

This Week in The Journal

● Cellular/Molecular

Cortactin-Binding Protein Regulates Cortactin Distribution

Yi-Kai Chen and Yi-Ping Hsueh

(see pages 1043–1055)

Cortactin is an actin-binding protein that stabilizes actin filaments and plays a role in endocytosis. Cortactin is enriched in dendritic spines, but NMDA receptor activation causes it to move from spines into the dendritic shaft, suggesting it contributes to neuronal plasticity, possibly by allowing remodeling of spine morphology. Indeed, knockdown of cortactin reduces spine density in cultured hippocampal neurons. Chen and Hsueh propose that cortactin distribution in neurons is regulated by cortactin-binding protein 2 (CTTNBP2). They found that CTTNBP2 was enriched in dendritic spines in cultured rat hippocampal neurons, but unlike cortactin and actin, CTTNBP2 remained in spine heads after glutamate treatment. Knockdown of CTTNBP2 reduced spine density, reduced levels of cortactin in remaining spines, and decreased the frequency of miniature EPSCs recorded in cultured hippocampal neurons. Spine density was rescued by expression of siRNA-resistant CTTNBP2 or overexpression of cortactin, but not by a mutated form of CTTNBP2 that could not bind to cortactin.

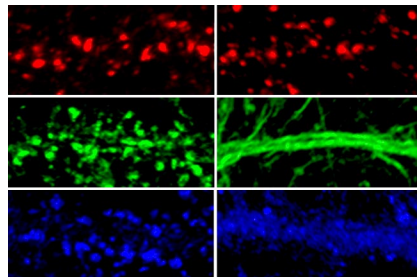
▲ Development/Plasticity/Repair

Adult Zebra Finch HVC Gains Neurons throughout Life

Clare Walton, Eben Pariser, and Fernando Nottebohm

(see pages 761–774)

Neurogenesis occurs in adults of many species, but its function is unclear. In seasonally breeding songbirds, the size of the high vocal center (HVC)—a region that influences the temporal order of syllables during singing—varies seasonally as a result of ongoing neuronal death and neurogenesis. This fluctuation was originally



Under normal conditions (left), CTTNBP2 (top), actin (middle), and cortactin (bottom) are concentrated in spines of cultured hippocampal neurons. NMDA treatment (right) causes actin and cortactin, but not CTTNBP2, to move into the shaft. See the article by Chen and Hsueh for details.

identified in canaries, which learn new songs during the fall when neuron addition peaks, and it was hypothesized to facilitate song alteration. But similar fluctuations also occur in species that sing the same song every spring. In these species, the song becomes more variable during non-breeding seasons, suggesting that the neurons lost and recruited contribute to song stability and maintenance. Walton et al. now report that zebra finches—which sing the same song throughout the year—also add HVC neurons throughout life, but without significant neuronal loss. Thus, the number of neurons in HVC doubles over the adult lifespan. The function of this neurogenesis remains a mystery.

■ Behavioral/Systems/Cognitive

Dyslexia-Linked ROBO1 Mutation Affects Auditory Processing

Satu Lamminmäki, Satu Massinen, Jaana Nopola-Hemmi, Juha Kere, and Riitta Hari

(see pages 966–971)

Dyslexia often results from deficits in the auditory processing required to distinguish phonemes in speech. This makes it difficult to relate written letters to phonemes, to combine letters into syllables, and therefore to learn to read. Dyslexia has a strong genetic component, and most of the genes proposed to cause the deficit are involved in neuronal migration or axon guidance. One such gene is *ROBO1*,

which regulates midline crossing by axons. Lamminmäki et al. studied a family in which mutations that reduce *ROBO1* expression are linked to dyslexia. To determine whether the mutation affects midline crossing, they measured binaural suppression, a reduction in auditory cortical responses to inputs from the ipsilateral ear that occurs when auditory stimuli are presented binaurally. This suppression depends on fibers crossing from the contralateral auditory cortex. Binaural suppression was greatly reduced in subjects harboring the abnormal *ROBO1* haplotype, and the reduced suppression was correlated with *ROBO1* expression level.

◆ Neurobiology of Disease

AMP Kinase Knockdown Attenuates Effects of SOD1 Mutation

M. A. Lim, M. A. Selak, Z. Xiang, D. Krainc, R. L. Neve, et al.

(see pages 1123–1141)

Mitochondrial dysfunction occurs in many neurodegenerative diseases. For example, amyotrophic lateral sclerosis (ALS) is sometimes caused by mutations in superoxide dismutase 1 (SOD1) that increase the protein's association with mitochondria, thus disrupting ATP production. Reductions in ATP/AMP ratios activate AMP kinase (AMPK), which initiates programs to increase energy supplies, such as increasing fatty acid oxidation and glucose uptake. But AMPK also activates pathways that conserve energy, e.g., by reducing protein synthesis. These processes might be detrimental to neurons and thus contribute to neuropathology. Indeed, Lim et al. found that expression of mutant SOD1 in rodent spinal cord neurons reduced mitochondrial respiration, increased activity of AMPK and an AMPK target that stimulates fatty acid oxidation, and reduced activity of an AMPK target that regulates protein translation. Knocking down AMPK greatly increased survival of neurons expressing mutant SOD1. Similarly, expressing mutant SOD1 in worms impaired locomotion, which was rescued by coexpressing nonfunctional AMPK.

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Cover legend: Cultured rat hippocampal neurons (18 days *in vitro*) that were treated with glutamate for 15 min, then stained for PSD-95 (red), CTTNBP2 (blue), and F-actin (green). Glutamate causes an NMDA receptor-dependent redistribution of F-actin from dendritic spines to a bundled pattern within dendrites; in contrast, PSD-95 and CTTNBP2 stably reside in dendritic spines. For more information, see the article by Chen and Hsueh in this issue (pages 1043–1055).

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1123 Reduced Activity of AMP-Activated Protein Kinase Protects against Genetic Models of Motor Neuron Disease

M. A. Lim, M. A. Selak, Z. Xiang, D. Krainc, R. L. Neve, B. C. Kraemer, J. L. Watts, and R. G. Kalb

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Sialic Acid on the Neuronal Glycocalyx Prevents Complement C1 Binding and Complement Receptor-3-Mediated Removal by Microglia

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Microglial cells are professional phagocytes of the CNS responsible for clearance of unwanted structures. Neuronal processes are marked by complement C1 before they are removed in development or during disease processes. Target molecules involved in C1 binding and mechanisms of clearance are still unclear. Here we show that the terminal sugar residue sialic acid of the mouse neuronal glycocalyx determines complement C1 binding and microglial-mediated clearance function. Several early components of the classical complement cascade including C1q, C1r, C1s, and C3 were produced by cultured mouse microglia. The opsonin C1q was binding to neurites after enzymatic removal of sialic acid residues from the neuronal glycocalyx. Desialylated neurites, but not neurites with intact sialic acid caps, were cleared and taken up by cocultured microglial cells. The removal of the desialylated neurites was mediated via the complement receptor-3 (CR3; CD11b/CD18). Data demonstrate that mouse microglial cells via CR3 recognize and remove neuronal structures with an altered neuronal glycocalyx lacking terminal sialic acid.

