

This Week in The Journal

● Cellular/Molecular

The Hair Cells of the Tokay Gecko

M. Eugenia Chiappe, Andrei S. Kozlov, and A. J. Hudspeth

(see pages 11978–11985)

What does a nocturnal, tree-climbing, not-so-friendly lizard have to offer neuroscience? These animals have finely tuned hearing, presumably because they emit vocal signals for territoriality, mating, and distress calls. Chiappe et al. show that, like evolutionarily distinct mammals and birds, geckos have two distinct classes of hair cells. Salletal hair cells in the gecko had afferent innervation, as expected for a role in sensory transduction and transmission, whereas tectorial hair cells had smaller ionic currents and lacked afferent innervation. Tectorial or outer hair cells are considered responsible for the “active process” of the cochlea because their hair bundles have active motility. The authors suggest that separate evolution of this pattern in three distinct animal groups [mammals, archosaurs (birds), and lepidosaurs (geckos)] reflects their shared abilities in high-frequency hearing. Two hair cell types may be necessary because of conflicting requirements for efficient mechanical transduction compared with mechanical amplification of high-frequency sounds.

▲ Development/Plasticity/Repair

Pericytes and Blood Vessels in the Germinal Matrix

Alex Braun, Hongmin Xu, Furong Hu, Praneeth Kocherlakota, Donald Siegel, Praveen Chander, Zoltan Ungvari, Anna Csiszar, Maiken Nedergaard, and Praveen Ballabh

(see pages 12012–12024)

The germinal matrix (GM), a richly vascularized collection of neural precursor cells in the neonatal brain, is particularly susceptible to hemorrhage in premature infants. Braun et al. reasoned that rapid angiogenesis in GM might contribute to

an unstable vasculature network. The authors focused on pericytes, cells that lend structural support to small blood vessels. Pericytes were sparser in GM than in white matter or cortex throughout gestation, as determined by labeling for pericyte marker proteins in postmortem samples of human fetuses and premature infants. Ultrastructural morphology from these samples as well as from premature rabbit pups confirmed the finding. When the authors suppressed angiogenesis in pregnant rabbits by inhibiting vascular endothelial growth factor (VEGF) signaling, pericyte coverage and density increased in the GM of premature pups. The GM also had a lower expression of molecules that can recruit pericytes including transforming growth factor- β 1.

■ Behavioral/Systems/Cognitive

Sleeping Fur Seals

Jennifer L. Lapierre, Peter O. Kosenko, Oleg I. Lyamin, Tohru Kodama, Lev M. Mukhametov, and Jerome M. Siegel

(see pages 11999–12006)

By necessity, whales and dolphins have mastered the art of underwater sleeping. Instead of us terrestrials who have bilateral slow-wave sleep (BSWS), these marine mammals show unihemispheric slow waves during sleep while the other hemisphere has desynchronized activity characteristic of the waking state. This week, Lapierre et al. investigated sleep in the northern fur seal that switches between BSWS and asymmetric slow-wave sleep (ASWS) as it moves from land to sea. At the Utrish Marine Station in Russia, microdialysis samples were collected from a set of bilateral, cortically implanted probes. Phases of the sleep–wake cycle were monitored by electroencephalogram (EEG) and physiological measures. Acetylcholine (ACh) release peaked during active waking, was lower during quiet waking and rapid eye movement (REM) states, and dramatically declined during BSWS. However, during ASWS, ACh levels were lateralized, with greater release in



Northern fur seals sleep not only on land, as shown here, but also in the water. In the latter case, their EEG activity slows only unilaterally. See the article by Lapierre et al. for details. This image is courtesy of National Oceanic and Atmospheric Administration (www.noaa.com).

the more “awake” hemisphere. Seems it’s OK for a seal to be half-asleep.

◆ Neurobiology of Disease

Imaging Axonal Injury

Christine L. Mac Donald, Krikor Dikranian, Philip Bayly, David Holtzman, and David Brody

(see pages 11869–11876)

Traumatic axonal injury can be dramatic as following a motor vehicle accident or more insidious as can occur with multiple concussions. This week, Mac Donald et al. evaluated the sensitivity of diffusion tensor imaging (DTI) in detecting axonal injury. DTI measures water diffusion in independent directions; thus disruption of axons reduces the anisotropy that is normally associated with highly laminated white matter. The authors evoked a cortical impact injury in anesthetized mice and assessed axonal injury to the corpus callosum and external capsule. Three phases could be identified histologically. In the first 24 h after injury, there was pure axonal injury that then was followed by marked gliosis by 4 d. After 7–30 d, axonal injury was less apparent, but thinning of myelin and active demyelination was prominent. DTI was quite sensitive, revealing reduced anisotropy at all intervals with changes that correlated with the degree of histological injury and the time after injury.

