linked to climbing fiber input were observed in multiple neighboring Purkinje cells. Spontaneous synchrony of calcium transients between individual Purkinje cells falls off over ~200 μm mediolaterally, consistent with the presence of cerebellar microzones organized by climbing fiber input. Synchrony was increased after administration of harmaline, consistent with an olivary origin. Periodic sensory stimulation also resulted in a transient increase of synchrony after stimulus onset. To examine how synchrony affects the neural population code provided by the spatial pattern of complex spikes, we analyzed its information content. We found that spatial patterns of calcium events from small ensembles of cells provided substantially more stimulus information (59% more for seven-cell ensembles) than available by counting events across the pool without taking into account spatial origin. Information theoretic analysis indicated that, rather than contributing significantly to sensory coding via stimulus dependence, correlational effects on sensory coding are dominated by redundancy attributable to the prevalent spontaneous synchrony. The olivocerebellar circuit thus uses a labeled line code to report sensory signals, leaving open a role for synchrony in flexible selection of signals for output to deep cerebellar nuclei.
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Visual Salience Affects Performance in a Working Memory Task

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Many studies of bottom-up visual attention have focused on identifying which features of a visual stimulus render it salient—i.e., make it "pop out" from its background—and on characterizing the extent to which salience predicts eye movements under certain task conditions. However, few studies have examined the relationship between salience and other cognitive functions, such as memory. We examined the impact of visual salience in an object–place working memory task, in which participants memorized the position of 3–5 distinct objects (icons) on a two-dimensional map. We found that their ability to recall an object's spatial location was positively correlated with the object's salience, as quantified using a previously published computational model (Itti et al., 1998). Moreover, the strength of this relationship increased with increasing task difficulty. The correlation between salience and error could not be explained by a biasing of overt attention in favor of more salient icons during memorization, since eye-tracking data revealed no relationship between an icon's salience and fixation time. Our findings show that the influence of bottom-up attention extends beyond oculomotor behavior to include the encoding of information into memory.
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Information about Complex Fingertip Parameters in Individual Human Tactile Afferent Neurons

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Although information in tactile afferent neurons represented by firing rates has been studied extensively over nearly a century, recent studies suggest that precise spike timing might be more important than firing rates. Here, we used information theory to compare the information content in the discharges of 92 tactile afferents distributed over the entire terminal segment of the fingertip when it was contacted by surfaces with different curvatures and force directions representative of everyday manipulations. Estimates of the information content with regard to curvature and force direction based on the precise timing of spikes were at least 2.2 times and 1.6 times, respectively, larger than that of spike counts during a 125 ms period of force increase. Moreover, the information regarding force direction based on the timing of the very first elicited spike was comparable with that provided by spike counts and more than twice as large with respect to object shape. For all encoding schemes, afferents terminating close to the stimulation site tended to convey more information about surface curvature than more remote afferents that tended to convey more information about force direction. Finally, coding schemes based on spike timing and spike counts overall contributed mostly independent information. We conclude that information about tactile stimuli in timing of spikes in primary afferents, even if limited to the first spikes, surpasses that contained in firing rates and that these measures of afferents' responses might capture different aspects of the stimulus.

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Searching for Targets within the Spatial Layout of Visual Short-Term Memory

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Recent studies have revealed that the internal representations that we construct from the environment and maintain in visual short-term memory (VSTM) to guide behavior are highly flexible and can be selectively modulated according to our task goals and expectations. In the current study, we conducted two experiments to compare and contrast neural mechanisms of selective attention related to searching for target items within perceptual versus VSTM representations. We used event-related potentials to investigate whether searching for relevant target items from within VSTM representations involves spatially specific biasing of neural activity in a manner analogous to that which occurs during visual search for target items in perceptual arrays. The results, replicated across the two experiments, revealed that selection of a target object within a search array maintained in VSTM proceeds through a similar mechanism as that in the perceptual domain. In line with previous results, N2pc potentials were obtained when targets were identified within a perceptual visual-search array. Interestingly, equivalent N2pcs, with similar time courses and scalp distributions, were also elicited when target items were identified within a VSTM representation. The findings reinforce the notion of highly flexible VSTM representations that can be modulated according to task goals and suggest a large degree of overlap in the spatially specific neural mechanisms of target selection across the perceptual and VSTM domains.