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Short-Term Plasticity of Unitary Inhibitory-to-Inhibitory Synapses Depends on the Presynaptic Interneuron Subtype

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Excitatory-to-inhibitory cortical synapses exhibit either short-term facilitation or depression, depending on the subtype identity of the postsynaptic interneuron, while the short-term plasticity (STP) of inhibitory-to-excitatory synapses depends on the presynaptic interneuron. However, the rules governing STP of inhibitory-to-inhibitory synapses have not yet been determined. We recorded 109 unitary connections made by the two major inhibitory interneuron subtypes in layer 4 of mouse somatosensory cortex, fast-spiking (FS) and somatostatin-containing (SOM) interneurons, on each other and on excitatory, regular-spiking (RS) neurons. In all pairs, we measured dynamic changes in the postsynaptic response to a 20 Hz train of presynaptic action potentials. In half of our dataset, we also measured kinetic properties of the unitary IPSC: latency, rise time, and decay time constant. We found a pronounced dependency of STP on the presynaptic, but not the postsynaptic, identity: FS interneurons made strongly depressing connections on FS, SOM, and RS targets, while in synapses made by SOM interneurons on FS and RS targets, weak early depression was followed by weak late facilitation. IPSC latency and rise time were also strongly dependent on the presynaptic interneuron subtype, being 1.5–2× slower in output synapses of SOM compared with FS interneurons. In contrast, the IPSC decay time constant depended only on the postsynaptic class, with 1.5× slower decay on excitatory compared with inhibitory targets. The properties of the inhibitory outputs of FS and SOM interneurons reciprocate the properties of their excitatory inputs and imply a dynamic spatiotemporal division of labor between these two major inhibitory subsystems.

The Journal of Neuroscience, January 18, 2012 • 32(3):983–988

The Rett Syndrome Protein MeCP2 Regulates Synaptic Scaling

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Synaptic scaling is a form of homeostatic synaptic plasticity characterized by cell-wide changes in synaptic strength in response to changes in overall levels of neuronal activity. Here we report that bicuculline-induced increase in neuronal activity leads to a decrease in mEPSC amplitude and a decrease in expression of the AMPA receptor subunit GluR2 in rat hippocampal cultures. Bicuculline treatment also leads to an increase in the levels of the transcriptional repressor MeCP2, which binds to the GluR2 promoter along with the corepressors HDAC1 and mSin3A. Downregulation of MeCP2 by shRNA expression or genetic deletion blocks the bicuculline-induced decrease in GluR2 expression and mEPSC amplitude. These observations indicate that MeCP2 mediates activity-dependent synaptic scaling, and suggest that the pathophysiology of Rett syndrome, which is caused by mutations in MeCP2, may involve defects in activity-dependent regulation of synaptic currents.

The Journal of Neuroscience, January 18, 2012 • 32(3):989–994

Optimal Encoding of Interval Timing in Expert Percussionists

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We measured temporal reproduction in human subjects with various levels of musical expertise: expert drummers, string musicians, and non-musicians. While duration reproduction of the non-percussionists showed a characteristic central tendency or regression to the mean, drummers responded veridically. Furthermore, when the stimuli were auditory tones rather than flashes, all subjects responded veridically. The behavior of all three groups in both modalities is well explained by a Bayesian model that seeks to minimize reproduction errors by incorporating a central tendency prior, a probability density function centered at the mean duration of the sample. We measured separately temporal precision thresholds with a bisection task; thresholds were twice as low in drummers as in the other two groups. These estimates of temporal precision, together with an adaptable Bayesian prior, predict well the reproduction results and the central tendency strategy under all conditions and for all subject groups. These results highlight the efficiency and flexibility of sensorimotor mechanisms estimating temporal duration.

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Articles

CELLULAR/MOLECULAR

Cellular Mechanisms Underlying Spatiotemporal Features of Cholinergic Retinal Waves

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Before vision, a transient network of recurrently connected cholinergic interneurons, called starburst amacrine cells (SACs), generates spontaneous retinal waves. Despite an absence of robust inhibition, cholinergic retinal waves initiate infrequently and propagate within finite boundaries. Here, we combine a variety of electrophysiological and imaging techniques and computational modeling to elucidate the mechanisms underlying these spatial and temporal properties of waves in developing mouse retina. Waves initiate via rare spontaneous depolarizations of SACs. Waves propagate through recurrent cholinergic connections between SACs and volume release of ACh as demonstrated using paired recordings and a cell-based ACh optical sensor. Perforated-patch recordings and two-photon calcium imaging reveal that individual SACs have slow afterhyperpolarizations that induce SACs to have variable depolarizations during sequential waves. Using a computational model in which the properties of SACs are based on these physiological measurements, we reproduce the slow frequency, speed, and finite size of recorded waves. This study represents a detailed description of the circuit that mediates cholinergic retinal waves and indicates that variability of the interneurons that generate this network activity may be critical for the robustness of waves across different species and stages of development.

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Neural Activity and Neurotransmission Regulate the Maturation of the Innervation Field of Cortical GABAergic Interneurons in an Age-Dependent Manner

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Neural activity guides the patterning of neuron synaptic territory in the developing nervous system. Evidence supporting this hypothesis comes from numerous studies on projection neurons in neuromuscular and visual systems. It is unknown whether the innervation field of GABAergic interneurons, which forms local dense innervations, follows similar rules.

Cortical basket cells innervate hundreds of pyramidal cell somata and proximal dendrites. Thanks to this connectivity pattern, they can tightly control neural excitability and synchronization. Here we show that reducing excitation, and thus neurotransmitter release, in mouse cortical single basket cells in slice cultures decreases the number of innervated cells without changing the pattern of perisomatic innervation, both at the peak and after the proliferation phase of perisomatic synapse formation. Conversely, suppressing neurotransmitter release in single basket cells can have completely opposite effects depending on the developmental stage. Our results reveal a remarkably specific and age-dependent role of neural activity and neurotransmission levels in the establishment of the synaptic territory of cortical GABAergic cells.