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Cover legend: Computation of higher-order binocular disparity. When our left and right eye view a three-dimensional scene, each eye receives a slightly different view of the world, owing to the spatial separation of the eyes in the head. These small differences in the images are called binocular disparity and are one source of information about the distance of objects from the observer. The way in which visual cortical neurons detect the binocular disparity of single visual features can be modeled with an energy computation: the behavior of this model has much in common with the complex-cell property discovered by Hubel and Wiesel in the primary visual cortex. Recently, new versions of the energy model have been used to detect higher-order properties, such as the relative disparity between two visual features, by acting on the outputs of two or more primary visual cortical neurons. The image illustrates the odd-symmetric interactions within an energy model. For more information, see the article by Roe et al. in this issue (pages 11820–11831).

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Spinal Cord Injury: Time to Move?

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This symposium aims at summarizing some of the scientific bases for current or planned clinical trials in patients with spinal cord injury (SCI). It stems from the interactions of four researchers involved in basic and clinical research who presented their work at a dedicated Symposium of the Society for Neuroscience in San Diego. After SCI, primary and secondary damage occurs and several endogenous processes are triggered that may foster or hinder axonal reconnection from supraspinal structures. Studies in animals show that some of these processes can be enhanced or decreased by exogenous interventions using drugs to diminish repulsive barriers (anti-Nogo, anti-Rho) that prevent regeneration and/or sprouting of axons. Cell grafts are also envisaged to enhance beneficial immunological mechanisms (autologous macrophages, vaccines) or remyelinate axons (oligodendrocytes derived from stem cells). Some of these treatments could be planned concurrently with neurosurgical approaches that are themselves beneficial to decrease secondary damage (e.g., decompression/reconstructive spinal surgery). Finally, rehabilitative approaches based on the presence of functional networks (i.e., central pattern generator) below the lesion combined with the above neurobiological approaches may produce significant functional recovery of some sensorimotor functions, such as locomotion, by ensuring an optimal function of endogenous spinal networks and establishing new dynamic interactions with supraspinal structures. More work is needed on all fronts, but already the results offer great hope for functional recovery after SCI based on sound basic and clinical neuroscience research.

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Modes of Vesicle Retrieval at Ribbon Synapses, Calyx-Type Synapses, and Small Central Synapses

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Neurobiology of Escalated Aggression and Violence

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Psychopathological violence in criminals and intense aggression in fruit flies and rodents are studied with novel behavioral, neurobiological, and genetic approaches that characterize the escalation from adaptive aggression to violence. One goal is to delineate the type of aggressive behavior and its escalation with greater precision; second, the prefrontal cortex (PFC) and brainstem structures emerge as pivotal nodes in the limbic circuitry mediating escalated aggressive behavior. The neurochemical and molecular work focuses on the genes that enable invertebrate aggression in males and females and genes that are expressed or suppressed as a result of aggressive experiences in mammals. The *fruitless* gene, immediate early genes in discrete serotonin neurons, or sex chromosome genes identify sexually differentiated mechanisms for escalated aggression. Male, but not female, fruit flies establish hierarchical relationships in fights and learn from previous fighting experiences. By manipulating either the *fruitless* or *transformer* genes in the brains of male or female flies, patterns of aggression can be switched with males using female patterns and vice versa. Work with *Sts* or *Sry* genes suggests so far that other genes on the X chromosomes may have a more critical role in female mouse aggression. New data from feral rats point to the regulatory influences on mesocortical serotonin circuits in highly aggressive animals via feedback to autoreceptors and via GABAergic and glutamatergic inputs. Imaging data lead to the hypothesis that antisocial, violent, and psychopathic behavior may in part be attributable to impairments in some of the brain structures (dorsal and ventral PFC, amygdala, and angular gyrus) subserving moral cognition and emotion.

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Neurotech for Neuroscience: Unifying Concepts, Organizing Principles, and Emerging Tools

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The ability to tackle analysis of the brain at multiple levels simultaneously is emerging from rapid methodological developments. The classical research strategies of “measure,” “model,” and “make” are being applied to the exploration of nervous system function. These include novel conceptual and theoretical approaches, creative use of mathematical modeling, and attempts to build brain-like devices and systems, as well as other developments including instrumentation and statistical modeling (not covered here). Increasingly, these efforts require teams of scientists from a variety of traditional scientific disciplines to work together. The potential of such efforts for understanding directed motor movement, emergence of cognitive function from neuronal activity, and development of neuromimetic computers are described by a team that includes individuals experienced in behavior and neuroscience, mathematics, and engineering. Funding agencies, including the National Science Foundation, explore the potential of these changing frontiers of research for developing research policies and long-term planning.

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Disparity Channels in Early Vision

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The past decade has seen a dramatic increase in our knowledge of the neural basis of stereopsis. New cortical areas have been found to represent binocular disparities, new representations of disparity information (e.g., relative disparity signals) have been uncovered, the first topographic maps of disparity have been measured, and the first causal links between neural activity and depth perception have been established. Equally exciting is the finding that training and experience affects how signals are channeled through different brain areas, a flexibility that may be crucial for learning, plasticity, and recovery of function. The collective efforts of several laboratories have established stereo vision as one of the most productive model systems for elucidating the neural basis of perception. Much remains to be learned about how the disparity signals that are initially encoded in primary visual cortex are routed to and processed by extrastriate areas to mediate the diverse capacities of three-dimensional vision that enhance our daily experience of the world.

