

This Week in The Journal

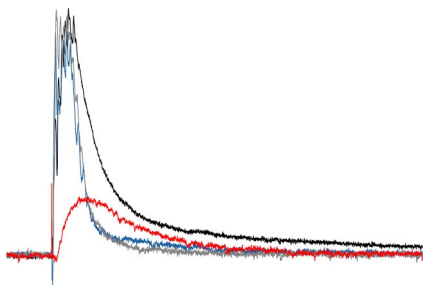
● Cellular/Molecular

Extrasynaptic GABA Receptors Modulate Phasic Inhibition

Murray B. Herd, Adam R. Brown, Jeremy J. Lambert, and Delia Belelli

(see pages 14850–14868)

GABAergic neurons in the thalamic reticular nucleus (nRT) inhibit thalamocortical relay neurons by acting on synaptic $\alpha 1\beta 2\gamma 2$ GABA_A receptors (GABA_ARs) and extrasynaptic $\alpha 4\beta 2\delta$ GABA_ARs. Activation of synaptic GABA_ARs produces phasic inhibition of thalamocortical neurons, whereas activation of extrasynaptic GABA_ARs underlies tonic inhibition. To investigate how these receptors interact, Herd et al. recorded from synaptically coupled pairs of nRT neurons and thalamocortical neurons of the ventrobasal complex (VB) in mouse brain slices. Surprisingly, knocking out $\alpha 4$ subunits and thus extrasynaptic GABA_ARs not only reduced tonic inhibitory currents in VB neurons, but also reduced the duration of phasic inhibition evoked by spike bursts in nRT neurons. Furthermore, a selective agonist of δ -subunit-containing (extrasynaptic) GABA_ARs prolonged inhibition evoked by nRT bursts, and stimulation of nRT evoked IPSCs even in VB neurons that lacked $\alpha 1$ subunits and thus the predominant synaptic GABA receptor. Together, these data indicate that extrasynaptic receptors not only mediate tonic inhibition of VB neurons, but also contribute to phasic inhibition evoked by nRT bursts.



IPSCs evoked by nRT stimulation were of shorter duration in VB neurons lacking extrasynaptic GABA_ARs (blue) than in wild-type neurons (black). IPSCs persisted in neurons lacking synaptic GABA_ARs (red). See the article by Herd et al. for details.

● Development/Plasticity/Repair

Adult-Born Neurons Are Unresponsive to GABA_B Agonist

Matthew T. Valley, Lansdale G. Henderson, Samuel A. Inverso, and Pierre-Marie Lledo

(see pages 14660–14665)

Neurons are continuously generated in the subventricular zone of adult mammals. Newborn neurons travel along the rostral migratory stream (RMS) to the olfactory bulb, where most differentiate into granule cells (GCs) that provide inhibitory input to mitral cells. Newborn GCs contribute to olfactory learning and discrimination, and it has been hypothesized that newborn GCs have functional properties that earlier-born GCs lack. To investigate this possibility, Valley et al. injected channelrhodopsin-expressing virus into mouse RMS, selectively infecting newborn GCs en route to the olfactory bulb. They then compared postsynaptic responses evoked by optical stimulation of newborn GCs to responses evoked by electrical stimulation, which activates GCs of all ages. Notably, GABA_B receptor (GABA_BR) agonists, which reduced IPSCs evoked by electrical stimulation by suppressing GABA release from GCs, did not affect IPSCs evoked by photoactivation of adult-born GCs. This reduced responsiveness to GABA_BR agonist was associated with altered patterns of GABA_BR expression, supporting the hypothesis that adult-born GCs are fundamentally different than earlier born neurons.

● Systems/Circuits

Hippocampal CA2 Directly Projects to Entorhinal Cortex

David C. Rowland, Aldis P. Weible, Ian R. Wickersham, Haiyan Wu, Mark Mayford, et al.

(see pages 14889–14898)

Neurons in layer II (LII) of the entorhinal cortex (EC) provide the main input to the hippocampal formation, projecting to the dentate gyrus, which in turn projects to CA3; CA3 projects to CA1, which projects

to deep layers of EC. Transmission of information through this circuit is involved in constructing spatial maps and episodic memories. To identify inputs to EC LII, Rowland et al. used a recombinant rabies virus in which the glycoprotein required for transsynaptic infection was deleted, the protein required to infect neurons was replaced by one that recognizes an avian receptor, and a fluorescent protein was inserted. This virus was injected into transgenic mice in which the deleted glycoprotein and the avian receptor were expressed exclusively in medial EC LII neurons. The virus therefore selectively infected these neurons and their presynaptic partners. In addition to labeling known inputs, this technique revealed direct projections from CA2 to EC. This suggests that CA2 has unique roles in hippocampal processing.

● Neurobiology of Disease

miR-26b Induces Pathologies Found in Alzheimer's Disease

Sabrina Absalon, Dawn M. Kochanek, Venkatesan Raghavan, and Anna M. Krichevsky

(see pages 14645–14659)

Although accumulation of toxic β -amyloid peptides is the chief defining feature of Alzheimer's disease (AD), many other pathologies are present, including accumulation of abnormally phosphorylated tau protein, cell cycle re-entry, and apoptosis. Absalon et al. propose that these other pathologies stem from increased levels of microRNA miR-26b, which they detected in temporal cortex in early stages of AD. Increasing miR-26b levels in cultured rat cortical neurons decreased levels of retinoblastoma protein (Rb) and p27, which normally prevent cell cycle entry by preventing transcription of cell cycle proteins. Consequently, increasing miR-26b levels also increased expression of cell cycle proteins, ultimately resulting in apoptosis. Additionally, because p27 forms a complex that localizes cyclin-dependent kinase 5 (Cdk5) to the nucleus, decreasing p27 allowed Cdk5 to exit the nucleus and phosphorylate cytoplasmic targets, including AD-associated sites on tau. Cell cycle entry, nuclear exit of Cdk5, and apoptosis also occur when neurons are treated with H₂O₂, but intriguingly, inhibiting miR-26b increased neuronal survival after H₂O₂ treatment.

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Cover legend: Confocal micrograph of cross section through a the forebrain of a stage 37/38 *Xenopus laevis* embryo. Immunostaining for nuclear lamins II/III (magenta) labeled the nuclear envelope. Subcellular localization of heterogeneous nuclear ribonucleoprotein K (hnRNP K) was visualized by its expression as a fusion with Enhanced Green Fluorescent Protein (green). During neuronal development, hnRNP K is highly enriched in the nuclear compartment, while a small subset shuttles to the cytoplasm, where its post-transcriptional regulation of mRNA targets essential for axon outgrowth is mediated by c-Jun N-terminal kinase. For more information, see Hutchins and Szaro (14666–14680).