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Microcircuits Mediating Feedforward and Feedback Synaptic Inhibition in the Piriform Cortex

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Local inhibition by GABA-releasing neurons is important for the operation of sensory cortices, but the details of these inhibitory circuits remain unclear. We addressed this question in the olfactory system by making targeted recordings from identified classes of inhibitory and glutamatergic neurons in the piriform cortex (PC) of mice. First, we looked for feedforward synaptic inhibition provided by interneurons located in the outermost layer of the PC, layer Ia, which is the unique recipient of afferent fibers from the olfactory bulb. We found two types of feedforward inhibition: a fast-rising, spatially restricted kind that was generated by horizontal cells, and a slow-rising, more diffuse kind generated by neurogliaform cells. Both cell types targeted the distal apical dendrites of layer II principal neurons. Next, we studied feedback synaptic inhibition in isolation by making a tissue cut across layer I to selectively remove feedforward inhibitory connections. We identified a powerful type of feedback inhibition of layer II neurons, mostly generated by soma-targeting fast-spiking multipolar cells in layer III, which in turn were driven by feedforward excitation from layer II semilunar cells. Dynamic clamp simulation of feedback inhibition revealed differential effects of this inhibition on the two main types of layer II principal neurons. Thus, our results articulate the connectivity and functions of two important classes of inhibitory microcircuits in the PC. Feedforward and feedback inhibition generated by these circuits is likely to be required for the operation of this sensory paleocortex during the processing of olfactory information.

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Cortactin-Binding Protein 2 Modulates the Mobility of Cortactin and Regulates Dendritic Spine Formation and Maintenance

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Dendritic spines, the actin-rich protrusions emerging from dendrites, are the locations of excitatory synapses in mammalian brains. Many molecules that regulate actin dynamics also influence the morphology and/or density of dendritic spines. Since dendritic spines are neuron-specific subcellular structures, neuron-specific proteins or signals are expected to control spinogenesis. In this report, we characterize the distribution and function of neuron-predominant cortactin-binding protein 2 (CTTNBP2) in rodents. An analysis of an Expressed Sequence Tag database revealed three splice variants of mouse CTTNBP2: short, long, and intron. Immunoblotting indicated that the short form is the dominant CTTNBP2 variant in the brain. CTTNBP2 proteins were highly concentrated at dendritic spines in cultured rat hippocampal neurons as well as in the mouse brain. Knockdown of CTTNBP2 in neurons reduced the density and size of dendritic spines. Consistent with these morphological changes, the frequencies of miniature EPSCs in CTTNBP2 knockdown neurons were lower than those in control neurons. Cortactin acts downstream of CTTNBP2 in spinogenesis, as the defects caused by CTTNBP2 knockdown were rescued by overexpression of cortactin but not expression of a CTTNBP2 mutant protein lacking the cortactin interaction. Finally, immunofluorescence staining demonstrated that, unlike cortactin, CTTNBP2 stably resided at dendritic spines even after glutamate stimulation. Fluorescence recovery after photobleaching further suggested that CTTNBP2 modulates the mobility of cortactin in neurons. CTTNBP2 may thus help to immobilize cortactin in dendritic spines and control the density of dendritic spines.

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DEVELOPMENT/PLASTICITY/REPAIR

The Zebra Finch Paradox: Song Is Little Changed, But Number of Neurons Doubles

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New neurons are added to the high vocal center (HVC) of adult males in seasonally breeding songbirds such as the canary (*Serinus canaria*) that learns new songs in adulthood, and the song sparrow (*Melospiza melodia*) that does not. In both cases, the new neurons numerically replace others that have died, resulting in a seasonal fluctuation in HVC volume and neuron number. Peaks in neuronal replacement in both species occur in the fall when breeding is over and song is variable. New neurons are added, too, to the HVC of zebra finches (*Taeniopygia guttata*) that do not learn new songs in adulthood and whose song remains stereotyped throughout the year. Here, we show that, in contrast to the observations in seasonal songbirds, neurons added to the zebra finch HVC are not part of a replacement process. Rather, they lead to a doubling in the number of neurons that project from HVC to the robust nucleus of the arcopallium (RA). As this happens, HVC volume remains constant and the packing density of its neurons increases. The HVC-RA neurons are part of a descending pathway that carries the pattern of learned song; some HVC-RA neurons are also responsive to song playback. The addition of HVC-RA neurons happens in zebra finches housed singly, but becomes more acute if the birds are housed communally. We speculate that new neurons added to the adult HVC may help with the production or perception of learned song, or both.

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TRPV1 Channels Regulate Cortical Excitability in Humans

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Studies in rodents show that transient receptor potential vanilloid 1 (TRPV1) channels regulate glutamate release at central and peripheral synapses. In humans, a number of nonsynonymous single-nucleotide polymorphisms (SNPs) have been described in the *TRPV1* gene, and some of them significantly alter the functionality of the channel. To address the possible role of TRPV1 channels in the regulation of synaptic transmission in humans, we studied how TRPV1 genetic polymorphisms affect cortical excitability measured with transcranial magnetic stimulation (TMS). Two SNPs of the *TRPV1* gene were selected and genotyped (rs222747 and rs222749) in a sample of 77 healthy subjects. In previous cell expression studies, the “G” allele of rs222747 was found to enhance the activity of the channel, whereas rs222749 had no functional effect. Allelic variants in the rs222749 region were not associated with altered cortical response to single, paired, and repetitive TMS. In contrast, subjects homozygous for the G allele in rs222747 exhibited larger short-interval intracortical facilitation (a measure of glutamate transmission) explored through paired-pulse TMS of the primary motor cortex. Recruitment curves, short-interval intracortical inhibition, intracortical facilitation, and long-interval intracortical inhibition were unchanged. LTP- and LTD-like plasticity explored through intermittent or continuous theta-burst stimulation was also similar in the “G” and “non-G” subjects. To our knowledge, our results provide the first evidence that TRPV1 channels regulate cortical excitability to paired-pulse stimulation in humans.

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Combinatorial Expression of Brn3 Transcription Factors in Somatosensory Neurons: Genetic and Morphologic Analysis

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The three members of the Brn3 family of POU-domain transcription factors (Brn3a/Pou4f1, Brn3b/Pou4f2, and Brn3c/Pou4f3) are expressed in overlapping subsets of visual, auditory/vestibular, and somatosensory neurons. Using unmarked *Brn3*-null alleles and *Brn3* conditional alleles in which gene loss is coupled to expression of an alkaline phosphatase reporter, together with sparse Cre-mediated recombination, we describe the following: (1) the overlapping patterns of *Brn3* gene expression in somatosensory neurons; (2) the manner in which these patterns correlate with molecular markers, peripheral afferent arbor morphologies, and dorsal horn projections; and (3) the consequences for these neurons of deleting individual *Brn3* genes in the mouse. We observe broad expression of *Brn3a* among DRG neurons, but subtype-restricted expression of *Brn3b* and *Brn3c*. We also observe a nearly complete loss of hair follicle-associated sensory endings among *Brn3a*^{−/−} neurons. Together with earlier analyses of *Brn3* gene expression patterns in the retina and inner ear, these experiments suggest a deep functional similarity among primary somatosensory neurons, spiral and vestibular ganglion neurons, and retinal ganglion cells. This work also demonstrates the utility of sparse genetically directed labeling for visualizing individual somatosensory afferent arbors and for defining cell-autonomous mutant phenotypes.