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MINI-SYMPOSIUM

β -Amyloid Modulation of Synaptic Transmission and Plasticity

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The Upshot of Up States in the Neocortex: From Slow Oscillations to Memory Formation

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Biomimetic Brain Machine Interfaces for the Control of Movement

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Quite recently, it has become possible to use signals recorded simultaneously from large numbers of cortical neurons for real-time control. Such brain machine interfaces (BMIs) have allowed animal subjects and human patients to control the position of a computer cursor or robotic limb under the guidance of visual feedback. Although impressive, such approaches essentially ignore the dynamics of the musculoskeletal system, and they lack potentially critical somatosensory feedback. In this mini-symposium, we will initiate a discussion of systems that more nearly mimic the control of natural limb movement. The work that we will describe is based on fundamental observations of sensorimotor physiology that have inspired novel BMI approaches. We will focus on what we consider to be three of the most important new directions for BMI development related to the control of movement. (1) We will present alternative methods for building decoders, including structured, nonlinear models, the explicit incorporation of limb state information, and novel approaches to the development of decoders for paralyzed subjects unable to generate an output signal. (2) We will describe the real-time prediction of dynamical signals, including joint torque, force, and EMG, and the real-time control of physical plants with dynamics like that of the real limb. (3) We will discuss critical factors that must be considered to incorporate somatosensory feedback to the BMI user, including its potential benefits, the differing representations of sensation and perception across cortical areas, and the changes in the cortical representation of tactile events after spinal injury.

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Transcriptional Regulation of Cortical Interneuron Development

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Stress and Disease: Is Being Female a Predisposing Factor?

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Noncoding RNAs in the Brain

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Cells transcribe thousands of RNAs that do not appear to encode proteins. The neuronal functions of these noncoding RNAs (ncRNAs) are for the most part not known, but specific ncRNAs have been shown to regulate dendritic spine development, neuronal fate specification and differentiation, and synaptic protein synthesis. ncRNAs have been implicated in a number of neuronal diseases including Tourette's syndrome and Fragile X syndrome. Future studies will likely identify additional neuronal functions for ncRNAs as well as roles for these molecules in other neuropsychiatric and neurodevelopmental disorders.

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Converging Evidence for a Fronto-Basal-Ganglia Network for Inhibitory Control of Action and Cognition

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The Roles of Kinases in Familial Parkinson's Disease

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The purpose of this mini-symposium is to discuss some of the inherited forms of Parkinson's disease (PD) in view of recent data suggesting that some of the proteins affect cellular signaling pathways. As an illustration, we shall focus on two different kinases associated with recessive and dominant forms of PD. Mutations in the mitochondrial kinase PTEN (phosphatase and tensin homolog)-induced kinase 1 (PINK1) are loss-of-function mutations in a normally neuroprotective protein. Loss-of-function mutations in model organisms have variable effects, from dramatic muscle and spermatid defects in *Drosophila* to more subtle neurophysiological abnormalities in mice. Several lines of evidence relate these to the action of a second gene for familial PD, parkin, an E3 ubiquitin ligase shown recently to have effects on Akt signaling. Mutations in leucine-rich repeat kinase 2 (LRRK2), a cytosolic kinase, are dominant and have the opposite effect of causing neuronal damage. The mechanism(s) involved are uncertain at this time because LRRK2 is a large and complex molecule with several domains. Increased kinase activity accounts for the action of at least some of the mutations, suggesting that hyperactive or misregulated kinase activity may lead to the damaging effects of LRRK2 in neurons. For both PINK1 and LRRK2, the following key question that needs to be answered: what are the physiological substrates that mediate effects in cells? Here, we will discuss some of the recent thinking about physiological and pathological roles for signaling in PD and how these may have therapeutic implications for the future.

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BRIEF COMMUNICATIONS

Opioid-Mediated Placebo Responses Boost Pain Endurance and Physical Performance: Is It Doping in Sport Competitions?

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The neurobiological investigation of the placebo effect has shown that placebos can activate the endogenous opioid systems in some conditions. So far, the impact of this finding has been within the context of the clinical setting. Here we present an experiment that simulates a sport competition, a situation in which opioids are considered to be illegal drugs. After repeated administrations of morphine in the precompetition training phase, its replacement with a placebo on the day of competition induced an opioid-mediated increase of pain endurance and physical performance, although no illegal drug was administered. The placebo analgesic responses were obtained after two morphine administrations that were separated as long as 1 week from each other. These long time intervals indicate that the pharmacological conditioning procedure has long-lasting effects and that opioid-mediated placebo responses may have practical implications and applications. For example, in the context of the present sport simulation, athletes can be preconditioned with morphine and then a placebo can be given just before competition, thus avoiding administration of the illegal drug on the competition day. However, these morphine-like effects of placebos raise the important question whether opioid-mediated placebo responses are ethically acceptable in sport competitions or whether they have to be considered a doping procedure in all respects.

