

This Week in The Journal

● Cellular/Molecular

Presynaptic LTP Requires RIM1 α –Munc13-1 Interaction

Ying Yang and Nicole Calakos

(see pages 12053–12057)

Long-term potentiation (LTP) can arise from presynaptic or postsynaptic changes. Postsynaptic changes include insertion of new neurotransmitter receptors, whereas presynaptic changes involve increased probability of neurotransmitter release. LTP at mossy fiber synapses between dentate granule cells and CA3 pyramidal cells is unusual in that it is driven primarily by presynaptic changes. The mechanisms underlying increased release probability are unclear, but are likely to involve enlargement of the pool of readily releasable vesicles. Yang and Calakos report that a crucial component of mossy fiber LTP in mice is interaction between the presynaptic active zone proteins RIM1 α and Munc13-1. Munc13-1 is involved in vesicle priming, in which vesicles docked at the active zone become associated with SNARE proteins and thus join the readily releasable pool. Interaction with RIM1 α appears to regulate Munc13-1 function. Disrupting the interaction by mutating the interaction domain of either protein prevented theta-burst LTP at mouse mossy fiber synapses.

▲ Development/Plasticity/Repair

APP Mutation Disrupts NGF/TrkA Signaling

Carmela Matrone, Alessia P.M. Barbagallo, Luca R. La Rosa, Fulvio Florenzano, Maria T. Ciotti, et al.

(see pages 11756–11761)

Amyloid precursor protein (APP) is cleaved to form extracellular and intracellular fragments, and abnormal cleavage leads to accumulation of β -amyloid peptides, which is associated with Alzheimer's disease (AD). The extent to which AD pathology results from β -amyloid accumu-

lation versus disruption of normal APP functions is unclear, however, in part because these functions are poorly understood. Several developmental roles have been proposed, including participation in neuronal degeneration in the absence of trophic support. Matrone et al. have identified an unexpected role for APP in NGF signaling via the TrkA receptor in mice. NGF increased tyrosine phosphorylation of APP, and this was prevented by TrkA inhibitors. APP and TrkA directly interacted, and a mutation that disrupted this interaction prevented NGF-induced activation of TrkA and its downstream signaling molecules. Accordingly, NGF failed to increase survival of dorsal root ganglion neurons in culture. APP mutation reduced membrane levels of TrkA, suggesting APP contributes to TrkA trafficking.

■ Behavioral/Systems/Cognitive

Effects of Maternal Stress Are Transmitted to Second Generation

Christopher P. Morgan and Tracy L. Bale

(see pages 11748–11755)

Chronic stress during pregnancy increases the risk of psychiatric disease in offspring. The effects of stress depend on the gestational age and sex of the fetus. In mice, for example, daily stress exposure during the first week of pregnancy increases depression-like behaviors (e.g., increased immobility during tail suspension) in male, but not female, offspring. Remarkably, the effects of prenatal stress can be passed on to subsequent (F2) generations. Morgan and Bale crossed prenatally stressed F1 males with control females. Although these females were not subjected to stress, their male offspring showed increased immobility during tail suspension. The immobility level of these second-generation offspring was similar to that of normal females, and the expression levels of sexually dimorphic genes was more similar to that of control females than that of control males. These results suggest that prenatal stress causes epigenetic changes resulting in dysmascu-

linization that can be passed from one generation to the next.

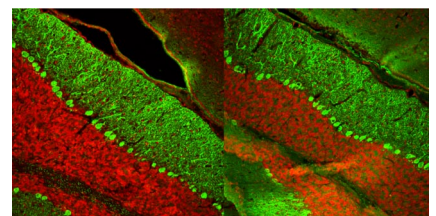
◆ Neurobiology of Disease

Blocking IK_A Ameliorates Spinocerebellar Ataxia

Raphael Hourez, Laurent Servais, David Orduz, David Gall, Isabelle Millard, et al.

(see pages 11795–11807)

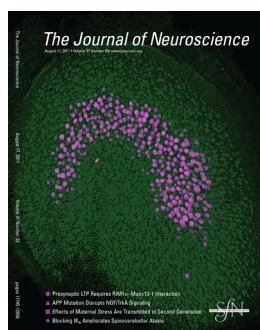
Spinocerebellar ataxia type 1 (SCA1) is characterized by progressive loss of coordination. It is caused by a polyglutamine expansion in ataxin-1, which aggregates in intranuclear inclusions in cerebellar Purkinje cells. Affected neurons atrophy and degenerate, but this does not appear to result from inclusion formation per se. Instead, the polyglutamine expansion appears to alter interactions between ataxin-1 and other proteins that regulate gene expression. Hourez et al. suggest that disrupted glutamate signaling contributes to motor impairments in mice expressing SCA1-linked ataxin-1. In these mice, Purkinje cell firing was reduced before the onset of motor impairment and Purkinje cell atrophy. The reduced firing was attributed to decreased strength of glutamatergic synapses onto Purkinje cells and increased A-type potassium current (IK_A), which delayed depolarization-induced spiking. Treating presymptomatic and early symptomatic mice with an IK_A blocker normalized Purkinje cell firing rate and restored motor function. Chronic treatment reduced neuronal atrophy and improved motor performance in old mice.



Cerebellum from 5-week-old control (left) and SCA1 model (right) mice. At this age, mice show motor deficits but no morphological changes in Purkinje cells. See the article by Hourez et al. for details.

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Cover legend: Neonatal mouse utricle labeled for F-actin (green) and the type I hair cell marker oncomodulin (purple), which demarks the striola, a central region in the utricle where supporting cells convert into hair cells when treated with γ -secretase inhibitors. For more information, see the article by Collado et al. in this issue (pages 11855–11866).

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- 12058 **Correction:** The article "Visual Experience Induces Long-Term Potentiation in the Primary Visual Cortex," by Sam F. Cooke and Mark F. Bear, originally appeared on pages 16304–16313 of the December 1, 2010 issue. A correction for that article appears on page 12058.