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Injury-Dependent Müller Glia and Ganglion Cell Reprogramming during Tissue Regeneration Requires Apobec2a and Apobec2b

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Unlike mammals, adult zebrafish are able to regenerate multiple tissues including those of the CNS. In the zebrafish retina, injury stimulates Müller glia dedifferentiation into a multipotent retinal progenitor that is capable of regenerating all lost cell types. This dedifferentiation is driven by the reactivation of gene expression programs that share many characteristics with those that operate during early development. Although the mechanisms underlying the reactivation of these programs remain unknown, it is likely that changes in DNA methylation play a significant role. To begin investigating whether DNA demethylation may contribute to retina regeneration, we characterized the expression of genes associated with DNA demethylation in the uninjured and injured retina. We found that two cytidine deaminases (*apobec2a* and *apobec2b*) were expressed basally in the uninjured retina and that they were induced in proliferating, dedifferentiated Müller glia. The maximal induction of *apobec2b* required *Ascl1a*, but was independent of *Lin28*, and therefore defines an independent signaling pathway stemming from *Ascl1a*. Strikingly, when *Apobec2a* or *Apobec2b* was knocked down by antisense morpholino oligonucleotides, the proliferative response of Müller glia following injury was significantly reduced and injury-dependent induction of *ascl1a* and its target genes were inhibited, suggesting the presence of a regulatory feedback loop between Apobec proteins and *ascl1a*. Finally, *Ascl1a*, *Apobec2a* and *Apobec2b* were found to be essential for optic nerve regeneration. These data identify an essential role for Apobec proteins during retina and optic nerve regeneration and suggest DNA demethylation may underlie the reprogramming of cells to mount a regenerative response.

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Learning Acts on Distinct Processes for Visual Form Perception in the Human Brain

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Learning is known to facilitate our ability to detect targets in clutter and optimize brain processes for successful visual recognition. Previous brain-imaging studies have focused on identifying spatial patterns (i.e., brain areas) that change with learning, implicating occipitotemporal and frontoparietal areas. However, little is known about the interactions within this network that mediate learning-dependent improvement in complex perceptual tasks (i.e., discrimination of visual forms in clutter). Here we take advantage of the complementary high spatial and temporal resolution of simultaneous EEG-fMRI to identify the learning-dependent changes in spatiotemporal brain patterns that mediate enhanced behavioral sensitivity in the discrimination of global forms after training. We measured the observers' choices when discriminating between concentric and radial patterns presented in noise before and after training. Similarly, we measured the choices of a pattern classifier when predicting each stimulus from EEG-fMRI signals. By comparing the performance of human observers and classifiers, we demonstrated that learning alters sensitivity to visual forms and EEG-fMRI activation patterns related to distinct visual recognition processes. In particular, behavioral improvement after training was associated with changes in (1) early processes involved in the integration of global forms in higher occipitotemporal and parietal areas, and (2) later processes related to categorical judgments in frontal circuits. Thus, our findings provide evidence that learning acts on distinct visual recognition processes and shapes feedforward interactions across brain areas to support performance in complex perceptual tasks.

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Neural Representations of Courtship Song in the *Drosophila* Brain

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Acoustic communication in drosophilid flies is based on the production and perception of courtship songs, which facilitate mating. Despite decades of research on courtship songs and behavior in *Drosophila*, central auditory responses have remained uncharacterized. In this study, we report on intracellular recordings from central neurons that innervate the *Drosophila* antennal mechanosensory and motor center (AMMC), the first relay for auditory information in the fly brain. These neurons produce graded-potential (nonspiking) responses to sound; we compare recordings from AMMC neurons to extracellular recordings of the receptor neuron population [Johnston's organ neurons (JONs)]. We discover that, while steady-state response profiles for tonal and broadband stimuli are significantly transformed between the JON population in the antenna and AMMC neurons in the brain, transient responses to pulses present in natural stimuli (courtship song) are not. For pulse stimuli in particular, AMMC neurons simply low-pass filter the receptor population response, thus preserving low-frequency temporal features (such as the spacing of song pulses) for analysis by postsynaptic neurons. We also compare responses in two closely related *Drosophila* species, *Drosophila melanogaster* and *Drosophila simulans*, and find that pulse song responses are largely similar, despite differences in the spectral content of their songs. Our recordings inform how downstream circuits may read out behaviorally relevant information from central neurons in the AMMC.

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Recurrent Neural Processing and Somatosensory Awareness

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The neural mechanisms of stimulus detection, despite extensive research, remain elusive. The recurrent processing hypothesis, a prominent theoretical account of perceptual awareness, states that, although stimuli might in principle evoke feedforward activity propagating through the visual cortex, stimuli that become consciously detected are further processed in feedforward–feedback loops established between cortical areas. To test this theory in the tactile modality, we applied dynamic causal modeling to electroencephalography (EEG) data acquired from humans in a somatosensory detection task. In the analysis of stimulation-induced event-related potentials (ERPs), we focused on model-based evidence for feedforward, feedback, and recurrent processing between primary and secondary somatosensory cortices. Bayesian model comparison revealed that, although early EEG components were well explained by both the feedforward and the recurrent models, the recurrent model outperformed the other models when later EEG segments were analyzed. Within the recurrent model, stimulus detection was characterized by a relatively early strength increase of the feedforward connection from primary to secondary somatosensory cortex (>80 ms). At longer latencies (>140 ms), also the feedback connection showed a detection-related strength increase. The modeling results on relative evidence between recurrent and feedforward model comparison support the hypothesis that the ERP responses from sensory areas arising after aware stimulus detection can be explained by increased recurrent processing within the somatosensory network in the later stages of stimulus processing.

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Dissociating the Role of Prefrontal and Premotor Cortices in Controlling Inhibitory Mechanisms during Motor Preparation

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Top-down control processes are critical to select goal-directed actions in flexible environments. In humans, these processes include two inhibitory mechanisms that operate during response selection: one is involved in solving a competition between different response options, the other ensures that a selected response is initiated in a timely manner. Here, we evaluated the role of dorsal premotor cortex (PMd) and lateral prefrontal cortex (LPF) of healthy subjects in these two forms of inhibition by using an innovative transcranial magnetic stimulation (TMS) protocol combining repetitive TMS (rTMS) over PMd or LPF and a single pulse TMS (sTMS) over primary motor cortex (M1). sTMS over M1 allowed us to assess inhibitory changes in corticospinal excitability, while rTMS was used to produce transient disruption of PMd or LPF. We found that rTMS over LPF reduces inhibition associated with competition resolution, whereas rTMS over PMd decreases inhibition associated with response impulse control. These results emphasize the dissociable contributions of these two frontal regions to inhibitory control during motor preparation. The association of LPF with competition resolution is consistent with the role of this area in relatively abstract aspects of control related to goal maintenance, ensuring that the appropriate response is selected in a variable context. In contrast, the association of PMd with impulse control is consistent with the role of this area in more specific processes related to motor preparation and initiation.