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Different Effects of Voluntary and Involuntary Attention on EEG Activity in the Gamma Band

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Previous studies have shown that EEG activity in the gamma range can be modulated by attention. Here, we compared this activity for voluntary and involuntary spatial attention in a spatial-cueing paradigm with faces as targets. The stimuli and trial timing were kept constant across attention conditions with only the predictive value of the cue changing. Gamma-band response was linked to voluntary shifts of attention, but not to the involuntary capture of attention. The presence of increased gamma responses for the voluntary allocation of attention, and its absence in cases of involuntary capture suggests that the neural mechanisms governing these two types of attention are different. Moreover, these data allow a description of the temporal dynamics contributing to the dissociation between voluntary and involuntary attention. The distribution of this correlate of voluntary attention is consistent with a top-down process involving contralateral anterior and posterior regions.

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Fructose-1,6-Bisphosphate Has Anticonvulsant Activity in Models of Acute Seizures in Adult Rats

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A variety of observations suggest that decreasing glycolysis and increasing levels of reduced glutathione, generated by metabolism of glucose through the pentose phosphate pathway, would have an anticonvulsant effect. Because fructose-1,6-bisphosphate (F1,6BP) shifts the metabolism of glucose from glycolysis to the pentose phosphate pathway, it was hypothesized to have anticonvulsant activity. The anticonvulsant activity of F1,6BP was determined in rat models of acute seizures induced by pilocarpine, kainic acid, or pentylenetetrazole. The efficacy of F1,6BP was compared with that of 2-deoxyglucose (2-DG; an inhibitor of glucose uptake and glycolysis), valproic acid (VPA), and the ketogenic diet. One hour before each convulsant, Sprague Dawley rats received either saline (as seizure controls), F1,6BP (0.25, 0.5 or 1 g/kg), 2-DG (0.25 or 0.5 g/kg), or VPA (0.3 g/kg). Additional animals received the ketogenic diet (starting at 20 or 60 d old). Time to seizure onset, seizure duration, and seizure score were measured in each group. F1,6BP had dose-dependent anticonvulsant activity in all three models, whereas VPA had partial efficacy. 2-DG was only effective in the pilocarpine model. The ketogenic diet had no effect in these models. F1,6BP was also partially effective when given at the first behavioral seizure after pilocarpine. Administration of sodium lactate, which bypasses the block in the glycolytic pathway, abolished the anticonvulsant activity of 2-DG in the pilocarpine model, but only decreased the efficacy of F1,6BP. These data demonstrate that F1,6BP has significant anticonvulsant efficacy.

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Articles

CELLULAR/MOLECULAR

The Structural and Functional Differentiation of Hair Cells in a Lizard's Basilar Papilla Suggests an Operational Principle of Amniote Cochleas

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The hair cells in the mammalian cochlea are of two distinct types. Inner hair cells are responsible for transducing mechanical stimuli into electrical responses, which they forward to the brain through a copious afferent innervation. Outer hair cells, which are thought to mediate the active process that sensitizes and tunes the cochlea, possess a negligible afferent innervation. For every inner hair cell, there are approximately three outer hair cells, so only one-quarter of the hair cells directly deliver information to the CNS. Although this is a surprising feature for a sensory system, the occurrence of a similar innervation pattern in birds and crocodylians suggests that the arrangement has an adaptive value. Using a lizard with highly developed hearing, the tokay gecko, we demonstrate in the present study that the same principle operates in a third major group of terrestrial animals. We propose that the differentiation of hair cells into signaling and amplifying classes reflects incompatible strategies for the optimization of mechano-electrical transduction and of an active process based on active hair-bundle motility.

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The *FGF14*^{F145S} Mutation Disrupts the Interaction of FGF14 with Voltage-Gated Na⁺ Channels and Impairs Neuronal Excitability

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Fibroblast growth factor 14 (FGF14) belongs to the intracellular FGF homologous factor subfamily of FGF proteins (iFGFs) that are not secreted and do not activate tyrosine kinase receptors. The iFGFs, however, have been shown to interact with the pore-forming (α) subunits of voltage-gated Na⁺ (Na_v) channels. The neurological phenotypes seen in *Fgf14*^{-/-} mice and the identification of an *FGF14* missense mutation (*FGF14*^{F145S}) in a Dutch family presenting with cognitive impairment and spinocerebellar ataxia suggest links between FGF14 and neuronal functioning. Here, we demonstrate that the expression of FGF14^{F145S} reduces Na_v α subunit expression at the axon initial segment, attenuates Na_v channel currents, and reduces the excitability of hippocampal neurons. In addition, and in contrast with wild-type FGF14, FGF14^{F145S} does not interact directly with Na_v channel α subunits. Rather, FGF14^{F145S} associates with wild-type FGF14 and disrupts the interaction between wild-type FGF14 and Na_v α subunits, suggesting that the mutant FGF14^{F145S} protein acts as a dominant negative, interfering with the interaction between wild-type FGF14 and Na_v channel α subunits and altering neuronal excitability.