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A Cholinergic-Dependent Role for the Entorhinal Cortex in Trace Fear Conditioning

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Trace conditioning is considered a model of higher cognitive involvement in simple associative tasks. Studies of trace conditioning have shown that cortical areas and the hippocampal formation are required to associate events that occur at different times. However, the mechanisms that bridge the trace interval during the acquisition of trace conditioning remain unknown. In four experiments with fear conditioning in rats, we explored the involvement of the entorhinal cortex (EC) in the acquisition of fear under a trace-30 s protocol. We first determined that pretraining neurotoxic lesions of the EC selectively impaired trace-, but not delay-conditioned fear as evaluated by freezing behavior. A local cholinergic deafferentation of the EC using 192-IgG-saporin did not replicate this deficit, presumably because cholinergic interneurons were spared by the toxin. However, pretraining local blockade of EC muscarinic receptors with the M1 antagonist pirenzepine yielded a specific and dose-dependent deficit in trace-conditioned responses. The same microinjections performed after conditioning were without effect on trace fear responses. These effects of blocking M1 receptors are consistent with the notion that conditioned stimulus (CS)-elicited, acetylcholine-dependent persistent activities in the EC are needed to maintain a representation of a tone CS across the trace interval during the acquisition of trace conditioning. This function of the EC is consistent with recent views of this region as a short-term stimulus buffer.

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GABAergic Neurons of the Medial Septum Lead the Hippocampal Network during Theta Activity

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Information processing in the hippocampus critically relies on its reciprocal interaction with the medial septum (MS). Synchronization of the septo-hippocampal system was demonstrated during both major hippocampal activity states, the regular theta rhythm and the large amplitude irregular activity. Previous experimental and modeling data suggest that the MS provides rhythmic drive to the hippocampus, and hippocampo-septal feedback synchronizes septal pacemaker units. However, this view has recently been questioned based on the possibility of intrahippocampal theta genesis. Previously, we identified putative pacemaker neurons expressing parvalbumin (PV) and/or the pacemaker hyperpolarization-activated and cyclic nucleotide-gated nonselective cation channel (HCN) in the MS. In this study, by analyzing the temporal relationship of activity between the PV/HCN-containing medial septal neurons and hippocampal local field potential, we aimed to uncover whether the sequence of events during theta formation supports the classic view of septal drive or the challenging theory of hippocampal pacing of theta. Importantly, by implementing a circular statistical method, a temporal lead of these septal neurons over the hippocampus was observed on the course of theta synchronization. Moreover, the activity of putative hippocampal interneurons also preceded hippocampal local field theta, but by a shorter time period compared with PV/HCN-containing septal neurons. Using the concept of mutual information, the action potential series of PV/HCN-containing neurons shared higher amount of information with hippocampal field oscillation than PV/HCN-immunonegative cells. Thus, a pacemaker neuron population of the MS leads hippocampal activity, presumably via the synchronization of hippocampal interneurons.
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Nonmotor Symptoms of Parkinson's Disease Revealed in an Animal Model with Reduced Monoamine Storage Capacity

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Parkinson's disease (PD) is a progressive neurodegenerative disorder that is characterized by the loss of dopamine neurons in the substantia nigra pars compacta, culminating in severe motor symptoms, including resting tremor, rigidity, bradykinesia, and postural instability. In addition to motor deficits, there are a variety of nonmotor symptoms associated with PD. These symptoms generally precede the onset of motor symptoms, sometimes by years, and include anosmia, problems with gastrointestinal motility, sleep disturbances, sympathetic denervation, anxiety, and depression. Previously, we have shown that mice with a 95% genetic reduction in vesicular monoamine transporter expression (VMAT2-deficient, VMAT2 LO) display progressive loss of striatal dopamine, L-DOPA-responsive motor deficits, α-synuclein accumulation, and nigral dopaminergic cell loss. We hypothesized that since these animals exhibit deficits in other monoamine systems (norepinephrine and serotonin), which are known to regulate some of these behaviors, the VMAT2-deficient mice may display some of the nonmotor symptoms associated with PD. Here we report that the VMAT2-deficient mice demonstrate progressive deficits in olfactory discrimination, delayed gastric emptying, altered sleep latency, anxiety-like behavior, and age-dependent depressive behavior. These results suggest that the VMAT2-deficient mice may be a useful model of the nonmotor symptoms of PD. Furthermore, monoamine dysfunction may contribute to many of the nonmotor symptoms of PD, and interventions aimed at restoring monoamine function may be beneficial in treating the disease.
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Cholinergic Stimulation Enhances Neural Activity Associated with Encoding but Reduces Neural Activity Associated with Retrieval in Humans