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Genetic Variants of *FOXP2* and *KIAA0319/TTRAP/THEM2* Locus Are Associated with Altered Brain Activation in Distinct Language-Related Regions

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Recent advances have been made in the genetics of two human communication skills: speaking and reading. Mutations of the *FOXP2* gene cause a severe form of language impairment and orofacial dyspraxia, while single-nucleotide polymorphisms (SNPs) located within a *KIAA0319/TTRAP/THEM2* gene cluster and affecting the *KIAA0319* gene expression are associated with reading disability. Neuroimaging studies of clinical populations point to partially distinct cerebral bases for language and reading impairments. However, alteration of *FOXP2* and *KIAA0319/TTRAP/THEM2* polymorphisms on typically developed language networks has never been explored. Here, we genotyped and scanned 94 healthy subjects using fMRI during a reading task. We studied the correlation of genetic polymorphisms with interindividual variability in brain activation and functional asymmetry in frontal and temporal cortices. In *FOXP2*, SNPs rs6980093 and rs7799109 were associated with variations of activation in the left frontal cortex. In the *KIAA0319/TTRAP/THEM2* locus, rs17243157 was associated with asymmetry in functional activation of the superior temporal sulcus (STS). Interestingly, healthy subjects bearing the *KIAA0319/TTRAP/THEM2* variants previously identified as enhancing the risk of dyslexia showed a reduced left-hemispheric asymmetry of the STS. Our results confirm that both *FOXP2* and *KIAA0319/TTRAP/THEM2* genes play an important role in human language development, but probably through different cerebral pathways. The observed cortical effects mirror previous fMRI results in developmental language and reading disorders, and suggest that a continuum may exist between these pathologies and normal interindividual variability.

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Disparity-Specific Spatial Interactions: Evidence from EEG Source Imaging

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Using cortical source estimation techniques based on high-density EEG and fMRI measurements in humans, we measured how a disparity-defined surround influenced the responses to the changing disparity of a central disk within five visual ROIs: V1, V4, lateral occipital complex (LOC), hMT+, and V3A. The responses in the V1 ROI were not consistently affected either by changes in the characteristics of the surround (correlated or uncorrelated) or by its disparity value, consistent with V1 being responsive only to absolute, not relative, disparity. Correlation in the surround increased the responses in the V4, LOC, and hMT+ ROIs over those measured with the uncorrelated surround. Thus, these extrastriate areas contain neurons that are sensitive to disparity differences. However, their evoked responses did not vary systematically with the surround disparity. Responses in the V3A ROI, in contrast, were increased by correlation in the surround and varied with its disparity. We modeled these V3A responses as attributable to a gain modulation of the absolute disparity response, where the gain amplitude is proportional to the center-surround disparity difference. An additional experiment identified a nonlinear center-surround interaction in V3A that facilitates the responses when center and surround are misaligned but suppresses it when they share the same disparity plane.

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Methylphenidate-Elicited Dopamine Increases in Ventral Striatum Are Associated with Long-Term Symptom Improvement in Adults with Attention Deficit Hyperactivity Disorder

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Stimulant medications, such as methylphenidate, which are effective treatments for attention deficit hyperactivity disorder (ADHD), enhance brain dopamine signaling. However, the relationship between regional brain dopamine enhancement and treatment response has not been evaluated. Here, we assessed whether the dopamine increases elicited by methylphenidate are associated with long-term clinical response. We used a prospective design to study 20 treatment-naïve adults with ADHD who were evaluated before treatment initiation and after 12 months of clinical treatment with a titrated regimen of oral methylphenidate. Methylphenidate-induced dopamine changes were evaluated with positron emission tomography and [¹¹C]raclopride (D₂/D₃ receptor radioligand sensitive to competition with endogenous dopamine). Clinical responses were assessed using the Conners' Adult ADHD Rating Scale and revealed a significant reduction in symptoms of inattention and hyperactivity with long-term methylphenidate treatment. A challenge dose of 0.5 mg/kg intravenous methylphenidate significantly increased dopamine in striatum (assessed as decreases in D₂/D₃ receptor availability). In the ventral striatum, these dopamine increases were associated with the reductions in ratings of symptoms of inattention with clinical treatment. Statistical parametric mapping additionally showed dopamine increases in prefrontal and temporal cortices with intravenous methylphenidate that were also associated with decreases in symptoms of inattention. Our findings indicate that dopamine enhancement in ventral striatum (the brain region involved with reward and motivation) was associated with therapeutic response to methylphenidate, further corroborating the relevance of the dopamine reward/motivation circuitry in ADHD. It also provides preliminary evidence that methylphenidate-elicited dopamine increases in prefrontal and temporal cortices may also contribute to the clinical response.

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Command and Compensation in a Neuromodulatory Decision Network

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The neural circuits that mediate behavioral choices must not only weigh internal demands and environmental circumstances, but also select and implement specific actions, including associated visceral or neuroendocrine functions. Coordinating these multiple processes suggests considerable complexity. As a consequence, even circuits that support simple behavioral decisions remain poorly understood. Here we show that the environmentally sensitive wing expansion decision of adult fruit flies is coordinated by a single pair of neuromodulatory neurons with command-like function. Targeted suppression of these neurons using the Split Gal4 system abrogates the fly's ability to expand its wings in the face of environmental challenges, while stimulating them forces expansion by coordinately activating both motor and neuroendocrine outputs. The arbitration and implementation of the wing expansion decision by this neuronal pair may illustrate a general strategy by which neuromodulatory neurons orchestrate behavior. Interestingly, the decision network exhibits a plasticity that is unmasked under conducive environmental conditions in flies lacking the function of the command-like neuromodulatory neurons. Such flies can often expand their wings using a motor program distinct from that of wild-type animals and controls. This compensatory program may be the vestige of an ancestral, environmentally insensitive program used for wing expansion that existed before the evolution of the environmentally adaptive program currently used by *Drosophila* and other cyclorrhaphan flies.