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14974 **Retraction:** The article “Whisker Dynamics Underlying Tactile Exploration” by S. Andrew Hires, Alexander L. Efron, and Karel Svoboda appeared on pages 9576–9591 of the June 5, 2013 issue. A retraction for that article appears on page 14974.

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Rapid Recalibration to Audiovisual Asynchrony

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To combine information from different sensory modalities, the brain must deal with considerable temporal uncertainty. In natural environments, an external event may produce simultaneous auditory and visual signals yet they will invariably activate the brain asynchronously due to different propagation speeds for light and sound, and different neural response latencies once the signals reach the receptors. One strategy the brain uses to deal with audiovisual timing variation is to adapt to a prevailing asynchrony to help realign the signals. Here, using psychophysical methods in human subjects, we investigate audiovisual recalibration and show that it takes place extremely rapidly without explicit periods of adaptation. Our results demonstrate that exposure to a single, brief asynchrony is sufficient to produce strong recalibration effects. Recalibration occurs regardless of whether the preceding trial was perceived as synchronous, and regardless of whether a response was required. We propose that this rapid recalibration is a fast-acting sensory effect, rather than a higher-level cognitive process. An account in terms of response bias is unlikely due to a strong asymmetry whereby stimuli with vision leading produce bigger recalibrations than audition leading. A fast-acting recalibration mechanism provides a means for overcoming inevitable audiovisual timing variation and serves to rapidly realign signals at onset to maximize the perceptual benefits of audiovisual integration.

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Defective Escape Behavior in DEAH-Box RNA Helicase Mutants Improved by Restoring Glycine Receptor Expression

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RNA helicases regulate RNA metabolism, but their substrate specificity and *in vivo* function remain largely unknown. We isolated spontaneous mutant zebrafish that exhibit an abnormal dorsal bend at the beginning of tactile-evoked escape swimming. Similar behavioral defects were observed in zebrafish embryos treated with strychnine, which blocks glycine receptors (GlyRs), suggesting that the abnormal motor response in mutants may be attributable to a deficit in glycinergic synaptic transmission. We identified a missense mutation in the gene encoding RNA helicase Dhx37. In Dhx37 mutants, ribosomal RNA levels were unchanged, whereas GlyR $\alpha 1$, $\alpha 3$, and $\alpha 4a$ subunit mRNA levels were decreased due to a splicing defect. We found that Dhx37 can interact with GlyR $\alpha 1$, $\alpha 3$, and $\alpha 4a$ transcripts but not with the GlyR $\alpha 2$ subunit mRNA. Overexpression of GlyR $\alpha 1$, $\alpha 3$, or $\alpha 4a$ subunits in Dhx37-deficient embryos restored normal behavior. Conversely, antisense-mediated knockdown of multiple GlyR α subunits in wild-type embryos was required to recapitulate the Dhx37 mutant phenotype. These results indicate that Dhx37 is specifically required for the biogenesis of a subset of GlyR α subunit mRNAs, thereby regulating glycinergic synaptic transmission and associated motor behaviors. To our knowledge, this is the first identification of pathologically relevant substrates for an RNA helicase.

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Adult Neurogenesis Produces Neurons with Unique GABAergic Synapses in the Olfactory Bulb

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Neuronal regeneration occurs naturally in a few restricted mammalian brain regions, but its functional significance remains debated. Here we search for unique features in the synaptic outputs made by adult-born granule cell interneurons in the mouse olfactory bulb using optogenetic targeting of specific neuronal ages. We find that adult-born interneurons are resistant to presynaptic GABA_B-mediated depression of GABA release compared with interneurons born just after birth that exhibit strong GABA_B neuromodulation. Correlated with this functional change, we found altered localization of the GABA_BR1 protein within adult-born granule cells. These results suggest that adult neurogenesis produces a population of functionally unique GABAergic synapses in the olfactory bulb.

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Endothelial VEGF Sculpts Cortical Cytoarchitecture

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Current models of brain development support the view that VEGF, a signaling protein secreted by neuronal cells, regulates angiogenesis and neuronal development. Here we demonstrate an autonomous and pivotal role for endothelial cell-derived VEGF that has far-reaching consequences for mouse brain development. Selective deletion of *Vegf* from endothelial cells resulted in impaired angiogenesis and marked perturbation of cortical cytoarchitecture. Abnormal cell clusters or heterotopias were detected in the marginal zone, and disorganization of cortical cells induced several malformations, including aberrant cortical lamination. Critical events during brain development—neuronal proliferation, differentiation, and migration—were significantly affected. In addition, axonal tracts in the telencephalon were severely defective in the absence of endothelial VEGF. The unique roles of endothelial VEGF cannot be compensated by neuronal VEGF and underscores the high functional significance of endothelial VEGF for cerebral cortex development and from disease perspectives.

The Journal of Neuroscience, September 11, 2013 • 33(37):14809–14815

Informational Basis of Sensory Adaptation: Entropy and Single-Spike Efficiency in Rat Barrel Cortex

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We showed recently that exposure to whisker vibrations enhances coding efficiency in rat barrel cortex despite increasing correlations in variability (Adibi et al., 2013). Here, to understand how adaptation achieves this improvement in sensory representation, we decomposed the stimulus information carried in neuronal population activity into its fundamental components in the framework of information theory. In the context of sensory coding, these components are the entropy of the responses across the entire stimulus set (response entropy) and the entropy of the responses conditional on the stimulus (conditional response entropy). We found that adaptation decreased response entropy and conditional response entropy at both the level of single neurons and the pooled activity of neuronal populations. However, the net effect of adaptation was to increase the mutual information because the drop in the conditional entropy outweighed the drop in the response entropy. The information transmitted by a single spike also increased under adaptation. As population size increased, the information content of individual spikes declined but the relative improvement attributable to adaptation was maintained.