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The cerebral cholinergic system is centrally involved in memory formation. Studies in rodents suggest that cholinergic stimulation may facilitate encoding of new information but may interfere with retrieval. We investigated the effect of cholinergic stimulation on encoding and retrieval of episodic memory in humans. We also tested whether the putative benefit of cholinergic stimulation on memory function depends on individual baseline performance. Since such effects were expected to be greatest in an older population resulting from an age-related degeneration of the cholinergic system, we recruited 22 healthy older subjects (51–68 years) for an event-related functional magnetic resonance imaging experiment. In two separate scanning sessions, subjects encoded and retrieved items and their spatial context under cholinergic stimulation or placebo with the acetylcholine-esterase inhibitor physostigmine or saline being administered intravenously in a double-blind cross-over design. Baseline performance was recorded at a separate occasion without scanning. Cholinergic stimulation enhanced neural activity for successful versus unsuccessful spatial context encoding in the right hippocampus but reduced activity for successful versus unsuccessful spatial context retrieval in the right amygdala. These data may bridge the gap between rodent and human studies by showing that also in man cholinergic stimulation enhances encoding but interferes with retrieval on a neural level. Furthermore, baseline performance negatively correlated with the effect of cholinergic stimulation. Thus, partici-

pants who were worse at baseline benefited more from cholinergic stimulation than those who had better baseline values, indicating that a cholinergic deficit contributes to the memory decline even in healthy older subjects.
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Impact of Serotonin 2C Receptor Null Mutation on Physiology and Behavior Associated with Nigrostriatal Dopamine Pathway Function

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The impact of serotonergic neurotransmission on brain dopaminergic pathways has substantial relevance to many neuropsychiatric disorders. A particularly prominent role has been ascribed to the inhibitory effects of serotonin 2C receptor (5-HT_{2C}R) activation on physiology and behavior mediated by the mesolimbic dopaminergic pathway, particularly in the terminal region of the nucleus accumbens. The influence of this receptor subtype on functions mediated by the nigrostriatal dopaminergic pathway is less clear. Here we report that a null mutation eliminating expression of 5-HT_{2C}Rs produces marked alterations in the activity and functional output of this pathway. 5-HT_{2C}R mutant mice displayed increased activity of substantia nigra pars compacta (SNc) dopaminergic neurons, elevated baseline extracellular dopamine concentrations in the dorsal striatum (DSt), alterations in grooming behavior, and enhanced sensitivity to the stereotypic behavioral effects of D-amphetamine and GBR 12909. These psychostimulant responses occurred in the absence of phenotypic differences in drug-induced extracellular dopamine concentration, suggesting a phenotypic alteration in behavioral responses to released dopamine. This was further suggested by enhanced behavioral responses of mutant mice to the D_1 receptor agonist SKF 81297. Differences in DSt D_1 or D_2 receptor expression were not found, nor were differences in medium spiny neuron firing patterns or intrinsic membrane properties following dopamine stimulation. We conclude that 5-HT_{2C}Rs regulate nigrostriatal dopaminergic activity and function both at SNc dopaminergic neurons and at a locus downstream of the DSt.
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Functional Significance of Nonspatial Information in Monkey Lateral Intraparietal Area