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Gating of Sensory Input at Spinal and Cortical Levels during Preparation and Execution of Voluntary Movement

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All bodily movements stimulate peripheral receptors that activate neurons in the brain and spinal cord through afferent feedback. How these reafferent signals are processed within the CNS during movement is a key question in motor control. We investigated cutaneous sensory-evoked potentials in the spinal cord, primary somatosensory and motor cortex, and premotor cortex in monkeys performing an instructed delay task. Afferent inputs from cutaneous receptors were suppressed at several levels in a task-dependent manner. We found two types of suppression. First, suppression during active limb movement was observed in the spinal cord and all three cortical areas. This suppression was induced by both bottom-up and top-down gating mechanisms. Second, during preparation for upcoming movement, evoked responses were suppressed exclusively in the motor cortical areas and the magnitude of suppression was correlated with the reaction time of the subsequent movement. This suppression could be induced by a top-down gating mechanism to facilitate the preparation and execution of upcoming movement.

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Kisspeptin-GPR54 Signaling in Mouse NO-Synthesizing Neurons Participates in the Hypothalamic Control of Ovulation

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Reproduction is controlled in the brain by a neural network that drives the secretion of gonadotropin-releasing hormone (GnRH). Various permissive homeostatic signals must be integrated to achieve ovulation in mammals. However, the neural events controlling the timely activation of GnRH neurons are not completely understood. Here we show that kisspeptin, a potent activator of GnRH neuronal activity, directly communicates with neurons that synthesize the gaseous transmitter nitric oxide (NO) in the preoptic region to coordinate the progression of the ovarian cycle. Using a transgenic *Gpr54*-null IRES-LacZ knock-in mouse model, we demonstrate that neurons containing neuronal NO synthase (nNOS), which are morphologically associated with kisspeptin fibers, express the kisspeptin receptor GPR54 in the preoptic region, but not in the tuberal region of the hypothalamus. The activation of kisspeptin signaling in preoptic neurons promotes the activation of nNOS through its phosphorylation on serine 1412 via the AKT pathway and mimics the positive feedback effects of estrogens. Finally, we show that while NO release restrains the reproductive axis at stages of the ovarian cycle during which estrogens exert their inhibitory feedback, it is required for the kisspeptin-dependent preovulatory activation of GnRH neurons. Thus, interactions between kisspeptin and nNOS neurons may play a central role in regulating the hypothalamic–pituitary–gonadal axis *in vivo*.

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Cervicolumbar Coordination in Mammalian Quadrupedal Locomotion: Role of Spinal Thoracic Circuitry and Limb Sensory Inputs

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Effective quadrupedal locomotion requires a close coordination between the spatially distant central pattern generators (CPGs) controlling forelimb and hindlimb movements. Using isolated preparations of the neonatal rat spinal cord, we explore the role of intervening thoracic circuitry in cervicolumbar CPG coordination and the contribution to this remote coupling of limb somatosensory inputs. In preparations activated with bath-applied *N*-methyl-D,L-aspartate, serotonin, and dopamine, the coordination between locomotor-related bursts recorded in cervical and lumbar ventral roots was substantially weakened, although not abolished, when the thoracic segments were selectively withheld from neurochemical stimulation or were exposed to a low Ca^{2+} solution to block synaptic transmission. Moreover, cervicolumbar CPG coordination was reduced after a thoracic midsagittal section, suggesting that cross-cord projections participate in the anteroposterior coupling. In quiescent preparations, either cyclic or tonic electrical stimulation of low-threshold afferent pathways in C8 or L2 dorsal roots (DRs) could elicit coordinated ventral root bursting at both cervical and lumbar levels via an activation of the underlying CPG networks. When lumbar rhythmogenesis was prevented by local synaptic transmission blockade, L2 DR stimulation could still drive left–right alternating cervical bursting in preparations otherwise exposed to normal bathing medium. In contrast, when the cervical generators were selectively blocked, C8 DR stimulation was unable to activate the lumbar CPGs. Thus, in the newborn rat, anteroposterior limb coordination relies on active burst generation within midcord thoracic circuitry that additionally conveys ascending and weaker descending coupling influences of distant limb proprioceptive inputs to the cervical and lumbar generators, respectively.

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Human *ROBO1* Regulates Interaural Interaction in Auditory Pathways

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In rodents, the *Robo1* gene regulates midline crossing of major nerve tracts, a fundamental property of the mammalian CNS. However, the neurodevelopmental function of the human *ROBO1* gene remains unknown, apart from a suggested role in dyslexia. We therefore studied axonal crossing with a functional approach, based on magnetoencephalography, in 10 dyslexic individuals who all share the same rare, weakly expressing haplotype of the *ROBO1* gene. Auditory-cortex responses were recorded separately to left- and right-ear sounds that were amplitude modulated at different frequencies. We found impaired interaural interaction that depended on the *ROBO1* in a dose-dependent manner. Our results indicate that normal crossing of the auditory pathways requires an adequate *ROBO1* expression level.

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Becoming Consistent: Developmental Reductions in Intraindividual Variability in Reaction Time Are Related to White Matter Integrity

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Cognitive development is known to involve improvements in accuracy, capacity, and processing speed. Less is known about the role of performance consistency, and there has been virtually no empirical examination of the neural underpinnings of within-person variability in development. In a sample of 92 healthy children and adolescents aged 8–19 years, we aimed to characterize age-related changes in trial-to-trial intraindividual variability (IIV) of reaction time (RT) and to test whether IIV is related to white matter (WM) integrity as indexed by diffusion tensor imaging. IIV was quantified as the SD of correct RTs in a speeded arrow flanker task, and Tract-Based Spatial Statistics was used to test relationships with diffusion characteristics. Large age-related reductions in IIV in both simple congruent trials and more complex incongruent trials were found. Independently of sex, age, and median RT (mRT), lower IIV was associated with higher fractional anisotropy and lower overall diffusivity. Effects were seen for IIV in one or both trial types in the corticospinal tract, the left superior longitudinal fasciculus, the uncinate fasciculus, the forceps minor, and in the genu and splenium of the corpus callosum. There were no significant associations between mRT and any of the diffusion indices. The findings support the proposition that developmental reductions in IIV reflect maturation of WM connectivity and highlight the importance of considering within-person variability in theories of cognitive development and its neurobiological foundation.

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Scaling of Movement Is Related to Pallidal γ Oscillations in Patients with Dystonia

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Neuronal synchronization in the gamma (γ) band is considered important for information processing through functional integration of neuronal assemblies across different brain areas. Movement-related γ synchronization occurs in the human basal ganglia where it is centered at ~ 70 Hz and more pronounced contralateral to the moved hand. However, its functional significance in motor performance is not yet well understood. Here, we assessed whether event-related γ synchronization (ERS) recorded from the globus pallidus internus in patients undergoing deep brain stimulation for medically intractable primary focal and segmental dystonia might code specific motor parameters. Pallidal local field potentials were recorded in 22 patients during performance of a choice-reaction-time task. Movement amplitude of the forearm pronation-supination movements was parametrically modulated with an angular degree of 30°, 60°, and 90°. Only patients with limbs not affected by dystonia were tested. A broad contralateral γ band (35–105 Hz) ERS occurred at movement onset with a maximum reached at peak velocity of the movement. The pallidal oscillatory γ activity correlated with movement parameters: the larger and faster the movement, the stronger was the synchronization in the γ band. In contrast, the event-related decrease in beta band activity was similar for all movements. Gamma band activity did not change with movement direction and did not occur during passive movements. The stepwise increase of γ activity with movement size and velocity suggests a role of neuronal synchronization in this frequency range in basal ganglia control of the scaling of ongoing movements.