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Articles

CELLULAR/MOLECULAR

c-Jun N-Terminal Kinase Phosphorylation of Heterogeneous Nuclear Ribonucleoprotein K Regulates Vertebrate Axon Outgrowth via a Posttranscriptional Mechanism

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c-Jun N-terminal kinase (JNK) mediates cell signaling essential for axon outgrowth, but the associated substrates and underlying mechanisms are poorly understood. We identified in *Xenopus laevis* embryos a novel posttranscriptional mechanism whereby JNK regulates axonogenesis by phosphorylating a specific site on heterogeneous nuclear ribonucleoprotein K (hnRNP K). Both JNK inhibition and hnRNP K knockdown inhibited axon outgrowth and translation of hnRNP K-regulated cytoskeletal RNAs (*tau* and *neurofilament medium*), effects that were alleviated by expressing phosphomimetic, but not phosphodeficient, forms of hnRNP K. Immunohistochemical and biochemical analyses indicated that JNK phosphorylation of hnRNP K occurred within the cytoplasm and was necessary for the translational initiation of hnRNP K-targeted RNAs but not for hnRNP K intracellular localization or RNA binding. Thus, in addition to its known roles in transcription and cytoskeletal organization, JNK acts posttranscriptionally through hnRNP K to regulate translation of proteins crucial for axonogenesis.

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P2X Receptor Intermediate Activation States Have Altered Nucleotide Selectivity

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Purinergic P2X receptors are widely distributed in the nervous system and are known to play roles in primary afferent transmission and central respiratory regulation. They are trimeric membrane proteins, with the extracellular domain that provides three intersubunit ATP binding sites. We expressed the rat P2X7 receptor in human embryonic kidney cells and measured membrane currents before and after photo-affinity labeling with the agonist 2'-(3')-O-(4-benzoylbenzoyl)-ATP (BzATP). After tethering BzATP with ultraviolet light, a persistent current remained after washing out the agonist. Additional current could now be elicited by other nucleotides (CTP and ADP) that are not normally effective as P2X receptor agonists. Similar results were obtained at P2X2 receptors even without previous agonist tethering: exposure to low concentrations of ATP caused the receptor to become sensitive to activation by CTP and ADP. The results show that ATP binding to the first of the three binding sites causes a conformational change to an intermediate closed state that shows increased effectiveness of pyrimidine and diphosphate nucleotide analogs.

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Extrasynaptic GABA_A Receptors Couple Presynaptic Activity to Postsynaptic Inhibition in the Somatosensory Thalamus

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Thalamocortical circuits govern cognitive, sensorimotor, and sleep-related network processes, and generate pathological activities during absence epilepsy. Inhibitory control of thalamocortical (TC) relay neurons is partially mediated by GABA released from neurons of the thalamic reticular nucleus (nRT), acting predominantly via synaptic $\alpha 1\beta 2\gamma 2$ GABA_A receptors (GABA_ARs). Importantly, TC neurons also express extrasynaptic $\alpha 4\beta 2\delta$ GABA_ARs, although how they cooperate with synaptic GABA_ARs to influence relay cell inhibition, particularly during physiologically relevant nRT output, is unknown. To address this question, we performed paired whole-cell recordings from synaptically coupled nRT and TC neurons of the ventrobasal (VB) complex in brain slices derived from wild-type and extrasynaptic GABA_AR-lacking, $\alpha 4$ “knock-out” ($\alpha 4^{0/0}$) mice. We demonstrate that the duration of VB phasic inhibition generated in response to nRT burst firing is greatly reduced in $\alpha 4^{0/0}$ pairs, suggesting that action potential-dependent phasic inhibition is prolonged by recruitment of extrasynaptic GABA_ARs. Furthermore, the influence of nRT tonic firing frequency on VB holding current is also greatly reduced in $\alpha 4^{0/0}$ pairs, implying that the $\alpha 4$ -GABA_AR-mediated tonic conductance of relay neurons is dynamically influenced, in an activity-dependent manner, by nRT tonic firing intensity. Collectively, our data reveal that extrasynaptic GABA_ARs of the somatosensory thalamus do not merely provide static tonic inhibition but can also be dynamically engaged to couple presynaptic activity to postsynaptic excitability. Moreover, these processes are highly sensitive to the δ -selective allosteric modulator, DS2 and manipulation of GABA transport systems, revealing novel opportunities for therapeutic intervention in thalamocortical network disorders.

The Journal of Neuroscience, September 11, 2013 • 33(37):14850–14868

cGMP Accumulation Causes Photoreceptor Degeneration in CNG Channel Deficiency: Evidence of cGMP Cytotoxicity Independently of Enhanced CNG Channel Function

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Photoreceptor cyclic nucleotide-gated (CNG) channels regulate Ca^{2+} influx in rod and cone photoreceptors. cGMP, the native ligand of the photoreceptor CNG channels, has been associated with cytotoxicity when its levels rise above normal due to defects in photoreceptor phosphodiesterase (PDE6) or regulation of retinal guanylyl cyclase (retGC). We found a massive accumulation of cGMP in CNGA3-deficient retina and investigated whether cGMP accumulation plays a role in cone degeneration in CNG channel deficiency. The time course study showed that the retinal cGMP level in *Cnga3*^{−/−}; *Nrl*^{−/−} mice with CNGA3 deficiency on a cone-dominant background was sharply increased at postnatal day 8 (P8), peaked around P10–P15, remained high through P30–P60, and returned to near control level at P90. This elevation pattern correlated with photoreceptor apoptotic death, which peaked around P15–P20. In *Cnga3*^{−/−}; *Gucy2e*^{−/−} mice lacking retGC1, cone density and expression levels of cone-specific proteins were significantly increased compared with *Cnga3*^{−/−}, consistent with a role of cGMP accumulation as the major contributor to cone death caused by CNG channel deficiency. The activity and expression levels of cGMP-dependent protein kinase G (PKG) were significantly increased in *Cnga3*^{−/−}; *Nrl*^{−/−} retina compared with *Nrl*^{−/−}, suggesting an involvement of PKG regulation in cell death. Our results indicate that cGMP accumulation in photoreceptors can itself exert cytotoxic effect in cones, independently of CNG channel activity and Ca^{2+} influx.

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Ontogeny of Excitatory Spinal Neurons Processing Distinct Somatic Sensory Modalities

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Spatial and temporal cues govern the genesis of a diverse array of neurons located in the dorsal spinal cord, including dI1–dI6, dIL_A, and dIL_B subtypes, but their physiological functions are poorly understood. Here we generated a new line of conditional knock-out (*CKO*) mice, in which the homeobox gene *Tlx3* was removed in dI5 and dIL_B cells. In these *CKO* mice, development of a subset of excitatory neurons located in laminae I and II was impaired, including itch-related GRPR-expressing neurons, PKC γ -expressing neurons, and neurons expressing three neuropeptide genes: somatostatin, preprotachykinin 1, and the gastrin-releasing peptide. These *CKO* mice displayed marked deficits in generating nocifensive motor behaviors evoked by a range of pain-related or itch-related stimuli. The mutants also failed to exhibit escape response evoked by dynamic mechanical stimuli but retained the ability to sense innocuous cooling and/or warm. Thus, our studies provide new insight into the ontogeny of spinal neurons processing distinct sensory modalities.