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Neurokinin-1 Receptor Enhances TRPV1 Activity in Primary Sensory Neurons via PKC ϵ : A Novel Pathway for Heat Hyperalgesia

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The neuropeptide substance P (SP) is expressed in unmyelinated primary sensory neurons and represents the best known “pain” neurotransmitter. It is generally believed that SP regulates pain transmission and sensitization by acting on neurokinin-1 receptor (NK-1), which is expressed in postsynaptic dorsal horn neurons. However, the expression and role of NK-1 in primary sensory neurons are not clearly characterized. Our data showed that NK-1 was expressed in both intact and dissociated dorsal root ganglion (DRG) neurons. In particular, NK-1 was mainly coexpressed with the capsaicin receptor TRPV1 (transient receptor potential vanilloid subtype 1), a critical receptor for the generation of heat hyperalgesia. NK-1 agonist [Sar⁹, Met(O₂)¹¹]-substance P (Sar-SP) significantly potentiated capsaicin-induced currents and increase of [Ca²⁺]_i in dissociated DRG neurons. NK-1 antagonist blocked not only the potentiation of TRPV1 currents but also heat hyperalgesia induced by intraplantar Sar-SP. NK-1 antagonist also inhibited capsaicin-induced spontaneous pain, and this inhibition was enhanced after inflammation. To analyze intracellular cross talking of NK-1 and TRPV1, we examined downstream signal pathways of G-protein-coupled NK-1 activation. Sar-SP-induced potentiation of TRPV1 was blocked by inhibition of G-protein, PLC β (phospholipase C- β), or PKC but not by inhibition of PKA (protein kinase A). In particular, PKC ϵ inhibitor completely blocked both Sar-SP-induced TRPV1 potentiation and heat hyperalgesia. Sar-SP also induced membrane translocation of PKC ϵ in a portion of small DRG neurons. These results reveal a novel mechanism of NK-1 in primary sensory neurons via a possible autocrine and paracrine action of SP. Activation of NK-1 in these neurons induces heat hyperalgesia via PKC ϵ -mediated potentiation of TRPV1.

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DEVELOPMENT/PLASTICITY/REPAIR

Changes of the EPSP Waveform Regulate the Temporal Window for Spike-Timing-Dependent Plasticity

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Using spike-timing-dependent plasticity (STDP) protocols that consist of pairing an EPSP and a postsynaptic backpropagating action potential (BAP), we investigated the contribution of the changes in EPSP waveform induced by the slow Ca²⁺-dependent K⁺-mediated afterhyperpolarization (sAHP) in the regulation of long-term potentiation (LTP). The “temporal window” between Schaffer collateral EPSPs and BAPs in CA1 pyramidal neurons required to induce LTP was narrowed by a reduction of the amplitude and decay time constant of the EPSP, which could be reversed with cyclothiazide. The EPSP changes were caused by the increased conductance induced by activation of the sAHP. Therefore, the EPSP waveform and its regulation by the sAHP are central in determining the duration of the temporal window for STDP, thus providing a possible dynamic regulatory mechanism for the encoding of cognitive processes.

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In Vivo Tracing of Neural Tracts in the Intact and Injured Spinal Cord of Marmosets by Diffusion Tensor Tractography

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In spinal cord injury, axonal disruption results in motor and sensory function impairment. The evaluation of axonal fibers is essential to assess the severity of injury and efficacy of any treatment protocol, but conventional methods such as tracer injection in brain parenchyma are highly invasive and require histological evaluation, precluding clinical applications. Previous advances in magnetic resonance imaging technology have led to the development of diffusion tensor tractography (DTT) as a potential modality to perform *in vivo* tracing of axonal fibers. The properties and clinical applications of DTT in the brain have been reported, but technical difficulties have limited DTT studies of the spinal cord. In this study, we report the effective use of DTT to visualize both intact and surgically disrupted spinal long tracts in adult common marmosets. To verify the feasibility of spinal cord DTT, we first performed DTT of postmortem marmosets. DTT clearly illustrated spinal projections such as the corticospinal tract and afferent fibers in control animals, and depicted the severed long tracts in the injured animals. Histology of the spinal cords in both control and injured groups were consistent with DTT findings, verifying the accuracy of DTT. We also conducted DTT in live marmosets and demonstrated that DTT can be performed in live animals to reveal *in vivo* nerve fiber tracing images, providing an essential tool to evaluate axonal conditions in the injured spinal cord. Taken together, these findings demonstrate the feasibility of applying DTT to preclinical and clinical studies of spinal cord injury.