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Although the parietal cortex is traditionally associated with spatial perception and motor planning, recent evidence shows that neurons in the lateral intraparietal area (LIP) carry both spatial and nonspatial signals. The functional significance of the nonspatial information in the parietal cortex is not understood. To address this question, we tested the effect of unilateral reversible inactivation of LIP on three behavioral tasks known to evoke nonspatial responses. Each task included a spatial component (target selection in the hemifield contralateral or ipsilateral to the inactivation) and a nonspatial component, namely limb motor planning, the estimation of elapsed time, and reward-based decisions. Although inactivation reliably impaired performance on all tasks, the deficits were spatially specific (restricted to contralateral target locations), and there were no effects on nonspatial aspects on performance. This suggests that modulatory nonspatial signals in LIP represent feedback about computations performed elsewhere rather than a primary role of LIP in these computations.
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Opioids Depress Cortical Centers Responsible for the Volitional Control of Respiration

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Respiratory depression limits provision of safe opioid analgesia and is the main cause of death in drug addicts. Although opioids are known to inhibit brainstem respiratory activity, their effects on cortical areas that mediate respiration are less well understood. Here, functional magnetic resonance imaging was used to examine how brainstem and cortical activity related to a short breath hold is modulated by the opioid remifentanil. We hypothesized that remifentanil would differentially depress brain areas that mediate sensory-affective components of respiration over those that mediate volitional motor control. Quantitative measures of cerebral blood flow were used to control for hypercapnia-induced changes in blood oxygen level-dependent (BOLD) signal. Awareness of respiration, reflected by an urge-to-breathe score, was profoundly reduced with remifentanil. Urge to breathe was associated with activity in the bilateral insula, frontal operculum, and secondary somatosensory cortex. Localized remifentanil-induced decreases in breath hold-related activity were observed in the left anterior insula and operculum. We also observed remifentanil-induced decreases in the BOLD

response to breath holding in the left dorsolateral prefrontal cortex, anterior cingulate, the cerebellum, and periaqueductal gray, brain areas that mediate task performance. Activity in areas mediating motor control (putamen, motor cortex) and sensory-motor integration (supramarginal gyrus) were unaffected by remifentanil. Breath hold-related activity was observed in the medulla. These findings highlight the importance of higher cortical centers in providing contextual awareness of respiration that leads to appropriate modulation of respiratory control. Opioids have profound effects on the cortical centers that control breathing, which potentiates their actions in the brainstem.
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The Formation of Recent and Remote Memory Is Associated with Time-Dependent Formation of Dendritic Spines in the Hippocampus and Anterior Cingulate Cortex

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Although hippocampal–cortical interactions are crucial for the formation of enduring declarative memories, synaptic events that govern long-term memory storage remain mostly unclear. We present evidence that neuronal structural changes, i.e., dendritic spine growth, develop sequentially in the hippocampus and anterior cingulate cortex (aCC) during the formation of recent and remote contextual fear memory. We found that mice placed in a conditioning chamber for one 7 min conditioning session and exposed to five footshocks (duration, 2 s; intensity, 0.7 mA; interstimulus interval, 60 s) delivered through the grid floor exhibited robust fear response when returned to the experimental context 24 h or 36 d after the conditioning. We then observed that their fear response at the recent, but not the remote, time point was associated with an increase in spine density on hippocampal neurons, whereas an inverse temporal pattern of spine density changes occurred on aCC neurons. At each time point, hippocampal or aCC structural alterations were achieved even in the absence of recent or remote memory tests, thus suggesting that they were not driven by retrieval processes. Furthermore, ibotenic lesions of the hippocampus impaired remote memory and prevented dendritic spine growth on aCC neurons when they were performed immediately after the conditioning, whereas they were ineffective when performed 24 d later. These findings reveal that gradual structural changes modifying connectivity in hippocampal–cortical networks underlie the formation and expression of remote memory, and that the hippocampus plays a crucial but time-limited role in driving structural plasticity in the cortex.
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Hyperdopaminergia and NMDA Receptor Hypofunction Disrupt Neural Phase Signaling