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Dynein-Dependent Transport of *nanos* RNA in *Drosophila* Sensory Neurons Requires Rumpelstiltskin and the Germ Plasm Organizer Oskar

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Intracellular mRNA localization is a conserved mechanism for spatially regulating protein production in polarized cells, such as neurons. The mRNA encoding the translational repressor Nanos (Nos) forms ribonucleoprotein (RNP) particles that are dendritically localized in *Drosophila* larval class IV dendritic arborization (da) neurons. In *nos* mutants, class IV da neurons exhibit reduced dendritic branching complexity, which is rescued by transgenic expression of wild-type *nos* mRNA but not by a localization-compromised *nos* derivative. While localization is essential for *nos* function in dendrite morphogenesis, the mechanism underlying the transport of *nos* RNP particles was unknown. We investigated the mechanism of dendritic *nos* mRNA localization by analyzing requirements for *nos* RNP particle motility in class IV da neuron dendrites through live imaging of fluorescently labeled *nos* mRNA. We show that dynein motor machinery components mediate transport of *nos* mRNA in proximal dendrites. Two factors, the RNA-binding protein Rumpelstiltskin and the germ plasm protein Oskar, which are required for diffusion/entrapment-mediated localization of *nos* during oogenesis, also function in da neurons for formation and transport of *nos* RNP particles. Additionally, we show that *nos* regulates neuronal function, most likely independent of its dendritic localization and function in morphogenesis. Our results reveal adaptability of localization factors for regulation of a target transcript in different cellular contexts.

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Neutrophils Express Oncomodulin and Promote Optic Nerve Regeneration

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Although neurons are normally unable to regenerate their axons after injury to the CNS, this situation can be partially reversed by activating the innate immune system. In a widely studied instance of this phenomenon, proinflammatory agents have been shown to cause retinal ganglion cells, the projection neurons of the eye, to regenerate lengthy axons through the injured optic nerve. However, the role of different molecules and cell populations in mediating this phenomenon remains unclear. We show here that neutrophils, the first responders of the innate immune system, play a central role in inflammation-induced regeneration. Numerous neutrophils enter the mouse eye within a few hours of inducing an inflammatory reaction and express high levels of the atypical growth factor oncomodulin (Ocm). Immunodepletion of neutrophils diminished Ocm levels in the eye without altering levels of CNTF, leukemia inhibitory factor, or IL-6, and suppressed the proregenerative effects of inflammation. A peptide antagonist of Ocm suppressed regeneration as effectively as neutrophil depletion. Macrophages enter the eye later in the inflammatory process but appear to be insufficient to stimulate extensive regeneration in the absence of neutrophils. These data provide the first evidence that neutrophils are a major source of Ocm and can promote axon regeneration in the CNS.

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Effects of Cathodal Trans-Spinal Direct Current Stimulation on Mouse Spinal Network and Complex Multijoint Movements

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Cathodal trans-spinal direct current (c-tsDC) stimulation is a powerful technique to modulate spinal excitability. However, the manner in which c-tsDC stimulation modulates cortically evoked simple single-joint and complex multijoint movements is unknown. To address this issue, anesthetized mice were suspended with the hindlimb allowed to move freely in space. Simple and complex multijoint movements were elicited with short and prolonged trains of electrical stimulation, respectively, delivered to the area of primary motor cortex representing the hindlimb. In addition, spinal cord burst generators are known to be involved in a variety of motor activities, including locomotion, postural control, and voluntary movements. Therefore, to shed light into the mechanisms underlying movements modulated by c-tsDC stimulation, spinal circuit activity was induced using GABA and glycine receptor blockers, which produced three rates of spinal bursting activity: fast, intermediate, and slow. Characteristics of bursting activity were assessed during c-tsDC stimulation. During c-tsDC stimulation, significant increases were observed in (1) ankle dorsiflexion amplitude and speed; (2) ankle plantarflexion amplitude, speed, and duration; and (3) complex multijoint movement amplitude, speed, and duration. However, complex multijoint movement tracing showed that c-tsDC did not change the form of movements. In addition, spinal bursting activity was significantly modulated during c-tsDC stimulation: (1) fast bursting activity showed increased rate, amplitude, and duration; (2) intermediate bursting activity showed increased rate and duration, but decreased amplitude; and (3) slow bursting activity showed increased rate, but decreased duration and amplitude. These results suggest that c-tsDC stimulation amplifies cortically evoked movements through spinal mechanisms.

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SYSTEMS/CIRCUITS

Lhx3-Chx10 Reticulospinal Neurons in Locomotor Circuits

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Motor behaviors result from the interplay between the brain and the spinal cord. Reticulospinal neurons, situated between the supraspinal structures that initiate motor movements and the spinal cord that executes them, play key integrative roles in these behaviors. However, the molecular identities of mammalian reticular formation neurons that mediate motor behaviors have not yet been determined, thus limiting their study in health and disease. In the medullary reticular formation of the mouse, we identified neurons that express the transcription factors Lhx3 and/or Chx10, and demonstrate that these neurons form a significant component of glutamatergic reticulospinal pathways. Lhx3-positive medullary reticular formation neurons express Fos following a locomotor task in the adult, indicating that they are active during walking. Furthermore, they receive functional inputs from the mesencephalic locomotor region and have electrophysiological properties to support tonic repetitive firing, both of which are necessary for neurons that mediate the descending command for locomotion. Together, these results suggest that Lhx3/Chx10 medullary reticular formation neurons are involved in locomotion.

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Emergence of Sensory Patterns during Sleep Highlights Differential Dynamics of REM and Non-REM Sleep Stages

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Despite the profound reduction in conscious awareness associated with sleep, sensory cortex remains highly active during the different sleep stages, exhibiting complex interactions between different cortical sites. The potential functional significance of such spatial patterns and how they change between different sleep stages is presently unknown. In this electrocorticography study of human patients, we examined this question by studying spatial patterns of activity (broadband gamma power) that emerge during sleep (sleep patterns) and comparing them to the functional organization of sensory cortex that is activated by naturalistic stimuli during the awake state. Our results show a high correlation ($p < 10^{-4}$, permutation test) between the sleep spatial patterns and the functional organization found during wakefulness. Examining how the sleep patterns changed through the night highlighted a stage-specific difference, whereby the repertoire of such patterns was significantly larger during rapid eye movement (REM) sleep compared with non-REM stages. These results reveal that intricate spatial patterns of sensory functional organization emerge in a stage-specific manner during sleep.