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APP is Phosphorylated by TrkA and Regulates NGF/TrkA Signaling

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The pathogenic model of Alzheimer's disease (AD) posits that aggregates of amyloid β , a product of amyloid precursor protein (APP) processing, cause dementia. However, alterations of normal APP functions could contribute to AD pathogenesis, and it is therefore important to understand the role of APP. APP is a member of a gene family that shows functional redundancy as documented by the evidence that single knock-out mice are viable, whereas mice with combined deletions of APP family genes die shortly after birth. A residue in the APP intracellular region, Y⁶⁸², is indispensable for these essential functions of APP. It is therefore important to identify pathways that regulate phosphorylation of Y⁶⁸² as well as the role of Y⁶⁸² *in vivo*. TrkA is associated with both phosphorylation of APP-Y⁶⁸² and alteration of APP processing, suggesting that tyrosine phosphorylation of APP links APP processing and neurotrophic signaling to intracellular pathways associated with cellular differentiation and survival. Here we have tested whether the NGF/TrkA signaling pathway is a physiological regulator of APP phosphorylation. We find that NGF induces tyrosine phosphorylation of APP, and that APP interacts with TrkA and this interaction requires Y⁶⁸². Unpredictably, we also uncover that APP, and specifically Y⁶⁸², regulates activation of the NGF/TrkA signaling pathway *in vivo*, the subcellular distribution of TrkA and the sensitivity of neurons to the trophic action of NGF. This evidence suggests that these two membrane protein's functions are strictly interconnected and that the NGF/TrkA signaling pathway is involved in AD pathogenesis and can be used as a therapeutic target.

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The Phase of Ongoing Oscillations Mediates the Causal Relation between Brain Excitation and Visual Perception

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Why does neuronal activity in sensory brain areas sometimes give rise to perception, and sometimes not? Although neuronal noise is often invoked as the key factor, a portion of this variability could also be due to the history and current state of the brain affecting cortical excitability. Here we directly test this idea by examining whether the phase of prestimulus oscillatory activity is causally linked with modulations of cortical excitability and with visual perception. Transcranial magnetic stimulation (TMS) was applied over human visual cortex to induce illusory perceptions (phosphenes) while electroencephalograms (EEGs) were simultaneously recorded. Subjects reported the presence or absence of an induced phosphene following a single pulse of TMS at perceptual threshold. The phase of ongoing alpha (~ 10 Hz) oscillations within 400 ms before the pulse significantly covaried with the perceptual outcome. This effect was observed in occipital regions around the site of TMS, as well as in a distant frontocentral region. In both regions, we found a systematic relationship between prepulse EEG phase and perceptual performance: phosphene probability changed by $\sim 15\%$ between opposite phases. In summary, we provide direct evidence for a chain of causal relations between the phase of ongoing oscillations, neuronal excitability, and visual perception: ongoing oscillations create periodic "windows of excitability," with sensory perception being more likely to occur at specific phases.

The Journal of Neuroscience, August 17, 2011 • 31(33):11889–11893

Dynamics of Executive Control and Motor Deficits in Parkinsonian Rats

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While there is general agreement that in Parkinson's disease (PD), striatal dopamine (DA) depletion causes motor deficits, the origin of the associated cognitive impairments remains a matter of debate. The present study aimed to decipher the influence of a partial 6-hydroxydopamine (6-OHDA) lesion of striatal DA nerve terminals in rats performing a reaction time task previously used to assess cognitive deficits in PD patients. The effects of two behavioral manipulations—foreperiod duration and stimulus–response congruence—known to affect motor processes and executive control, respectively, were studied over 8 weeks postsurgery in control and lesion animals.

Two weeks after surgery, the lesion abolished the effect of foreperiod, confirming the direct involvement of striatal DA in motor processes, but failed to alter the effect of congruence. During the following weeks, the effect of foreperiod was reinstated, indicating a recovery of lesion-induced motor symptoms. This recovery was accompanied by a progressive increase of the congruence effect, signaling an executive control deficit in lesion animals. This result provides the first evidence that 6-OHDA lesioned rats exhibit the same cognitive impairment as PD patients in this task. The deficit, however, built up progressively after the lesion and may result from adaptations mitigating lesion-induced motor deficits.

The Journal of Neuroscience, August 17, 2011 • 31(33):11929–11933

Munc13-1 Is Required for Presynaptic Long-Term Potentiation

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Long-lasting forms of synaptic plasticity involve modification of presynaptic strength in many brain regions. Although a presynaptic site for expression is well established, the detailed molecular mechanisms that lead to sustained changes in neurotransmitter release remain unclear. Here, we use acute *in vivo* genetic manipulation of synaptic proteins to investigate the molecular basis for presynaptic long-term potentiation (LTP) at hippocampal mossy fiber synapses. Munc13 proteins are active zone proteins that are essential for synaptic vesicle priming and neurotransmitter release. Munc13 proteins also interact with RIM1 α , an active zone protein required for presynaptic long-term plasticity. By taking advantage of the observation that the RIM-binding domain of Munc13 is separable from the domain that is required for neurotransmitter release, we selectively tested whether Munc13-1 is an effector for RIM1 α in presynaptic LTP. Our results provide the first evidence for the involvement of Munc13-1 in presynaptic long-term synaptic plasticity. We further demonstrate that the interaction between RIM1 α and Munc13-1 is required for this plasticity. These results advance our understanding of the molecular mechanisms of presynaptic plasticity and suggest that modulation of vesicle priming may provide the cellular substrate for expression of LTP at mossy fiber synapses.

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Articles

CELLULAR/MOLECULAR

Spinal Synthesis of Estrogen and Concomitant Signaling by Membrane Estrogen Receptors Regulate Spinal κ - and μ -Opioid Receptor Heterodimerization and Female-Specific Spinal Morphine Antinociception

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We previously demonstrated that the spinal cord κ -opioid receptor (KOR) and μ -opioid receptor (MOR) form heterodimers (KOR/MOR). KOR/MOR formation and the associated KOR dependency of spinal morphine antinociception are most robust during proestrus. Using Sprague Dawley rats, we now demonstrate that (1) spinal synthesis of estrogen is critical to these processes, and (2) blockade of either estrogen receptor (ER) α -, β -, or G-protein-coupled ER1 or progesterone receptor (PR) substantially reduces KOR/MOR and eliminates mediation by KOR of spinal morphine antinociception. Effects of blocking ERs were manifest within 15 min, whereas those of PR blockade were manifest after 18 h, indicating the requirement for rapid signaling by estrogen and transcriptional effects of progesterone. Individual or combined blockade of ERs produced the same magnitude of effect, suggesting that they work in tandem as part of a macromolecular complex to regulate KOR/MOR formation. Consistent with this inference, we found that KOR and MOR were coexpressed with ER α and G-protein-coupled ER1 in the spinal dorsal horn. Reduction of KOR/MOR by ER or PR blockade or spinal aromatase inhibition shifts spinal morphine antinociception from KOR dependent to KOR independent. This indicates a sex steroid-dependent plasticity of spinal KOR functionality, which could explain the greater analgesic potency of KOR agonists in women versus men. We suggest that KOR/MOR is a molecular switch that shifts the function of KOR and thereby endogenous dynorphin from pronociceptive to antinociceptive. KOR/MOR could thus serve as a novel molecular target for pain management in women.