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Processing of Emotional Reactivity and Emotional Memory over Sleep

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Sleep enhances memories, particularly emotional memories. As such, it has been suggested that sleep deprivation may reduce posttraumatic stress disorder. This presumes that emotional memory consolidation is paralleled by a reduction in emotional reactivity, an association that has not yet been examined. In the present experiment, we used an incidental memory task in humans and obtained valence and arousal ratings during two sessions separated either by 12 h of daytime wake or 12 h including overnight sleep. Recognition accuracy was greater following sleep relative to wake for both negative and neutral pictures. While emotional reactivity to negative pictures was greatly reduced over wake, the negative emotional response was relatively preserved over sleep. Moreover, protection of emotional reactivity was associated with greater time in REM sleep. Recognition accuracy, however, was not associated with REM. Thus, we provide the first evidence that sleep enhances emotional memory while preserving emotional reactivity.

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Maximal Variability of Phase Synchrony in Cortical Networks with Neuronal Avalanches

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Ongoing interactions among cortical neurons often manifest as network-level synchrony. Understanding the spatiotemporal dynamics of such spontaneous synchrony is important because it may (1) influence network response to input, (2) shape activity-dependent microcircuit structure, and (3) reveal fundamental network properties, such as an imbalance of excitation (*E*) and inhibition (*I*). Here we delineate the spatiotemporal character of spontaneous synchrony in rat cortex slice cultures and a computational model over a range of different *E–I* conditions including disfacilitated (antagonized AMPA, NMDA receptors), unperturbed, and disinhibited (antagonized GABA_A receptors). Local field potential was recorded with multielectrode arrays during spontaneous burst activity. Synchrony among neuronal groups was quantified based on phase-locking among recording sites. As network excitability was increased from low to high, we discovered three phenomena at an intermediate excitability level: (1) onset of synchrony, (2) maximized variability of synchrony, and (3) neuronal avalanches. Our computational model predicted that these three features occur when the network operates near a unique balanced *E–I* condition called “criticality.” These results were invariant to changes in the measurement spatial extent, spatial resolution, and frequency bands. Our findings indicate that moderate average synchrony, which is required to avoid pathology, occurs over a limited range of *E–I* conditions and emerges together with maximally variable synchrony. If variable synchrony is detrimental to cortical function, this is a cost paid for moderate average synchrony. However, if variable synchrony is beneficial, then by operating near criticality the cortex may doubly benefit from moderate mean and maximized variability of synchrony.

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Amygdala Central Nucleus Interacts with Dorsolateral Striatum to Regulate the Acquisition of Habits

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The role of the amygdala central nucleus (CeN) in habit learning was assessed in two experiments. First, we examined the effects of bilateral lesions of the anterior CeN on an overtraining-induced lever press habit evaluated using an outcome devaluation protocol. Overtraining generated habitual performance and rendered sham lesioned rats insensitive to outcome devaluation, an effect that was also found in rats given control lesions of the posterior CeN. In contrast, rats with lesions of the anterior CeN did not show normal habit acquisition and their performance remained goal-directed and sensitive to outcome devaluation. Nevertheless, lesions of either the posterior or the anterior CeN abolished the general excitatory influence of a Pavlovian conditioned stimulus on instrumental performance. Second, we assessed the functional interaction between the CeN and dorsolateral striatum (DLS), a region previously implicated in the acquisition of habits, using asymmetrical lesions to disconnect these structures. Rats were given a unilateral lesion of anterior CeN and a unilateral lesion of the DLS, made either ipsilateral (control) or contralateral (disconnection) to the CeN lesion, and given overtraining followed by outcome devaluation. Although the ipsilateral lesioned rats were insensitive to devaluation, the contralateral CeN–DLS lesion impaired habit acquisition, rendering performance sensitive to the devaluation treatment. These results are the first to implicate the CeN and its connection with a circuit involving DLS in habit learning. They imply that, in instrumental conditioning, regions of amygdala parse the instrumental outcome into the reward and reinforcement signals mediating goal-directed and habitual actions, respectively.

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Predicting Aversive Events and Terminating Fear in the Mouse Anterior Cingulate Cortex during Trace Fear Conditioning

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A variety of studies have implicated the anterior cingulate cortex (ACC) in fear, including permanent storage of fear memory. Recent pharmacological and genetic studies indicate that early synaptic plasticity in the ACC may also contribute to certain forms of fear memory at early time points. However, no study has directly examined the possible changes in neuronal activity of ACC neurons in freely behaving mice during early learning. In the present study, we examined the neural responses of the ACC during trace fear conditioning. We found that ACC putative pyramidal and nonpyramidal neurons were involved in the termination of fear behavior (“un-freezing”), and the spike activity of these neurons was reduced during freezing. Some of the neurons were also found to acquire un-freezing locked activity and change their tuning. The results implicate the ACC neurons in fear learning and controlling the abolition of fear behavior. We also show that the ACC is important for making cue-related fear memory associations in the trace fear paradigm as measured with tone-evoked potentials and single-unit activity. Collectively, our findings indicate that the ACC is involved in predicting future aversive events and terminating fear during trace fear.

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Attentional Capture? Synchronized Feedback Signals from the Isthmi Boost Retinal Signals to Higher Visual Areas

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When a salient object in the visual field captures attention, the neural representation of that object is enhanced at the expense of competing stimuli. How neural activity evoked by a salient stimulus evolves to take precedence over the neural activity evoked by other stimuli is a matter of intensive investigation. Here, we describe in pigeons (*Columba livia*) how retinal inputs to the optic tectum (TeO, superior colliculus in mammals), triggered by moving stimuli, are selectively relayed on to the rotundus (Rt, caudal pulvinar) in the thalamus, and to its pallial target, the entopallium (E, extrastriate cortex). We show that two satellite nuclei of the TeO, the nucleus isthmi parvocellularis (Ipc) and isthmi semilunaris (SLu), send synchronized feedback signals across tectal layers. Preventing the feedback from Ipc but not from SLu to a tectal location suppresses visual responses to moving stimuli from the corresponding region of visual space in all Rt subdivisions. In addition, the bursting feedback from the Ipc imprints a bursting rhythm on the visual signals, such that the visual responses of the Rt and the E acquire a bursting modulation significantly synchronized to the feedback from Ipc. As the Ipc feedback signals are selected by competitive interactions, the visual responses within the receptive fields in the Rt tend to synchronize with the tectal location receiving the “winning” feedback from Ipc. We propose that this selective transmission of afferent activity combined with the cross-regional synchronization of the areas involved represents a bottom-up mechanism by which salient stimuli capture attention.