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Transgenically Targeted Rabies Virus Demonstrates a Major Monosynaptic Projection from Hippocampal Area CA2 to Medial Entorhinal Layer II Neurons

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The enormous potential of modern molecular neuroanatomical tools lies in their ability to determine the precise connectivity of the neuronal cell types comprising the innate circuitry of the brain. We used transgenically targeted viral tracing to identify the monosynaptic inputs to the projection neurons of layer II of medial entorhinal cortex (MEC-LII) in mice. These neurons are not only major inputs to the hippocampus, the structure most clearly implicated in learning and memory, they also are “grid cells.” Here we address the question of what kinds of inputs are specifically targeting these MEC-LII cells. Cell-specific infection of MEC-LII with recombinant rabies virus results in unambiguous labeling of monosynaptic inputs. Furthermore, ratios of labeled neurons in different regions are largely consistent between animals, suggesting that label reflects density of innervation. While the results mostly confirm prior anatomical work, they also reveal a novel major direct input to MEC-LII from hippocampal pyramidal neurons. Interestingly, the vast majority of these direct hippocampal inputs arise not from the major hippocampal subfields of CA1 and CA3, but from area CA2, a region that has historically been thought to merely be a transitional zone between CA3 and CA1. We confirmed this unexpected result using conventional tracing techniques in both rats and mice.

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Dynamic Tuning of Electrical and Chemical Synaptic Transmission in a Network of Motion Coding Retinal Neurons

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Recently, we demonstrated that gap junction coupling in the population of superior coding ON-OFF directionally selective ganglion cells (DSGCs) genetically labeled in the Hb9::eGFP mouse retina allows the passage of lateral anticipatory signals that help track moving stimuli. Here, we examine the properties of gap junctions in the DSGC network, and address how interactions between electrical and chemical synapses and intrinsic membrane properties contribute to the dynamic tuning of lateral anticipatory signals. When DSGC subtypes coding all four cardinal directions were individually loaded with the gap junction-permeable tracer Neurobiotin, only superior coding DSGCs exhibited homologous coupling. Consistent with these anatomical findings, gap junction-dependent feedback spikelets were only observed in Hb9⁺ DSGCs. Recordings from pairs of neighboring Hb9⁺ DSGCs revealed that coupling was reciprocal, non-inactivating, and relatively weak, and provided a substrate for an extensive subthreshold excitatory receptive field around each cell. This subthreshold activity appeared to boost coincident light-driven chemical synaptic responses. However, during responses to moving stimuli, gap junction-mediated boosting appeared to be dynamically modulated such that upstream DSGCs primed downstream cells, but not vice versa, giving rise to highly skewed responses in individual cells. We show that the asymmetry in priming arises from a combination of spatially offset GABAergic inhibition and activity-dependent changes in intrinsic membrane properties of DSGCs. Thus, dynamic interactions between electrical and chemical synapses and intrinsic membrane properties allow the network of DSGCs to propagate anticipatory responses most effectively along their preferred direction without leading to runaway excitation.

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Interacting Linear and Nonlinear Characteristics Produce Population Coding Asymmetries between ON and OFF Cells in the Retina

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The early visual system is a model for understanding the roles of cell populations in parallel processing. Cells in this system can be classified according to their responsiveness to different stimuli; a prominent example is the division between cells that respond to stimuli of opposite contrasts (ON vs OFF cells). These two cell classes display many asymmetries in their physiological characteristics (including temporal characteristics, spatial characteristics, and nonlinear characteristics) that, individually, are known to have important roles in population coding. Here we describe a novel distinction between the information that ON and OFF ganglion cell populations carry in mouse—that OFF cells are able to signal motion information about both light and dark objects, while ON cells have a selective deficit at signaling the motion of dark objects. We found that none of the previously reported asymmetries in physiological characteristics could account for this distinction. We therefore analyzed its basis via a recently developed linear–nonlinear–Poisson model that faithfully captures input/output relationships for a broad range of stimuli (Bomash et al., 2013). While the coding differences between ON and OFF cell populations could not be ascribed to the linear or nonlinear components of the model individually, they had a simple explanation in the way that these components interact. Sensory transformations in other systems can likewise be described by these models, and thus our findings suggest that similar interactions between component properties may help account for the roles of cell classes in population coding more generally.

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Opiate Exposure and Withdrawal Induces a Molecular Memory Switch in the Basolateral Amygdala between ERK1/2 and CaMKII α -Dependent Signaling Substrates

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Opiate reward memories are powerful triggers for compulsive opiate-seeking behaviors. The basolateral amygdala (BLA) is an important structure for the processing of opiate-related associative memories and is functionally linked to the mesolimbic dopamine (DA) pathway. Transmission through intra-BLA DA D1-like and D2-like receptors independently modulates the formation of opiate reward memories as a function of opiate-exposure state. Thus, in the opiate-naïve state, intra-BLA D1 transmission is required for opiate-related memory formation. Once opiate dependence and withdrawal has developed, a functional switch to a DA D2-mediated memory mechanism takes place. However, the downstream molecular signaling events that control this functional switch between intra-BLA DA D1 versus D2 receptor transmission are not currently understood. Using an unbiased place conditioning procedure in rats combined with molecular analyses, we report that opiate reward memory acquisition requires intra-BLA ERK1/2 signaling only in the previously opiate-naïve state. However, following chronic opiate exposure and withdrawal, intra-BLA reward memory processing switches to a CaMKII α -dependent memory substrate. Furthermore, the ability of intra-BLA DA D1 or D2 receptor transmission to modulate the motivational salience of opiates similarly operates through a D1-mediated ERK-dependent mechanism in the opiate-naïve state, but switches to a D2-mediated CaMKII α -dependent mechanism in the dependent/withdrawn state. Protein analysis of BLA tissue revealed a downregulation of ERK1/2 phosphorylation and a dramatic reduction in both total and phosphorylated CaMKII α signaling, specifically in the opiate-dependent/withdrawn state, demonstrating functional control of ERK1/2-dependent versus CaMKII α -dependent memory mechanisms within the BLA, controlled by opiate-exposure state.