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Determination of Transmembrane Water Fluxes in Neurons Elicited by Glutamate Ionotropic Receptors and by the Cotransporters KCC2 and NKCC1: A Digital Holographic Microscopy Study

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Digital holographic microscopy (DHM) is a noninvasive optical imaging technique that provides quantitative phase images of living cells. In a recent study, we showed that the quantitative monitoring of the phase signal by DHM was a simple label-free method to study the effects of glutamate on neuronal optical responses (Pavillon et al., 2010). Here, we refine these observations and show that glutamate produces the following three distinct optical responses in mouse primary cortical neurons in culture, predominantly mediated by NMDA receptors: biphasic, reversible decrease (RD) and irreversible decrease (ID) responses. The shape and amplitude of the optical signal were not associated with a particular cellular phenotype but reflected the physiopathological status of neurons linked to the degree of NMDA activity. Thus, the biphasic, RD, and ID responses indicated, respectively, a low-level, a high-level, and an “excitotoxic” level of NMDA activation. Moreover, furosemide and bumetanide, two inhibitors of sodium-coupled and/or potassium-coupled chloride movement strongly modified the phase shift, suggesting an involvement of two neuronal cotransporters, NKCC1

(Na-K-Cl) and KCC2 (K-Cl) in the genesis of the optical signal. This observation is of particular interest since it shows that DHM is the first imaging technique able to monitor dynamically and *in situ* the activity of these cotransporters during physiological and/or pathological neuronal conditions.
The Journal of Neuroscience, August 17, 2011 • 31(33):11846–11854

Dual Regulation of Anterograde and Retrograde Transmission by Endocannabinoids

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Endocannabinoids (eCBs) are feedback messengers in the nervous system that act at the presynaptic nerve terminal to inhibit transmitter release. Here we report that in brain slices from rat, eCBs are released from vasopressin (VP) neurons in the paraventricular nucleus of the hypothalamus following coincident bursts of presynaptic and postsynaptic spiking. eCBs transiently depress glutamate release from excitatory terminals and, in doing so, prevent the synapses from undergoing long-term depression (LTD). Specifically, we show that blockade of CB1 receptors unmasks LTD following coincident presynaptic and postsynaptic activity. This LTD is presynaptic in nature, but requires the release of the opioid peptide dynorphin from the postsynaptic neuron. Dynorphin release and subsequent LTD require the activation of postsynaptic metabotropic glutamate receptors (mGluRs). Our findings indicate that eCBs, by transiently depressing glutamate release, limit mGluR activation and indirectly gate release of dynorphin from the postsynaptic neuron. We propose that eCBs, in addition to their well described role in the rapid modulation of transmitter release from the nerve terminal, also regulate the release of other retrograde transmitters and thus encode for multiple temporal windows of synaptic plasticity.

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Cyclin-Dependent Kinase 5 Regulates PSD-95 Ubiquitination in Neurons

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Cyclin-dependent kinase 5 (Cdk5) and its activator p35 have been implicated in drug addiction, neurodegenerative diseases such as Alzheimer's, learning and memory, and synapse maturation and plasticity. However, the molecular mechanisms by which Cdk5 regulates synaptic plasticity are still unclear. PSD-95 is a major postsynaptic scaffolding protein of glutamatergic synapses that regulates synaptic strength and plasticity. PSD-95 is ubiquitinated by the ubiquitin E3 ligase Mdm2, and rapid and transient PSD-95 ubiquitination has been implicated in NMDA receptor-induced AMPA receptor endocytosis. Here we demonstrate that genetic or pharmacological reduction of Cdk5 activity increases the interaction of Mdm2 with PSD-95 and enhances PSD-95 ubiquitination without affecting PSD-95 protein levels *in vivo* in mice, suggesting a nonproteolytic function of ubiquitinated PSD-95 at synapses. We show that PSD-95 ubiquitination correlates with increased interaction with β -adaptin, a subunit of the clathrin adaptor protein complex AP-2. This interaction is increased by genetic reduction of Cdk5 activity or NMDA receptor stimulation and is dependent on Mdm2. Together these results support a function for Cdk5 in regulating PSD-95 ubiquitination and its interaction with AP-2 and suggest a mechanism by which PSD-95 may regulate NMDA receptor-induced AMPA receptor endocytosis.

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DEVELOPMENT/PLASTICITY/REPAIR

TrkB as a Potential Synaptic and Behavioral Tag

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Late-phase long-term potentiation (L-LTP), a cellular model for long-term memory (LTM), requires *de novo* protein synthesis. An attractive hypothesis for synapse specificity of long-term memory is "synaptic tagging": synaptic activity generates a tag, which "captures" the PRPs (plasticity-related proteins) derived outside of synapses. Here we provide evidence that TrkB, the receptor of BDNF (brain-derived neurotrophic factor), may serve as a "synaptic tag." TrkB is transiently activated by weak theta-burst stimulation (TBS) that induces only early-phase LTP (E-LTP). This TrkB activation is independent of protein synthesis, and confined to stimulated synapses. Induction of L-LTP by strong stimulation in one synaptic pathway converts weak TBS-induced E-LTP to L-LTP in a second, independent pathway. Transient inhibition of TrkB around the time of weak TBS to the second pathway diminished L-LTP in that pathway without affecting the first one. Behaviorally, weak training, which induces short-term memory (STM) but not LTM, can be consolidated into LTM by exposing animals to novel but not familiar environment 1 h before training. Inhibition of TrkB during STM training blocked such consolidation. These results suggest TrkB as a potential tag for synapse-specific expression of L-LTP and LTM.