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Neural phase signaling has gained attention as a putative coding mechanism through which the brain binds the activity of neurons across distributed brain areas to generate thoughts, percepts, and behaviors. Neural phase signaling has been shown to play a role in various cognitive processes, and it has been suggested that altered phase signaling may play a role in mediating the cognitive deficits observed across neuropsychiatric illness. Here, we investigated neural phase signaling in two mouse models of cognitive dysfunction: mice with genetically induced hyperdopaminergia [dopamine transporter knock-out (DAT-KO) mice] and mice with genetically induced NMDA receptor hypofunction [NMDA receptor subunit-1 knockdown (NR1-KD) mice]. Cognitive function in these mice was assessed using a radial-arm maze task, and local field potentials were recorded from dorsal hippocampus and prefrontal cortex as DAT-KO mice, NR1-KD mice, and their littermate controls engaged in behavioral exploration. Our results demonstrate that both DAT-KO and NR1-KD mice display deficits in spatial cognitive performance. Moreover, we show that persistent hyperdopaminergia alters interstructural phase signaling, whereas NMDA receptor hypofunction alters interstructural and intrastructural phase signaling. These results demonstrate that dopamine and NMDA receptor dependent glutamate signaling play a critical role in coordinating neural phase signaling, and encourage further studies to investigate the role that deficits in phase signaling play in mediating cognitive dysfunction.
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Suppression of Spreading Depression-Like Events in Locusts by Inhibition of the NO/cGMP/PKG Pathway

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Despite considerable research attention focused on mechanisms underlying neural spreading depression (SD), because of its association with important human CNS pathologies, such as stroke and migraine, little attention has been given to explaining its occurrence and regulation in invertebrates. In the locust metathoracic ganglion (MTG), an SD-like event occurs during heat and anoxia stress, which results in cessation of neuronal output for the duration of the applied stress. SD-like events were characterized by an abrupt rise in extracellular potassium ion concentration ($[K^+]_o$) from a baseline concentration of ~8 to >30 mM, which returned to near baseline concentrations after removal of the applied stress. After return to baseline $[K^+]_o$, neuronal output (ventilatory motor pattern activity) from the MTG recovered. Unlike mammalian neurons, which depolarize almost completely during SD, locust neurons only partially depolarized. SD-like events in the locust CNS were suppressed by pharmacological inhibition of the nitric oxide/cyclic guanosine monophosphate/protein kinase G (NO/cGMP/PKG) pathway and were exacerbated by its activation. Also,

environmental stressors such as heat and anoxia increased production of nitric oxide in the locust CNS. Finally, for the intact animal, manipulation of the pathway affected the speed of recovery from suffocation by immersion under water. We propose that SD-like events in locusts provide an adaptive mechanism for surviving extreme environmental conditions. The highly conserved nature of the NO/cGMP/PKG signaling pathway suggests that it may be involved in modulating SD in other organisms, including mammals.
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Selecting for Memory? The Influence of Selective Attention on the Mnemonic Binding of Contextual Information

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Not all of what is experienced is remembered later. Behavioral evidence suggests that the manner in which an event is processed influences which aspects of the event will later be remembered. The present experiment investigated the neural correlates of "selective encoding," or the mechanisms that support the encoding of some elements of an event in preference to others. Event-related MRI data were acquired while volunteers selectively attended to one of two different contextual features of study items (color or location). A surprise memory test for the items and both contextual features was subsequently administered to determine the influence of selective attention on the neural correlates of contextual encoding. Activity in several cortical regions indexed later memory success selectively for color or location information, and this encoding-related activity was enhanced by selective attention to the relevant feature. Critically, a region in the hippocampus responded selectively to attended source information (whether color or location), demonstrating encoding-related activity for attended but not for nonattended source features. Together, the findings suggest that selective attention modulates the magnitude of activity in cortical regions engaged by different aspects of an event, and hippocampal encoding mechanisms seem to be sensitive to this modulation. Thus, the information that is encoded into a memory representation is biased by selective attention, and this bias is mediated by cortical– hippocampal interactions.
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Evidence of Action Sequence Chunking in Goal-Directed Instrumental Conditioning and Its Dependence on the Dorsomedial Prefrontal Cortex