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Repetition Suppression and Multi-Voxel Pattern Similarity Differentially Track Implicit and Explicit Visual Memory

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Repeated exposure to a visual stimulus is associated with corresponding reductions in neural activity, particularly within visual cortical areas. It has been argued that this phenomenon of repetition suppression is related to increases in processing fluency or implicit memory. However, repetition of a visual stimulus can also be considered in terms of the similarity of the pattern of neural activity elicited at each exposure—a measure that has recently been linked to explicit memory. Despite the popularity of each of these measures, direct comparisons between the two have been limited, and the extent to which they differentially (or similarly) relate to behavioral measures of memory has not been clearly established. In the present study, we compared repetition suppression and pattern similarity as predictors of both implicit and explicit memory. Using functional magnetic resonance imaging, we scanned 20 participants while they viewed and categorized repeated presentations of scenes. Repetition priming (facilitated categorization across repetitions) was used as a measure of implicit memory, and subsequent scene recognition was used as a measure of explicit memory. We found that repetition priming was predicted by repetition suppression in prefrontal, parietal, and occipitotemporal regions; however, repetition priming was not predicted by pattern similarity. In contrast, subsequent explicit memory was predicted by pattern similarity (across repetitions) in some of the same occipitotemporal regions that exhibited a relationship between priming and repetition suppression; however, explicit memory was not related to repetition suppression. This striking double dissociation indicates that repetition suppression and pattern similarity differentially track implicit and explicit learning.

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Subthalamic Nucleus Local Field Potential Activity during the Eriksen Flanker Task Reveals a Novel Role for Theta Phase during Conflict Monitoring

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The subthalamic nucleus (STN) is thought to play a central role in modulating responses during conflict. Computational models have suggested that the location of the STN in the basal ganglia, as well as its numerous connections to conflict-related cortical structures, allows it to be ideally situated to act as a global inhibitor during conflict. Additionally, recent behavioral experiments have shown that deep brain stimulation to the STN results in impulsivity during high-conflict situations. However, the precise mechanisms that mediate the “hold-your-horses” function of the STN remain unclear. We recorded from deep brain stimulation electrodes implanted bilaterally in the STN of 13 human subjects with Parkinson's disease while they performed a flanker task. The incongruent trials with the shortest reaction times showed no behavioral or electrophysiological differences from congruent trials, suggesting that the distracter stimuli were successfully ignored. In these trials, cue-locked STN theta band activity

demonstrated phase alignment across trials and was followed by a periresponse increase in theta power. In contrast, incongruent trials with longer reaction times demonstrated a relative reduction in theta phase alignment followed by higher theta power. Theta phase alignment negatively correlated with subject reaction time, and theta power positively correlated with trial reaction time. Thus, when conflicting stimuli are not properly ignored, disruption of STN theta phase alignment may help operationalize the hold-your-horses role of the nucleus, whereas later increases in the amplitude of theta oscillations may help overcome this function.

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Transfer of Cognitive Training across Magnitude Dimensions Achieved with Concurrent Brain Stimulation of the Parietal Lobe

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Improvement in performance following cognitive training is known to be further enhanced when coupled with brain stimulation. Here we ask whether training-induced changes can be maintained long term and, crucially, whether they can extend to other related but untrained skills. We trained overall 40 human participants on a simple and well established paradigm assessing the ability to discriminate numerosity— or the number of items in a set—which is thought to rely on an “approximate number sense” (ANS) associated with parietal lobes. We coupled training with parietal stimulation in the form of transcranial random noise stimulation (tRNS), a noninvasive technique that modulates neural activity. This yielded significantly better and longer lasting improvement (up to 16 weeks post-training) of the precision of the ANS compared with cognitive training in absence of stimulation, stimulation in absence of cognitive training, and cognitive training coupled to stimulation to a control site (motor areas). Critically, only ANS improvement induced by parietal tRNS + Training transferred to proficiency in other parietal lobe-based quantity judgment, i.e., time and space discrimination, but not to quantity-unrelated tasks measuring attention, executive functions, and visual pattern recognition. These results indicate that coupling intensive cognitive training with tRNS to critical brain regions resulted not only in the greatest and longer lasting improvement of numerosity discrimination, but importantly in this enhancement being transferable when trained and untrained abilities are carefully chosen to share common cognitive and neuronal components.

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Forebrain Deletion of the Vesicular Acetylcholine Transporter Results in Deficits in Executive Function, Metabolic, and RNA Splicing Abnormalities in the Prefrontal Cortex

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One of the key brain regions in cognitive processing and executive function is the prefrontal cortex (PFC), which receives cholinergic input from basal forebrain cholinergic neurons. We evaluated the contribution of synaptically released acetylcholine (ACh) to executive function by genetically targeting the vesicular acetylcholine transporter (VACHT) in the mouse forebrain. Executive function was assessed using a pairwise visual discrimination paradigm and the 5-choice serial reaction time task (5-CSRT). In the pairwise test, VACHT-deficient mice were able to learn, but were impaired in reversal learning, suggesting that these mice present cognitive inflexibility. Interestingly, VACHT-targeted mice took longer to reach criteria in the 5-CSRT. Although their performance was indistinguishable from that of control mice during low attentional demand, increased attentional demand revealed striking deficits in VACHT-deleted mice. Galantamine, a cholinesterase inhibitor used in Alzheimer's disease, significantly improved the performance of control mice, but not of VACHT-deficient mice on the 5-CSRT. *In vivo* magnetic resonance spectroscopy showed altered levels of two neurochemical markers of neuronal function, taurine and lactate, suggesting altered PFC metabolism in VACHT-deficient mice. The PFC of these mice displayed a drastic reduction in the splicing factor heterogeneous nuclear ribonucleoprotein A2/B1 (hnRNP A2/B1), whose cholinergic-mediated reduction was previously demonstrated in Alzheimer's disease. Consequently, several key hnRNP A2/B1 target transcripts involved in neuronal function present changes in alternative splicing in VACHT-deficient mice, including pyruvate kinase M, a key enzyme involved in lactate metabolism. We propose that VACHT-targeted mice can be used to model and to dissect the neurochemical basis of executive abnormalities.