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Regulation of Temporal and Spatial Organization of Newborn GnRH Neurons by IGF Signaling in Zebrafish

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When and how newborn neurons are organized to form a functional network in the developing brain remains poorly understood. An attractive model is the gonadotropin-releasing hormone (GnRH) neuron system, master regulator of the reproductive axis. Here we show that blockage of IGF signaling, a central growth-promoting signaling pathway, by the induced expression of a dominant-negative form of IGF1 receptor (IGF1R) or specific IGF1R inhibitors delayed the emergence of GnRH2 neurons in the midbrain and GnRH3 neurons in the olfactory bulb region. Blockage of IGF signaling also resulted in an abnormal appearance of GnRH3 neurons outside of the olfactory bulb region, although it did not change the locations of other olfactory neurons, GnRH2 neurons, or brain patterning. This IGF action is developmental stage-dependent because the blockade of IGF signaling in advanced embryos had no such effect. An application of phosphatidylinositol 3-kinase (PI3K) inhibitors phenocopied the IGF signaling deficient embryos, whereas the MAPK inhibitors had no effect, suggesting that this IGF action is mediated through the PI3K pathway. Real-time *in vivo* imaging studies revealed that the ectopic GnRH3 neurons emerged at the same time as the normal GnRH3 neurons in IGF-deficient embryos. Further experiments suggest that IGF signaling affects the spatial distribution of newborn GnRH3 neurons by influencing neural crest cell migration and/or differentiation. These results suggest that the IGF-IGF1R-PI3K pathway regulates the precise temporal and spatial organization of GnRH neurons in zebrafish and provides new insights into the regulation of GnRH neuron development.

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The Postnatal Accumulation of Junctional E-Cadherin Is Inversely Correlated with the Capacity for Supporting Cells to Convert Directly into Sensory Hair Cells in Mammalian Balance Organs

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Mammals experience permanent impairments from hair cell (HC) losses, but birds and other non-mammals quickly recover hearing and balance senses after supporting cells (SCs) give rise to replacement HCs. Avian HC epithelia express little or no E-cadherin, and differences in the thickness of F-actin belts at SC junctions strongly correlate with different species' capacities for HC replacement, so we investigated junctional cadherins in human and murine ears. We found strong E-cadherin expression at SC–SC junctions that increases more than sixfold postnatally in mice. When we cultured utricles from young mice with γ -secretase inhibitors (GSIs), striolar SCs completely internalized their E-cadherin, without affecting N-cadherin. *Hes* and *Hey* expression also decreased and the SCs began to express *Atoh1*. After 48 h, those SCs expressed myosins VI and VIIA, and by 72 h, they developed hair bundles. However, some scattered striolar SCs retained E-cadherin and the SC phenotype. In extrastriolar regions, the vast majority of SCs also retained E-cadherin and failed to convert into HCs even after long GSI treatments. Microscopic measurements revealed that the junctions between extrastriolar SCs were more developed than those between striolar SCs. In GSI-treated utricles as old as P12, differentiated striolar SCs converted into HCs, but such responses declined with age and ceased by P16. Thus, temporal and spatial differences in postnatal SC-to-HC phenotype conversion capacity are linked to the structural attributes of E-cadherin containing SC junctions in mammals, which differ substantially from their counterparts in non-mammalian vertebrates that readily recover from hearing and balance deficits through hair cell regeneration.

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TrkB and Protein Kinase M ζ Regulate Synaptic Localization of PSD-95 in Developing Cortex

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Postsynaptic density 95 (PSD-95), the major scaffold at excitatory synapses, is critical for synapse maturation and learning. In rodents, eye opening, the onset of pattern vision, triggers a rapid movement of PSD-95 from visual neuron somata to synapses. We showed previously that the PI3 kinase–Akt pathway downstream of BDNF/TrkB signaling stimulates synaptic delivery of PSD-95 via vesicular transport. However, vesicular transport requires PSD-95 palmitoylation to attach it to a lipid membrane. Also, PSD-95 insertion at synapses is known to require this lipid modification. Here, we show that BDNF/TrkB signaling is also necessary for PSD-95 palmitoylation and its transport to synapses in mouse visual cortical layer 2/3 neurons. However, palmitoylation of PSD-95 requires the activation of another pathway downstream of BDNF/TrkB, namely, signaling through phospholipase C γ and the brain-specific PKC variant protein kinase M ζ (PKM ζ). We find that PKM ζ selectively regulates phosphorylation of the palmitoylation enzyme ZDHHC8. Inhibition of PKM ζ results in a reduction of synaptic PSD-95 accumulation *in vivo*, which can be rescued by overexpressing ZDHHC8. Therefore, TrkB and PKM ζ , two critical regulators of synaptic plasticity, facilitate PSD-95 targeting to synapses. These results also indicate that palmitoylation can be regulated by a trophic factor. Our findings have implications for neurodevelopmental disorders as well as aging brains.

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Fas-Associated Factor 1 as a Regulator of Olfactory Axon Guidance

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Axon guidance is a crucial part of neural circuit formation. While precise axonal targeting forms the basis of accurate information delivery, the mechanisms that regulate this process are still unclear. Apoptotic signaling molecules have been identified in the axon terminal, but their specific role in axon guidance is not well understood. Here we use the mouse olfactory system as an *in vivo* model to demonstrate that by modulating Fas-associated factor 1 (FAF1), an apoptosis regulatory molecule, we can rewire axonal projections. Interestingly, FAF1 is highly expressed in the developing mouse olfactory system, but its expression is downregulated postnatally. Using a tetracycline-inducible promoter Tet-Off system, we generated transgenic mice in which FAF1 is specifically expressed in immature olfactory sensory neurons (OSNs) and show that overexpression of FAF1 not only misroutes OSN axons to deep layers of the olfactory bulb but also leads to widespread disruption of the glomerular layer. In addition, we also demonstrate that the specific convergence of P2 receptor OSN axons is completely distorted in the FAF1 mice. Strikingly, all of the mutant phenotypes can be recovered by shutting down FAF1 expression through the administration of doxycycline. Together, our study provides clear *in vivo* evidence that an apoptotic molecule can indeed regulate axon targeting and that OSNs can restore their organization even after broad disruption.