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Paucity of Pericytes in Germinal Matrix Vasculature of Premature Infants

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Germinal matrix (GM) is a richly vascularized collection of neuronal–glial precursor cells in the developing brain, which is selectively vulnerable to hemorrhage in premature infants. It has rapid angiogenesis associated with high levels of vascular endothelial growth factor (VEGF). Because pericytes provide structural stability to blood vessels, we asked whether pericytes were fewer in the GM than in the subjacent white matter and neocortex and, if so, whether angiogenic inhibition could increase the pericyte density in the GM. We found pericyte coverage and density less in the GM vasculature than in the cortex or white matter in human fetuses, premature infants, and premature rabbit pups. Notably, although VEGF suppression significantly enhanced pericyte coverage in the GM, it remained less than in other brain regions. Therefore, to further elucidate the basis of fewer pericytes in the GM vasculature, we examined expression of ligand–receptor systems responsible for pericyte recruitment. Transforming growth factor- β 1 (TGF- β 1) protein expression was lower, whereas sphingosine-1-phosphate1 (S1P1) and N-cadherin levels were higher in the GM than in the cortex or white matter. Low TGF- β 1 may be involved in promoting endothelial proliferation, whereas elevated S1P1 with N-cadherin may assist vascular maturation. Hence, a paucity of pericytes in the GM vasculature may contribute to its propensity to hemorrhage, and a lower expression of TGF- β 1 could be a basis of reduced pericyte density in its vasculature.

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Synaptic Plasticity (and the Lack Thereof) in Hippocampal CA2 Neurons

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The hippocampus is critical for some forms of memory and spatial navigation, but previous research has mostly neglected the CA2, a unique region situated between CA3 and CA1. Here, we show that CA2 pyramidal neurons have distinctive physiological characteristics that include an unprecedented synaptic stability. Although basal synaptic currents in CA1 and CA2 are quite similar, synaptic plasticity including long-term potentiation and long-term depression is absent or less likely to be induced with conventional methods of stimulation in CA2. We also find that CA2 neurons have larger leak currents and more negative resting membrane potentials than CA1 neurons, and consequently, more current is required for action potential generation in CA2 neurons. These data suggest that the molecular “conspiracy against plasticity” in CA2 makes it functionally distinct from the other hippocampal CA regions. This work provides critical insight into hippocampal function and may lead to an understanding of the resistance of CA2 to damage from disease, trauma, and hypoxia.

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Differential Modulation of Motor Cortical Plasticity and Excitability in Early and Late Phases of Human Motor Learning

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Different phases of motor skill learning appear to involve different physiological processes, with long-term potentiation (LTP) occurring at existing synapses in early and cortical reorganization involving synaptogenesis in later phases. Here, we test the evolution of skill learning-dependent changes in motor plasticity and excitability in six subjects trained to perform rapid thumb abductions over 5 d. Plasticity was examined using paired-associative stimulation (PAS) of the median nerve and motor cortex to induce LTP-like [PAS given with an interstimulus interval of 25 ms (PAS25)] or long-term depression (LTD)-like [PAS given with an interstimulus interval of 10 ms (PAS10)] plasticity. Excitability was tested by measuring recruitment of motor-evoked-potentials [input–output (IO) curve] and of short-latency intracortical inhibition (SICI curve), and sensorimotor organization (SMO). Task performance improved continuously over 5 d. After practice on day 1, the PAS25 effect reversed from facilitation to inhibition whereas the slope of the IO curve increased and the level of SICI decreased. These effects on IO curve and SICI were still present or even enhanced before the last practice on day 5, and were not changed by it. The effect of proprioceptive input from the trained muscle on SMO was also strengthened before practice on day 5. In contrast, PAS-induced plasticity was not influenced by motor practice on day 5, and had returned to prepractice values. The interference with PAS-induced plasticity suggests that the initial performance improvement relies on increasing the efficacy of existing synaptic connections. However, the long-lasting changes in the IO curve, SICI curve, and SMO suggest that continued practice enhances performance by changing Motor cortical organization. We hypothesize that new synaptic connections might have formed that allow LTP/LTD-susceptibility to be restored without reducing synaptic strength and performance skill.

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Regulation of Long-Term Depression and Climbing Fiber Territory by Glutamate Receptor $\delta 2$ at Parallel Fiber Synapses through its C-Terminal Domain in Cerebellar Purkinje Cells