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NEUROBIOLOGY OF DISEASE

GDNF Is Predominantly Expressed in the PV + Neostriatal Interneuronal Ensemble in Normal Mouse and after Injury of the Nigrostriatal Pathway

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Glial cell line-derived neurotrophic factor (GDNF) is absolutely required for survival of dopaminergic (DA) nigrostriatal neurons and protect them from toxic insults. Hence, it is a promising, albeit experimental, therapy for Parkinson's disease (PD). However, the source of striatal GDNF is not well known. GDNF seems to be normally synthesized in neurons, but numerous reports suggest GDNF production in glial cells, particularly in the injured brain. We have studied in detail striatal GDNF production in normal mouse and after damage of DA neurons with MPTP. Striatal *GDNF* mRNA was present in neonates but markedly increased during the first 2–3 postnatal weeks. Cellular identification of GDNF by unequivocal histochemical methods demonstrated that in normal or injured adult animals GDNF is expressed by striatal neurons and is not synthesized in significant amounts by astrocytes or microglial cells. *GDNF* mRNA expression was not higher in reactive astrocytes than in normal ones. Approximately 95% of identified neostriatal GDNF-expressing cells in normal and injured animals are parvalbumin-positive (PV+) interneurons, which only represent ~0.7% of all striatal neurons. The remaining 5% of GDNF+ cells are cholinergic and somatostatin+ interneurons. Surprisingly, medium spiny projection neurons (MSNs), the vast majority of striatal neurons that receive a strong DA innervation, do not express GDNF. PV+ interneurons constitute an oscillatory functional ensemble of electrically connected cells that control MSNs' firing. Production of GDNF in the PV+ neurons might be advantageous to supply synchronous activity-dependent release of GDNF in broad areas of the striatum. Stimulation of the GDNF-producing striatal PV+ ensemble in PD patients could have therapeutic effects.

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Epilepsy Gene *LGII* Regulates Postnatal Developmental Remodeling of Retinogeniculate Synapses

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Retinogeniculate connections undergo postnatal refinement in the developing visual system. Here we report that non-ion channel epilepsy gene *LGII* (leucine-rich glioma-inactivated), mutated in human autosomal dominant lateral temporal lobe epilepsy (ADLTE), regulates postnatal pruning of retinal axons in visual relay thalamus. By introducing an ADLTE-associated truncated mutant LGI1 (836delC) or excess full-length LGI1 into transgenic mice, we found that mutant LGI1 blocks, whereas excess LGI1 accelerates, retinogeniculate axon pruning. The normal postnatal single fiber strengthening was arrested by mutant LGI1 and, contrastingly, was enhanced by excess wild-type LGI1. The maximum response of the retinogeniculate synapses, conversely, remained the same in mature *LGII* transgenic mice, indicating that mutant LGI1 blocks, whereas excess wild-type LGI1 promotes, weak axon fiber elimination. Heterozygous deletion of the *LGII* gene, as found in ADLTE patients, inhibited postnatal

retinogeniculate synapse elimination, an effect similar to the ADLTE truncated mutant LGI1. The results identify sensory axon remodeling defects in a sensory aura-associated human epilepsy disorder.

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Cdk5/p25-Induced Cytosolic PLA2-Mediated Lysophosphatidylcholine Production Regulates Neuroinflammation and Triggers Neurodegeneration

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The deregulation of cyclin-dependent kinase 5 (Cdk5) by p25 has been shown to contribute to the pathogenesis in a number of neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD) and Alzheimer's disease (AD). In particular, p25/Cdk5 has been shown to produce hyperphosphorylated tau, neurofibrillary tangles as well as aberrant amyloid precursor protein processing found in AD. Neuroinflammation has been observed alongside the pathogenic process in these neurodegenerative diseases, however the precise mechanism behind the induction of neuroinflammation and the significance in the AD pathogenesis has not been fully elucidated. In this report, we uncover a novel pathway for p25-induced neuroinflammation where p25 expression induces an early trigger of neuroinflammation *in vivo* in mice. Lipidomic mass spectrometry, *in vitro* coculture and conditioned media transfer experiments show that the soluble lipid mediator lysophosphatidylcholine (LPC) is released by p25 overexpressing neurons to initiate astrogliosis, neuroinflammation and subsequent neurodegeneration. Reverse transcriptase PCR and gene silencing experiments show that cytosolic phospholipase 2 (cPLA2) is the key enzyme mediating the p25-induced LPC production and cPLA2 upregulation is critical in triggering the p25-mediated inflammatory and neurodegenerative process. Together, our findings delineate a potential therapeutic target for the reduction of neuroinflammation in neurodegenerative diseases including AD.

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Reduced Activity of AMP-Activated Protein Kinase Protects against Genetic Models of Motor Neuron Disease

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A growing body of research indicates that amyotrophic lateral sclerosis (ALS) patients and mouse models of ALS exhibit metabolic dysfunction. A subpopulation of ALS patients possesses higher levels of resting energy expenditure and lower fat-free mass compared to healthy controls. Similarly, two mutant copper zinc superoxide dismutase 1 (mSOD1) mouse models of familial ALS possess a hypermetabolic phenotype. The pathophysiological relevance of the bioenergetic defects observed in ALS remains largely elusive. AMP-activated protein kinase (AMPK) is a key sensor of cellular energy status and thus might be activated in various models of ALS. Here, we report that AMPK activity is increased in spinal cord cultures expressing mSOD1, as well as in spinal cord lysates from mSOD1 mice. Reducing AMPK activity either pharmacologically or genetically prevents mSOD1-induced motor neuron death *in vitro*. To investigate the role of AMPK *in vivo*, we used *Caenorhabditis elegans* models of motor neuron disease. *C. elegans* engineered to express human mSOD1 (G85R) in neurons develops locomotor dysfunction and severe fecundity defects when compared to transgenic worms expressing human wild-type SOD1. Genetic reduction of *aak-2*, the ortholog of the AMPK $\alpha 2$ catalytic subunit in nematodes, improved locomotor behavior and fecundity in G85R animals. Similar observations were made with nematodes engineered to express mutant tat-activating regulatory (TAR) DNA-binding protein of 43 kDa molecular weight. Altogether, these data suggest that bioenergetic abnormalities are likely to be pathophysiologically relevant to motor neuron disease.

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