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MiR-26b, Upregulated in Alzheimer's Disease, Activates Cell Cycle Entry, Tau-Phosphorylation, and Apoptosis in Postmitotic Neurons

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MicroRNA (miRNA) functions in the pathogenesis of major neurodegenerative diseases such as Alzheimer's disease (AD) are only beginning to emerge. We have observed significantly elevated levels of a specific miRNA, miR-26b, in the defined pathological areas of human postmortem brains, starting from early stages of AD (Braak III). Ectopic overexpression of miR-26b in rat primary postmitotic neurons led to the DNA replication and aberrant cell cycle entry (CCE) and, in parallel, increased tau-phosphorylation, which culminated in the apoptotic cell death of neurons. Similar tau hyperphosphorylation and CCE are typical features of neurons in pre-AD brains. Sequence-specific inhibition of miR-26b in culture is neuroprotective against oxidative stress. Retinoblastoma protein (Rb1), a major tumor suppressor, appears as the key direct miR-26b target, which mediates the observed neuronal phenotypes. The downstream signaling involves upregulation of Rb1/E2F cell cycle and pro-apoptotic transcriptional targets, including cyclin E1, and corresponding downregulation of cell cycle inhibitor p27/Kip1. It further leads to nuclear export and activation of Cdk5, a major kinase implicated in tau phosphorylation, regulation of cell cycle, and death in postmitotic neurons. Therefore, upregulation of miR-26b in neurons causes pleiotropic phenotypes that are also observed in AD. Elevated levels of miR-26b may thus contribute to the AD neuronal pathology.

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Abnormal Striatal Dopaminergic Neurotransmission during Rest and Task Production in Spasmodic Dysphonia

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Spasmodic dysphonia is a primary focal dystonia characterized by involuntary spasms in the laryngeal muscles during speech production. The pathophysiology of spasmodic dysphonia is thought to involve structural and functional abnormalities in the basal ganglia–thalamo-cortical circuitry; however, neurochemical correlates underpinning these abnormalities as well as their relations to spasmodic dysphonia symptoms remain unknown. We used positron emission tomography with the radioligand [¹¹C]raclopride (RAC) to study striatal dopaminergic neurotransmission at the resting state and during production of symptomatic sentences and asymptomatic finger tapping in spasmodic dysphonia patients. We found that patients, compared to healthy controls, had bilaterally decreased RAC binding potential (BP) to striatal dopamine D₂/D₃ receptors on average by 29.2%, which was associated with decreased RAC displacement (RAC ΔBP) in the left striatum during symptomatic speaking (group average difference 10.2%), but increased RAC ΔBP in the bilateral striatum during asymptomatic tapping (group average difference 10.1%). Patients with more severe voice symptoms and subclinically longer reaction time to initiate the tapping sequence had greater RAC ΔBP measures, while longer duration of spasmodic dysphonia was associated with a decrease in task-induced RAC ΔBP. Decreased dopaminergic transmission during symptomatic speech production may represent a disorder-specific pathophysiological trait involved in symptom generation, whereas increased dopaminergic function during unaffected task performance may be explained by a compensatory adaptation of the nigrostriatal dopaminergic system possibly due to decreased striatal D₂/D₃ receptor availability. These changes can be linked to the clinical and subclinical features of spasmodic dysphonia and may represent the neurochemical basis of basal ganglia alterations in this disorder.

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Alterations in Endogenous Opioid Functional Measures in Chronic Back Pain

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The absence of consistent end organ abnormalities in many chronic pain syndromes has led to a search for maladaptive CNS mechanisms that may explain their clinical presentations and course. Here, we addressed the role of brain regional μ -opioid receptor-mediated neurotransmission, one of the best recognized mechanisms of pain regulation, in chronic back pain in human subjects. We compared μ -opioid receptor availability *in vivo* at baseline, during pain expectation, and with moderate levels of sustained pain in 16 patients with chronic nonspecific back pain (CNBP) and in 16 age- and gender-matched healthy control subjects, using the μ -opioid receptor-selective radioligand [¹¹C]carfentanil and positron emission tomography. We found that CNBP patients showed baseline increases in thalamic μ -opioid receptor availability, contrary to a previously studied sample of patients diagnosed with fibromyalgia. During both pain expectation and sustained pain challenges, CNBP patients showed regional reductions in the capacity to activate this neurotransmitter system compared with their control sample, further associated with clinical pain and affective state

ratings. Our results demonstrate heterogeneity in endogenous opioid system functional measures across pain conditions, and alterations in both receptor availability and endogenous opioid function in CNBP that are relevant to the clinical presentation of these patients and the effects of opioid analgesics on μ -opioid receptors.
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Deficiency of p62/Sequestosome 1 Causes Hyperphagia Due to Leptin Resistance in the Brain

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The cytoplasmic regulatory protein p62 (Sequestosome 1/A170) is known to modulate various receptor-mediated intracellular signaling pathways. *p62* deficiency was shown to result in mature-onset obesity in mice, but the mechanisms underlying this abnormality remained unclear. Here we report that hyperphagia due to central leptin resistance is the cause of obesity in *p62*^{−/−} mice. We found that these mice show hyperphagia. Restriction of food to the amount eaten by wild-type mice prevented excess body weight gain and fat accumulation, suggesting that overfeeding is the primary cause of obesity in *p62*^{−/−} mice. Brain-specific p62 deficiency caused mature-onset obesity to the same extent as in *p62*^{−/−} mice, further supporting a neuronal mechanism as the major cause of obesity in these mice. Immunohistochemical analysis revealed that p62 is highly expressed in hypothalamic neurons, including POMC neurons in the arcuate nucleus. Central leptin resistance was observed even in young preobese *p62*^{−/−} mice. We found a defect in intracellular distribution of the transcription factor Stat3, which is essential for the action of leptin, in *p62*^{−/−} mice. These results indicate that brain p62 plays an important role in bodyweight control by modulating the central leptin-signaling pathway and that lack of p62 in the brain causes leptin resistance, leading to hyperphagia. Thus, p62 could be a clinical target for treating obesity and metabolic syndrome.

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WldS and PGC-1 α Regulate Mitochondrial Transport and Oxidation State after Axonal Injury

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Mitochondria carry out many of the processes implicated in maintaining axon health or causing axon degeneration, including ATP and reactive oxygen species (ROS) generation, as well as calcium buffering and protease activation. Defects in mitochondrial function and transport are common in axon degeneration, but how changes in specific mitochondrial properties relate to degeneration is not well understood. Using cutaneous sensory neurons of living larval zebrafish as a model, we examined the role of mitochondria in axon degeneration by monitoring mitochondrial morphology, transport, and redox state before and after laser axotomy. Mitochondrial transport terminated locally after injury in wild-type axons, an effect that was moderately attenuated by expressing the axon-protective fusion protein Wallerian degeneration slow (WldS). However, mitochondrial transport arrest eventually occurred in WldS-protected axons, indicating that later in the lag phase, mitochondrial transport is not required for axon protection. By contrast, the redox-sensitive biosensor roGFP2 was rapidly oxidized in the mitochondrial matrix after injury, and WldS expression prevented this effect, suggesting that stabilization of ROS production may mediate axon protection. Overexpression of PGC-1 α , a transcriptional coactivator with roles in both mitochondrial biogenesis and ROS detoxification, dramatically increased mitochondrial density, attenuated roGFP2 oxidation, and delayed Wallerian degeneration. Collectively, these results indicate that mitochondrial oxidation state is a more reliable indicator of axon vulnerability to degeneration than mitochondrial motility.