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Glutamate receptor (GluR) $\delta 2$ selectively expressed in cerebellar Purkinje cells (PCs) plays key roles in long-term depression (LTD) induction at parallel fiber (PF)–PC synapses, motor learning, the matching and connection of PF–PC synapses in developing and adult cerebella, the elimination of multiple climbing fibers (CFs) during development, and the regulation of CF territory on PCs. However, it remains unsolved how GluR $\delta 2$ regulates cerebellar synaptic plasticity, PF–PC synapse formation, and CF wiring. One possible signaling mechanism through GluR $\delta 2$ is signaling by protein–protein interactions. The C-terminal region of GluR $\delta 2$ contains at least three domains for protein–protein interactions. The PDZ (postsynaptic density-95/Discs large/zona occludens 1)-binding domain at the C terminal, named as the T site, interacts with several postsynaptic density proteins. Here, we generated GluR $\delta 2\Delta T$ mice carrying mutant GluR $\delta 2$ lacking the T site. There were no significant differences in the amount of receptor proteins at synapses, histological features, and the fine structures of PF–PC synapses between wild-type and GluR $\delta 2\Delta T$ mice. However, LTD induction at PF–PC synapses and improvement in the accelerating rotarod test were impaired in GluR $\delta 2\Delta T$ mice. Furthermore, CF territory expanded distally and ectopic innervation of CFs occurred at distal dendrites in GluR $\delta 2\Delta T$ mice, but the elimination of surplus CF innervation at proximal dendrites appeared to proceed normally. These results suggest that the C-terminal T site of GluR $\delta 2$ is essential for LTD induction and the regulation of CF territory but is dispensable for PF–PC synapse formation and the elimination of surplus CFs at proximal dendrites during development.

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BEHAVIORAL/SYSTEMS/COGNITIVE

Parieto-Frontal Connectivity during Visually Guided Grasping

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Grasping an object requires processing visuospatial information about the extrinsic features (spatial location) and intrinsic features (size, shape, orientation) of the object. Accordingly, manual prehension has been subdivided into a reach component, guiding the hand toward the object on the basis of its extrinsic features, and a grasp component, preshaping the fingers around the center of mass of the object on the basis of its intrinsic features. In neural terms, this distinction has been linked to a dedicated dorsomedial “reaching” circuit and a dorsolateral “grasping” circuit that process extrinsic and intrinsic features, linking occipital areas via parietal regions with

the dorsal and ventral premotor cortex, respectively. We have tested an alternative possibility, namely that the relative contribution of the two circuits is related to the degree of on-line control required by the prehension movement.

We used dynamic causal modeling of functional magnetic resonance imaging time series to assess how parieto-frontal connectivity is modulated by planning and executing prehension movements toward objects of different size and width. This experimental manipulation evoked different movements, with different planning and execution phases for the different objects. Crucially, grasping large objects increased inter-regional couplings within the dorsomedial circuit, whereas grasping small objects increased the effective connectivity of a mainly dorsolateral circuit, with a degree of overlap between these circuits. These results argue against the presence of dedicated cerebral circuits for reaching and grasping, suggesting that the contributions of the dorsolateral and the dorsomedial circuits are a function of the degree of on-line control required by the movement.

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Dissociable Performance on Scene Learning and Strategy Implementation after Lesions to Magnocellular Mediodorsal Thalamic Nucleus

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Monkeys with aspiration lesions of the magnocellular division of the mediodorsal thalamus (MDmc) are impaired in object-in-place scene learning, object recognition, and stimulus-reward association. These data have been interpreted to mean that projections from MDmc to prefrontal cortex are required to sustain normal prefrontal function in a variety of task settings. In the present study, we investigated the extent to which bilateral neurotoxic lesions of the MDmc impair a preoperatively learnt strategy implementation task that is impaired by a crossed lesion technique that disconnects the frontal cortex in one hemisphere from the contralateral inferotemporal cortex. Postoperative memory impairments were also examined using the object-in-place scene memory task. Monkeys learnt both strategy implementation and scene memory tasks separately to a stable level preoperatively. Bilateral neurotoxic lesions of the MDmc, produced by $10 \times 1 \mu\text{l}$ injections of a mixture of ibotenate and NMDA did not affect performance in the strategy implementation task. However, new learning of object-in-place scene memory was substantially impaired. These results provide new evidence about the role of the magnocellular mediodorsal thalamic nucleus in memory processing, indicating that interconnections with the prefrontal cortex are essential during new learning, but are not required when implementing a preoperatively acquired strategy task. Thus, not all functions of the prefrontal cortex require MDmc input. Instead, the involvement of MDmc in prefrontal function may be limited to situations in which new learning must occur.

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Topographic Organization in and near Human Visual Area V4

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The existence and location of a human counterpart of macaque visual area V4 are disputed. To resolve this issue, we used functional magnetic resonance imaging to obtain topographic maps from human subjects, using visual stimuli and tasks designed to maximize accuracy of topographic maps of the fovea and parafovea and to measure the effects of attention on topographic maps. We identified multiple topographic transitions, each clearly visible in $\geq 75\%$ of the maps, that we interpret as boundaries of distinct cortical regions. We call two of these regions dorsal V4 and ventral V4 (together comprising human area V4) because they share several defining characteristics with the macaque regions V4d and V4v (which together comprise macaque area V4). Ventral V4 is adjacent to V3v, and dorsal V4 is adjacent to parafoveal V3d. Ventral V4 and dorsal V4 meet in the foveal confluence shared by V1, V2, and V3. Ventral V4 and dorsal V4 represent complementary regions of the visual field, because ventral V4 represents the upper field and a subregion of the lower field, whereas dorsal V4 represents lower-field locations that are not represented by ventral V4. Finally, attentional modulation of spatial tuning is similar across dorsal and ventral V4, but attention has a smaller effect in V3d and V3v and a larger effect in a neighboring lateral occipital region.