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Macroglial Plasticity and the Origins of Reactive Astroglia in Experimental Autoimmune Encephalomyelitis

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Accumulations of hypertrophic, intensely glial fibrillary acidic protein-positive (GFAP⁺) astroglia, which also express immunoreactive nestin and vimentin, are prominent features of multiple sclerosis lesions. The issues of the cellular origin of hypertrophic GFAP⁺/vimentin⁺/nestin⁺ “reactive” astroglia and also the plasticities and lineage relationships among three macroglial progenitor populations—oligodendrocyte progenitor cells (OPCs), astrocytes and ependymal cells—during multiple sclerosis and other CNS diseases remain controversial. We used genetic fate-mappings with a battery of inducible Cre drivers (Olig2-Cre-ER^{T2}, GFAP-Cre-ER^{T2}, FoxJ1-Cre-ER^{T2} and Nestin-Cre-ER^{T2}) to explore these issues in adult mice with myelin oligodendrocyte glycoprotein peptide-induced experimental autoimmune encephalomyelitis (EAE). The proliferative rate of spinal cord OPCs rose fivefold above control levels during EAE, and numbers of oligodendroglia increased as well, but astrogenesis from OPCs was rare. Spinal cord ependymal cells, previously reported to be multipotent, did not augment their low proliferative rate, nor give rise to astroglia or OPCs. Instead, the hypertrophic, vimentin⁺/nestin⁺, reactive astroglia that accumulated in spinal cord in this multiple sclerosis model were derived by proliferation and phenotypic transformation of fibrous astroglia in white matter, and solely by phenotypic transformation of protoplasmic astroglia in gray matter. This comprehensive analysis of macroglial plasticity in EAE helps to clarify the origins of astrogliosis in CNS inflammatory demyelinating disorders.

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Oxygen/Glucose Deprivation Induces a Reduction in Synaptic AMPA Receptors on Hippocampal CA3 Neurons Mediated by mGluR1 and Adenosine A₃ Receptors

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Hippocampal CA1 pyramidal neurons are highly sensitive to ischemic damage, whereas neighboring CA3 pyramidal neurons are less susceptible. It is proposed that switching of AMPA receptor (AMPA) subunits on CA1 neurons during an *in vitro* model of ischemia, oxygen/glucose deprivation (OGD), leads to an enhanced permeability of AMPARs to Ca²⁺, resulting in delayed cell death. However, it is unclear whether the same mechanisms exist in CA3 neurons and whether this underlies the differential sensitivity to ischemia. Here, we investigated the consequences of OGD for AMPAR function in CA3 neurons using electrophysiological recordings in rat hippocampal slices. Following a 15 min OGD protocol, a substantial depression of AMPAR-mediated synaptic transmission was observed at CA3 associational/commissural and mossy fiber synapses but not CA1 Schaffer collateral synapses. The depression of synaptic transmission following OGD was prevented by metabotropic glutamate receptor 1 (mGluR1) or A₃ receptor antagonists, indicating a role for both glutamate and adenosine release. Inhibition of PLC, PKC, or chelation of intracellular Ca²⁺ also prevented the depression of synaptic transmission. Inclusion of peptides to interrupt the interaction between GluA2 and PICK1 or dynamin and amphiphysin prevented the depression of transmission, suggesting a dynamin and PICK1-dependent internalization of AMPARs after OGD. We also show that a reduction in surface and total AMPAR protein levels after OGD was prevented by mGluR1 or A₃ receptor antagonists, indicating that AMPARs are degraded following internalization. Thus, we describe a novel mechanism for the removal of AMPARs in CA3 pyramidal neurons following OGD that has the potential to reduce excitotoxicity and promote neuroprotection.

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Early Prenatal Stress Epigenetically Programs Dysmasculinization in Second-Generation Offspring via the Paternal Lineage

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Studies have linked sex-biased neurodevelopmental disorders, including autism and schizophrenia, with fetal antecedents such as prenatal stress. Further, these outcomes can persist into subsequent generations, raising the possibility that aspects of heritability in these diseases involve epigenetic mechanisms. Utilizing a mouse model in which we previously identified a period in early gestation when stress results in dysmasculinized and stress-sensitive male offspring, we have examined programming effects in second-generation offspring of prenatally stressed (F2-S) or control (F2-C) sires. Examination of gene expression patterns during the perinatal sensitive period, when organizational gonadal hormones establish the sexually dimorphic brain, confirmed dysmasculinization in F2-S males, where genes important in neurodevelopment showed a female-like pattern. Analyses of the epigenomic miRNA environment detected significant reductions in miR-322, miR-574, and miR-873 in the F2-S male brain, levels that were again more similar to those of control females. Increased expression of a common gene target for these three miRNAs, β -glycan, was confirmed in these males. These developmental effects were associated with the transmission of a stress-sensitive phenotype and shortened anogenital distance in adult F2-S males. As confirmation that the miRNA environment is responsive to organizational testosterone, neonatal males administered the aromatase inhibitor formestane exhibited dramatic changes in brain miRNA patterns, suggesting that miRNAs may serve a previously unappreciated role in organizing the sexually dimorphic brain. Overall, these data support the existence of a sensitive period of early gestation when epigenetic programming of the male germline can occur, permitting transmission of specific phenotypes into subsequent generations.

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Cellular-Resolution Population Imaging Reveals Robust Sparse Coding in the *Drosophila* Mushroom Body

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Sensory stimuli are represented in the brain by the activity of populations of neurons. In most biological systems, studying population coding is challenging since only a tiny proportion of cells can be recorded simultaneously. Here we used two-photon imaging to record neural activity in the relatively simple *Drosophila* mushroom body (MB), an area involved in olfactory learning and memory. Using the highly sensitive calcium indicator GCaMP3, we simultaneously monitored the activity of >100 MB neurons *in vivo* (~5% of the total population). The MB is thought to encode odors in sparse patterns of activity, but the code has yet to be explored either on a population level or with a wide variety of stimuli. We therefore imaged responses to odors chosen to evaluate the robustness of sparse representations. Different odors activated distinct patterns of MB neurons; however, we found no evidence for spatial organization of neurons by either response probability or odor tuning within the cell body layer. The degree of sparseness was consistent across a wide range of stimuli, from monomolecular odors to artificial blends and even complex natural smells. Sparseness was mainly invariant across concentrations, largely because of the influence of recent odor experience. Finally, in contrast to sensory processing in other systems, no response features distinguished natural stimuli from monomolecular odors. Our results indicate that the fundamental feature of odor processing in the MB is to create sparse stimulus representations in a format that facilitates arbitrary associations between odor and punishment or reward.