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The current study investigated the contribution of the dorsomedial prefrontal cortex (dmPFC) to instrumental action selection. We found that cell body lesions of the dmPFC, centered on the medial agranular area, spared rats' ability to choose between actions based on either the value or the discriminative stimulus properties of an outcome. We next examined the effects of these lesions on action sequence learning using a concurrent bidirectional heterogeneous chain task in which the identity of the reward delivered was determined by the order in which the two lever press actions were performed. Although both lesioned rats and sham controls learned to perform the task, we found that they relied on different behavioral strategies to do so. In subsequent tests, rats in the sham group were able to withhold their performance of a sequence when either its associated outcome was devalued or the contingency between that sequence and its outcome was degraded by delivering the outcome noncontingently. Interestingly, lesioned rats failed to reorganize their performance at the action sequence level and, rather, were found to withhold their performance of the terminal response in the sequence that had earned the devalued outcome relative to the more distal response, suggesting that they represented the elements of the sequence as distinct behavioral units. These findings demonstrate that rats can use sequence-level representations, or action chunks, to organize their behavior in a goal-directed manner and indicate that the dmPFC plays a critical role in this process.
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NEUROBIOLOGY OF DISEASE

Amyloid Reduction by Amyloid-β Vaccination Also Reduces Mouse Tau Pathology and Protects from Neuron Loss in Two Mouse Models of Alzheimer's Disease

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Shown to lower amyloid deposits and improve cognition in APP transgenic mouse models, immunotherapy appears to be a promising approach for the treatment of Alzheimer's disease (AD). Due to limitations in available animal models, however, it has been unclear whether targeting amyloid is sufficient to reduce the other pathological hallmarks of AD—namely, accumulation of pathological, nonmutated tau and neuronal loss. We have now developed two transgenic mouse models (APPSw/NOS2 $^{-/-}$ and APPSwDI/NOS2 $^{-/-}$) that more closely model AD. These mice show amyloid pathology, hyperphosphorylated and aggregated normal mouse tau, significant

neuron loss, and cognitive deficits. Aβ_{1-42} or KLH vaccinations were started in these animals at 12 months, when disease progression and cognitive decline are well underway, and continued for 4 months. Vaccinated APPSwDI/NOS2 $^{-/-}$ mice, which have predominantly vascular amyloid pathology, showed a 30% decrease in brain Aβ and a 35–45% reduction in hyperphosphorylated tau. Neuron loss and cognitive deficits were partially reduced. In APPSw/NOS2 $^{-/-}$ vaccinated mice, brain Aβ was reduced by 65–85% and hyperphosphorylated tau by 50–60%. Furthermore, neurons were completely protected, and memory deficits were fully reversed. Microhemorrhage was observed in all vaccinated APPSw/NOS2 $^{-/-}$ mice and remains a significant adverse event associated with immunotherapy. Nevertheless, by providing evidence that reducing amyloid pathology also reduces nonmutant tau pathology and blocks neuron loss, these data support the development of amyloid-lowering therapies for disease-modifying treatment of AD.
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FOXO3a Is Broadly Neuroprotective *In Vitro* and *In Vivo* against Insults Implicated in Motor Neuron Diseases

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Aging is a risk factor for the development of adult-onset neurodegenerative diseases. Although some of the molecular pathways regulating longevity and stress resistance in lower organisms are defined (i.e., those activating the transcriptional regulators DAF-16 and HSF-1 in *Caenorhabditis elegans*), their relevance to mammals and disease susceptibility are unknown. We studied the signaling controlled by the mammalian homolog of DAF-16, FOXO3a, in model systems of motor neuron disease. Neuron death elicited *in vitro* by excitotoxic insult or the expression of mutant SOD1, mutant p150^{glued}, or polyQ-expanded androgen receptor was abrogated by expression of nuclear-targeted FOXO3a. We identify a compound [Psammaplysene A (PA)] that increases nuclear localization of FOXO3a *in vitro* and *in vivo* and show that PA also protects against these insults *in vitro*. Administration of PA to invertebrate model systems of neurodegeneration similarly blocked neuron death in a DAF-16/FOXO3a-dependent manner. These results indicate that activation of the DAF-16/FOXO3a pathway, genetically or pharmacologically, confers protection against the known causes of motor neuron diseases.
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