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The Pattern of Cortical Dysfunction in a Mouse Model of a Schizophrenia-Related Microdeletion

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We used a mouse model of the schizophrenia-predisposing 22q11.2 microdeletion to evaluate how this genetic lesion affects cortical neural circuits at the synaptic, cellular, and molecular levels. Guided by cognitive deficits, we demonstrated that mutant mice display robust deficits in high-frequency synaptic transmission and short-term plasticity (synaptic depression and potentiation), as well as alterations in long-term plasticity and dendritic spine stability. Apart from previously reported reduction in dendritic complexity of layer 5 pyramidal neurons, altered synaptic plasticity occurs in the context of relatively circumscribed and often subtle cytoarchitectural changes in neuronal density and inhibitory neuron numbers. We confirmed the pronounced DiGeorge critical region 8 (*Dgcr8*)-dependent deficits in primary micro-RNA processing and identified additional changes in gene expression and RNA splicing that may underlie the effects of this mutation. Reduction in *Dgcr8* levels appears to be a major driver of altered short-term synaptic plasticity in prefrontal cortex and working memory but not of long-term plasticity and cytoarchitecture. Our findings inform the

cortical synaptic and neuronal mechanisms of working memory impairment in the context of psychiatric disorders. They also provide insight into the link between micro-RNA dysregulation and genetic liability to schizophrenia and cognitive dysfunction.

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Inhibiting Subthalamic D₅ Receptor Constitutive Activity Alleviates Abnormal Electrical Activity and Reverses Motor Impairment in a Rat Model of Parkinson's Disease

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Burst firing has been reported as a pathological activity of subthalamic nucleus (STN) neurons in Parkinson's disease. However, the origin of bursts and their causal link with motor deficits remain unknown. Here we tested the hypothesis that dopamine D₅ receptors (D₅Rs), characterized by a high constitutive activity, may contribute to the emergence of burst firing in STN. We tested whether inhibiting D₅R constitutive activity depresses burst firing and alleviates motor impairments in the 6-OHDA rat model of Parkinson's disease. Intrastubthalamic microinjections of either an inverse agonist of D₅Rs, flupenthixol, or a D₂R antagonist, raclopride, were applied. Behavioral experiments, *in vivo* and *in vitro* electrophysiological recordings, and *ex vivo* functional neuroanatomy studies were performed. Using [³S]GTPγ binding autoradiography, we show that application of flupenthixol inhibits D₅R constitutive activity within the STN. Furthermore, flupenthixol reduced evoked burst in brain slices and converted pathological burst firing into physiological tonic, single-spike firing in 6-OHDA rats *in vivo*. This later action was mimicked by calcisepine, a Cav1 channel blocker. Moreover, the same treatment dramatically attenuated motor impairment in this model and normalized metabolic hyperactivity in both STN and substantia nigra pars reticulata, the main output structure of basal ganglia in rats. In contrast, raclopride as well as saline did not reverse burst firing and motor deficits, confirming the selective action of flupenthixol on D₅Rs. These results are the first to demonstrate that subthalamic D₅Rs are involved in the pathophysiology of Parkinson's disease and that administering an inverse agonist of these receptors may lessen motor symptoms.

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Endocannabinoids in the Brainstem Modulate Dural Trigemino-vascular Nociceptive Traffic via CB₁ and “Triptan” Receptors: Implications in Migraine

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Activation and sensitization of trigemino-vascular nociceptive pathways is believed to contribute to the neural substrate of the severe and throbbing nature of pain in migraine. Endocannabinoids, as well as being physiologically analgesic, are known to inhibit dural trigemino-vascular nociceptive responses. They are also involved in the descending modulation of cutaneous-evoked C-fiber spinal nociceptive responses from the brainstem. The purpose of this study was to determine whether endocannabinoids are involved in the descending modulation of dural and/or cutaneous facial trigemino-vascular nociceptive responses, from the brainstem ventrolateral periaqueductal gray (vlPAG). CB₁ receptor activation in the vlPAG attenuated dural-evoked Aδ-fiber neurons (maximally by 19%) and basal spontaneous activity (maximally by 33%) in the rat trigemino-cervical complex, but there was no effect on cutaneous facial receptive field responses. This inhibitory vlPAG-mediated modulation was inhibited by specific CB₁ receptor antagonism, given via the vlPAG, and with a 5-HT_{1B/1D} receptor antagonist, given either locally in the vlPAG or systemically. These findings demonstrate for the first time that brainstem endocannabinoids provide descending modulation of both basal trigemino-vascular neuronal tone and Aδ-fiber dural-nociceptive responses, which differs from the way the brainstem modulates spinal nociceptive transmission. Furthermore, our data demonstrate a novel interaction between serotonergic and endocannabinoid systems in the processing of somatosensory nociceptive information, suggesting that some of the therapeutic action of triptans may be via endocannabinoid containing neurons in the vlPAG.

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P-Selectin-Mediated Monocyte–Cerebral Endothelium Adhesive Interactions Link Peripheral Organ Inflammation To Sickness Behaviors

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Sickness behaviors, such as fatigue, mood alterations, and cognitive dysfunction, which result from changes in central neurotransmission, are prevalent in systemic inflammatory diseases and greatly impact patient quality of life. Although, microglia (resident cerebral immune cells) and cytokines (e.g., TNFα) are associated with changes in central neurotransmission, the link between peripheral organ inflammation, circulating cytokine signaling, and microglial activation remains poorly understood. Here we demonstrate, using cerebral intravital microscopy, that in response to liver inflammation, there is increased monocyte specific rolling and adhesion along cerebral endothelial cells (CECs). Peripheral TNFα–TNFR1 signaling and the adhesion molecule P-selectin are central mediators of these monocyte–CEC adhesive interactions which were found to be closely associated with microglial activation, decreased central neural excitability and sickness behavior development. Similar monocyte–CEC adhesive interactions were also observed in another mouse model of peripheral organ inflammation (i.e., 2,4-dinitrobenzene sulfonic acid-induced colitis). Our

observations provide a clear link between peripheral organ inflammation and cerebral changes that impact behavior, which can potentially allow for novel therapeutic interventions in patients with systemic inflammatory diseases.
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