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The General and Outcome-Specific Forms of Pavlovian-Instrumental Transfer Are Differentially Mediated by the Nucleus Accumbens Core and Shell

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Tests of Pavlovian-instrumental transfer (PIT) demonstrate that reward-predictive stimuli can exert a powerful motivational influence on the performance of instrumental actions. Recent evidence suggests that predictive stimuli produce this effect through either the general arousal (general PIT) or the specific predictions (outcome-specific PIT) produced by their association with reward. In two experiments, we examined the effects of pretraining lesions (Experiment 1) or muscimol-induced inactivation (Experiment 2) of either the core or shell regions of the nucleus accumbens (NAC) on these forms of PIT. Rats received Pavlovian training in which three auditory stimuli each predicted the delivery of a distinct food outcome. Separately, the rats were trained to perform two instrumental actions, each of which earned one of the outcomes used in Pavlovian conditioning. Finally, the effects of the three stimuli on performance of the two actions were assessed in extinction. Here we report evidence of a double dissociation between general and outcome-specific PIT at the level of the accumbens. Shell lesions eliminated outcome-specific PIT but spared general PIT, whereas lesions of the core abolished general PIT but spared outcome-specific PIT. Importantly, the infusion of muscimol into core or shell made immediately before the PIT tests produced a similar pattern of results. These results suggest that whereas the NAC core mediates the general excitatory effects of reward-related cues, the NAC shell mediates the effect of outcome-specific reward predictions on instrumental performance, and thereby serve to clarify reported discrepancies regarding the role of the NAC core and shell in PIT.

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One Week of Motor Adaptation Induces Structural Changes in Primary Motor Cortex That Predict Long-Term Memory One Year Later

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The neural bases of motor adaptation have been extensively explored in human and nonhuman primates. A network including the cerebellum, primary motor cortex, and posterior parietal cortex appears to be crucial for this type of learning. Yet, to date, it is unclear whether these regions contribute directly or indirectly to the formation of motor memories. Here we trained subjects on a complex visuomotor rotation associated with long-term memory (in the order of months) to identify potential sites of structural plasticity induced by adaptation. One week of training led to (1) an increment in local gray matter concentration over the hand area of the contralateral primary motor cortex and (2) an increase in fractional anisotropy in an area underneath this region that correlated with the speed of learning. Moreover, the change in gray matter concentration measured immediately after training predicted improvements in the speed of learning during readaptation 1 year later. Our study suggests that motor adaptation induces structural plasticity in primary motor circuits. In addition, it provides the first piece of evidence indicating that early structural changes induced by motor learning may impact on behavior up to 1 year after training.

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Fasting and 17 β -Estradiol Differentially Modulate the M-Current in Neuropeptide Y Neurons

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Multiple K⁺ conductances are targets for many peripheral and central signals involved in the control of energy homeostasis. Potential K⁺ channel targets are the KCNQ subunits that form the channels underlying the M-current, a subthreshold, non-inactivating K⁺ current that is a common target for G-protein-coupled receptors. Whole-cell recordings were made from GFP (*Renilla*)-tagged neuropeptide Y (NPY) neurons from the arcuate nucleus of the hypothalamus using protocols to isolate and characterize the M-current in these orexigenic neurons. We recorded robust K⁺ currents in the voltage range of the M-current, which were inhibited by the selective KCNQ channel blocker 10,10-bis(4-pyridinylmethyl)-9(10H)-anthracene dihydrochloride (XE991) (40 μ M), in both intact males and ovariectomized, 17 β -estradiol (E2)-treated females. Since NPY neurons are orexigenic and are active during fasting, the M-current was measured in fed and fasted male mice. Fasting attenuated the XE991-sensitive current by threefold, which correlated with decreased expression of the KCNQ2 and KCNQ3 subunits as measured with quantitative real-time PCR. Furthermore, E2 treatment augmented the XE991-sensitive M-current by threefold in ovariectomized (vs oil-treated) female mice. E2 treatment increased the expression of the KCNQ5 subunit in females but not KCNQ2 or KCNQ3 subunits. Fasting in females abrogated the effects of E2 on M-current activity, at least in part, by decreasing KCNQ2 and KCNQ3 expression. In summary, these data suggest that the M-current plays a pivotal role in the modulation of NPY neuronal excitability and may be an important cellular target for neurotransmitter and hormonal signals in the control of energy homeostasis in both males and females.

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Extra-Classical Tuning Predicts Stimulus-Dependent Receptive Fields in Auditory Neurons

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The receptive fields of many sensory neurons are sensitive to statistical differences among classes of complex stimuli. For example, excitatory spectral bandwidths of midbrain auditory neurons and the spatial extent of cortical visual neurons differ during the processing of natural stimuli compared to the processing of artificial stimuli. Experimentally characterizing neuronal nonlinearities that contribute to stimulus-dependent receptive fields is important for understanding how neurons respond to different stimulus classes in multiple sensory modalities. Here we show that in the zebra finch, many auditory midbrain neurons have extra-classical receptive fields, consisting of sideband excitation and sideband inhibition. We also show that the presence, degree, and asymmetry of stimulus-dependent receptive fields during the processing of complex sounds are predicted by the presence, valence, and asymmetry of extra-classical tuning. Neurons for which excitatory bandwidth expands during the processing of song have extra-classical excitation. Neurons for which frequency tuning is static and for which excitatory bandwidth contracts during the processing of song have extra-classical inhibition. Simulation experiments further demonstrate that stimulus-dependent receptive fields can arise from extra-classical tuning with a static spike threshold nonlinearity. These findings demonstrate that a common neuronal nonlinearity can account for the stimulus dependence of receptive fields estimated from the responses of auditory neurons to stimuli with natural and non-natural statistics.

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Downregulation of the Posterior Medial Frontal Cortex Prevents Social Conformity

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We often change our behavior to conform to real or imagined group pressure. Social influence on our behavior has been extensively studied in social psychology, but its neural mechanisms have remained largely unknown. Here we demonstrate that the transient downregulation of the posterior medial frontal cortex by theta-burst transcranial magnetic stimulation reduces conformity, as indicated by reduced conformal adjustments in line with group opinion. Both the extent and probability of conformal behavioral adjustments decreased significantly relative to a sham and a control stimulation over another brain area. The posterior part of the medial frontal cortex has previously been implicated in behavioral and attitudinal adjustments. Here, we provide the first interventional evidence of its critical role in social influence on human behavior.

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ERK2 Contributes to the Control of Social Behaviors in Mice

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Signaling through extracellular signal-regulated kinase (ERK) is important in multiple signal transduction networks in the CNS. However, the specific role of ERK2 in *in vivo* brain functions is not fully understood. Here we show that ERK2 play a critical role in regulating social behaviors as well as cognitive and emotional behaviors in mice. To study the brain function of ERK2, we used a conditional, region-specific, genetic approach to target *Erk2* using the Cre/loxP strategy with a *nestin* promoter-driven *cre* transgenic mouse line to induce recombination in the CNS. The resulting *Erk2* conditional knock-out (CKO) mice, in which *Erk2* was abrogated specifically in the CNS, were viable and fertile with a normal appearance. These mice, however, exhibited marked anomalies in multiple aspects of social behaviors related to facets of autism-spectrum disorders: elevated aggressive behaviors, deficits in maternal nurturing, poor nest-building, and lower levels of social familiarity and social interaction. *Erk2* CKO mice also exhibited decreased anxiety-related behaviors and impaired long-term memory. Pharmacological inhibition of ERK1 phosphorylation in *Erk2* CKO mice did not affect the impairments in social behaviors and learning disabilities, indicating that ERK2, but not ERK1 plays a critical role in these behaviors. Our findings suggest that ERK2 has complex and multiple roles in the CNS, with important implications for human psychiatric disorders characterized by deficits in social behaviors.

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Descending Corticospinal Control of Intersegmental Dynamics

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To make an accurate movement, the CNS has to overcome the inherent complexities of the multijoint limb. For example, interaction torques arise when motion of individual arm segments propagates to adjacent segments causing their movement without any muscle contractions. Since these passive joint torques significantly add to the overall torques generated by active muscular contractions, they must be taken into account during planning or execution of goal-directed movements. We investigated the role of the corticospinal tract in compensating for the interaction torques during arm movements in humans. Twelve subjects reached to visual targets with their arm supported by a robotic exoskeleton. Reaching to one target was accompanied by interaction torques that assisted the movement, while reaching to the other target was accompanied by interaction torques that resisted the movement. Corticospinal excitability was assessed at different times during movement using single-pulse transcranial magnetic stimulation (TMS) over the upper-arm region of M1 (primary motor cortex). We found that TMS responses in shoulder monoarticular and elbow-shoulder biarticular muscles changed together with the interaction torques during movements in which the interaction torques were resistive. In contrast, TMS responses did not correlate with assistive interaction torques or with co-contraction. This suggests that the descending motor command includes compensation for passive limb dynamics. Furthermore, our results suggest that compensation for interaction torques involves the biarticular muscles, which span both shoulder and elbow joints and are in a biomechanically advantageous position to provide such compensation.

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The Control of Mimicry by Eye Contact Is Mediated by Medial Prefrontal Cortex

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Spontaneous mimicry of other people's actions serves an important social function, enhancing affiliation and social interaction. This mimicry can be subtly modulated by different social contexts. We recently found behavioral evidence that direct eye gaze rapidly and specifically enhances mimicry of intransitive hand movements (Wang et al., 2011). Based on past findings linking medial prefrontal cortex (mPFC) to both eye contact and the control of mimicry, we hypothesized that mPFC might be the neural origin of this behavioral effect. The present study aimed to test this hypothesis. During functional magnetic resonance imaging (fMRI) scanning, 20 human participants performed a simple mimicry or no-mimicry task, as previously described (Wang et al., 2011), with direct gaze present on half of the trials. As predicted, fMRI results showed that performing the task activated mirror systems, while direct gaze and inhibition of the natural tendency to mimic both engaged mPFC. Critically, we found an interaction between mimicry and eye contact in mPFC, superior temporal sulcus (STS) and inferior frontal gyrus. We then used dynamic causal modeling to contrast 12 possible models of information processing in this network. Results supported a model in which eye contact controls mimicry by modulating the connection strength from mPFC to STS. This suggests that mPFC is the originator of the gaze–mimicry interaction and that it modulates sensory input to the mirror system. Thus, our results demonstrate how different components of the social brain work together to on-line control mimicry according to the social context.

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Associative Learning Increases Trial-by-Trial Similarity of BOLD-MRI Patterns

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Associative learning is a dynamic process that allows us to incorporate new knowledge within existing semantic networks. Even after years, a seemingly stable association can be altered by a single significant experience. Here, we investigate whether the acquisition of new associations affects the neural representation of stimuli and how the brain categorizes stimuli according to preexisting and emerging associations. Functional MRI data were collected during a differential fear conditioning procedure and at test (4–5 weeks later). Two pictures of faces and two pictures of houses served as stimuli. One of each pair coterminated with a shock in half of the trials (partial reinforcement). Applying Multivoxel Pattern Analysis (MVPA) in a trial-by-trial manner, we quantified changes in the similarity of neural representations of stimuli over the course of conditioning. Our findings show an increase in similarity of neural patterns throughout the cortex on consecutive trials of the reinforced stimuli. Furthermore, neural pattern similarity reveals a shift from original categories (faces/houses) toward new categories (reinforced/unreinforced) over the course of conditioning. This effect was differentially represented in the cortex, with visual areas primarily reflecting similarity of low-level stimulus properties (original categories) and frontal areas reflecting similarity of stimulus significance (new categories). Effects were not dependent on overall response amplitude and were still present during follow-up. We conclude that trial-by-trial MVPA is a useful tool for examining how the human brain encodes relevant associations and forms new associative networks.

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Representation of Vestibular and Visual Cues to Self-Motion in Ventral Intraparietal Cortex

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Convergence of vestibular and visual motion information is important for self-motion perception. One cortical area that combines vestibular and optic flow signals is the ventral intraparietal area (VIP). We characterized unisensory and multisensory responses of macaque VIP neurons to translations and rotations in three dimensions. Approximately one-half of VIP cells show significant directional selectivity in response to optic flow, one-half show tuning to vestibular stimuli, and one-third show multisensory responses. Visual and vestibular direction preferences of multisensory VIP neurons could be congruent or opposite. When visual and vestibular stimuli were combined, VIP responses could be dominated by either input, unlike the medial superior temporal area (MSTd) where optic flow tuning typically dominates or the visual posterior sylvian area (VPS) where vestibular tuning dominates. Optic flow selectivity in VIP was weaker than in MSTd but stronger than in VPS. In contrast, vestibular tuning for translation was strongest in VPS, intermediate in VIP, and weakest in MSTd. To characterize response dynamics, direction–time data were fit with a spatiotemporal model in which temporal responses were modeled as weighted sums of velocity, acceleration, and position components. Vestibular responses in VIP reflected balanced contributions of velocity and acceleration, whereas visual responses were dominated by velocity. Timing of vestibular responses in VIP was significantly faster than in MSTd, whereas timing of optic flow responses did not differ significantly among areas. These findings suggest that VIP may be proximal to MSTd in terms of vestibular processing but hierarchically similar to MSTd in terms of optic flow processing.

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Aminopyridines Correct Early Dysfunction and Delay Neurodegeneration in a Mouse Model of Spinocerebellar Ataxia Type 1

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The contribution of neuronal dysfunction to neurodegeneration is studied in a mouse model of spinocerebellar ataxia type 1 (SCA1) displaying impaired motor performance ahead of loss or atrophy of cerebellar Purkinje cells. Presymptomatic SCA1 mice show a reduction in the firing rate of Purkinje cells (both *in vivo* and in slices) associated with a reduction in the efficiency of the main glutamatergic synapse onto Purkinje cells and with increased A-type potassium current. The A-type potassium channel Kv4.3 appears to be internalized in response to glutamatergic stimulation in Purkinje cells and accumulates in presymptomatic SCA1 mice. SCA1 mice are treated with aminopyridines, acting as potassium channel blockers to test whether the treatment could improve neuronal dysfunction, motor behavior, and neurodegeneration. In acutely treated young SCA1 mice, aminopyridines normalize the firing rate of Purkinje cells and the motor behavior of the animals. In chronically treated old SCA1 mice, 3,4-diaminopyridine improves the firing rate of Purkinje cells, the motor behavior of the animals, and partially protects against cell atrophy. Chronic treatment with 3,4-diaminopyridine is associated with increased cerebellar levels of BDNF, suggesting that partial protection against atrophy of Purkinje cells is possibly provided by an increased production of growth factors secondary to the reincrease in electrical activity. Our data suggest that aminopyridines might have symptomatic and/or neuroprotective beneficial effects in SCA1, that reduction in the firing rate of Purkinje cells can cause cerebellar ataxia, and that treatment of early neuronal dysfunction is relevant in neurodegenerative disorders such as SCA1.

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Regulator of G-Protein Signaling-10 Negatively Regulates NF- κ B in Microglia and Neuroprotects Dopaminergic Neurons in Hemiparkinsonian Rats

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Microglia are the brain-resident macrophages responsible for immune surveillance that become activated in response to injury, infection, environmental toxins, and other stimuli that threaten neuronal survival. Previous work from our group demonstrated that mice deficient in Regulator of G-protein Signaling 10 (RGS10), a microglia-enriched GTPase activating protein (GAP) for G-protein α subunits, displayed increased microglial burden in the CNS at birth and developed a parkinsonian phenotype after exposure to chronic systemic inflammation, implicating a neuroprotective role for RGS10 in the nigrostriatal pathway. While it is known that RGS10 is expressed in both microglia and certain subsets of neurons, it is not known whether RGS10 functions similarly in both cell types. In this study we sought to delineate the specific role of RGS10 in microglia and identify the molecular pathway(s) required for RGS10 to exert its actions in microglia. Here, we identify RGS10 as a negative regulator of the nuclear factor κ B (NF- κ B) pathway in microglia and demonstrate that the proinflammatory and cytotoxic phenotype of Rgs10-null microglia can be reversed by lentiviral-mediated restoration of RGS10 expression. *In vivo* gene transfer of RGS10 into the substantia nigra pars compacta (SNpc) of rats reduced microgliosis and protected against 6-OHDA neurotoxin-induced death of dopaminergic (DA) neurons. Together, our findings suggest that modulation of RGS10 activity in microglia may afford therapeutic benefit in the treatment of chronic neuroinflammatory conditions as well as neuroprotection against inflammation-related degeneration in Parkinson's disease (PD), the second most common neurodegenerative disorder affecting individuals over age 65.

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Palmitoyl Acyltransferase zD17 Mediates Neuronal Responses in Acute Ischemic Brain Injury by Regulating JNK Activation in a Signaling Module

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Although the palmitoyl acyltransferase (PAT) zinc-finger DHHC containing 17 (zD17) has been implicated in genetic neurological disorders by regulating protein palmitoylation, the role of zD17 in acute brain injury remains unknown. Here, we report that zD17 contributes to acute ischemic brain injury via a mechanism independent of its PAT activity. We have found that zD17 directly interacts with c-Jun N terminus kinase (JNK) to form a signaling module for JNK activation. Pathological stressors induce the zD17–JNK interaction, which promotes downstream neuronal cell death signals. We have developed novel peptides targeting the JNK-interacting motif on zD17 to selectively block the enhancement of the zD17–JNK interaction and the activation of JNK isoforms 2 and 3. Application of these peptides successfully blocks JNK activation and neuronal cell death pathways, protects cultured neurons from excitotoxicity, and dramatically reduces brain damage and behavioral deficits in a rat model of focal ischemic stroke. Our findings indicate zD17 as a key player in ischemic stroke and suggest the potential therapeutic value of targeting the zD17–JNK interaction for acute brain injury.

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Small Heat Shock Proteins Induce a Cerebral Inflammatory Reaction

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More than 80% of Alzheimer's disease (AD) patients have some degree of cerebral amyloid angiopathy (CAA). In addition to arteries and veins, capillaries can also be affected. Capillary CAA (capCAA), rather than CAA in larger vessels, is associated with flame-like amyloid-beta ($A\beta$) deposits that may extend beyond the vessel wall and radiate into the neuropil, a phenomenon also known as "dyshoric angiopathy." $A\beta$ deposits in AD, parenchymal as well as (cap)CAA and dyshoric angiopathy, are associated with a local inflammatory reaction, including activation of microglial cells and astrocytes that, among others, produce cytokines and reactive oxygen species. This neuroinflammatory reaction may account for at least part of the cognitive decline. In previous studies we observed that small heat shock proteins (sHsps) are associated with $A\beta$ deposits in AD. In this study the molecular chaperones Hsp20, HspB8 and HspB2B3 were found to colocalize with CAA and capCAA in AD brains. In addition, Hsp20, HspB8 and HspB2B3 colocalized with intercellular adhesion molecule 1 (ICAM-1) in capCAA-associated dyshoric angiopathy. Furthermore, we demonstrated that Hsp20, HspB8 and HspB2B3 induced production of interleukin 8, soluble ICAM-1 and monocyte chemoattractant protein 1 by human leptomeningeal smooth muscle cells and human brain astrocytes *in vitro* and that Hsp27 inhibited production of transforming growth factor beta 1 and CD40 ligand. Our results suggest a central role for sHsps in the neuroinflammatory reaction in AD and CAA and thus in contributing to cognitive decline.

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