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Evidence Accumulation and the Moment of Recognition: Dissociating Perceptual Recognition Processes Using fMRI

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Decision making can be conceptualized as the culmination of an integrative process in which evidence supporting different response options accumulates gradually over time. We used functional magnetic resonance imaging to investigate brain activity leading up to and during decisions about perceptual object identity. Pictures were revealed gradually and subjects signaled the time of recognition (T_R) with a button press. We examined the time course of T_R -dependent activity to determine how brain regions tracked the timing of recognition. In several occipital regions, activity increased primarily as stimulus information increased, suggesting a role in lower-level sensory processing. In inferior temporal, frontal, and parietal regions, a gradual buildup in activity peaking in correspondence with T_R suggested that these regions participated in the accumulation of evidence supporting object identity. In medial frontal cortex, anterior insula/frontal operculum, and thalamus, activity remained near

baseline until T_R , suggesting a relation to the moment of recognition or the decision itself. The findings dissociate neural processes that function in concert during perceptual recognition decisions.

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Medial Prefrontal Theta Bursts Precede Rapid Motor Responses during Visual Selective Attention

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After visual target stimuli presented infrequently at a covertly attended location, quicker speeded button presses immediately followed a larger positive (P3f) ramp in averaged electroencephalographic (EEG) recordings from the forehead. We show this peak in the mean response time locked to the button press to be principally composed of triphasic, primarily low-theta band (4.5 Hz) complexes preceding but only partially phase-locked to the button press, with larger complexes preceding quicker motor responses. For 10 of 15 subjects, independent component analysis of the unaveraged 31-channel data identified a temporally independent medial frontal EEG process contributing to these phenomena. Low-resolution tomographic modeling localized related components of two 253-channel data sets to medial frontal polar cortex (BA32/10). The far-frontal low-theta complexes and concomitant mean P3f positivity may index cortical activity induced by paralimbic processes involved in disinhibiting impulsive motor responses to rewarding or goal-fulfilling stimuli or events.

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Processing of Odor Mixtures in the *Drosophila* Antennal Lobe Reveals both Global Inhibition and Glomerulus-Specific Interactions

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To understand how odor information is represented and processed in the antennal lobe (AL) of *Drosophila melanogaster*, we have optically recorded glomerular calcium responses to single odors and odor mixtures from olfactory sensory neurons (OSNs) and projection neurons (PNs). Odor mixtures offer a good tool to analyze odor processing because experimental results can be tested against clear predictions. At the level of the OSNs, the representation of odor mixtures could be predicted from the response patterns of the components in most cases. PN responses to mixtures, however, provide evidences of interglomerular inhibition. Application of picrotoxin (PTX), an antagonist of GABA_A-like receptors, enhanced odor responses, modified their temporal course, and eliminated mixture suppression at the PN level. Our results can be best explained by postulating the existence of at least two local networks in the fly AL: a glomerulus specific network, which includes excitatory and inhibitory connections and a PTX sensitive inhibitory global network that acts on all glomeruli with proportional strength to the global AL input.

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Cortical Acetylcholine Release Is Lateralized during Asymmetrical Slow-Wave Sleep in Northern Fur Seals

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Fur seals are unique in that they display both bilateral slow-wave sleep (BSWS), as seen in all terrestrial mammals, and slow-wave sleep with interhemispheric electroencephalogram (EEG) asymmetry, resembling the unihemispheric slow waves of cetaceans. Little is known about the underlying mechanisms of this phenomenon, which is also termed asymmetrical slow wave sleep (ASWS). However, we may begin to understand the expression of ASWS by studying the neurotransmitter systems thought to be involved in the generation and maintenance of sleep–wake states in terrestrial mammals. We examined bilaterally the release of cortical acetylcholine (ACh), a neurotransmitter implicated in the regulation of cortical EEG and behavioral arousal, across the sleep–wake cycle in four juvenile northern fur seals (*Callorhinus ursinus*). *In vivo* microdialysis and high-performance liquid chromatography coupled with electrochemical detection were used to measure cortical ACh levels during polygraphically defined behavioral states. Cortical ACh release was state-dependent, showing maximal release during active waking (AW), similar levels during quiet waking (QW), and rapid eye movement (REM) sleep, and minimal release during BSWS. When compared with BSWS, cortical ACh levels increased ~300% during AW, and ~200% during QW and REM sleep. During these bilaterally symmetrical EEG states, ACh was synchronously released from both hemispheres. However, during ASWS, ACh release was lateralized with greater release in the hemisphere displaying lower voltage activity, at levels approximating those seen in QW. These findings demonstrate that cortical ACh release is tightly linked to hemispheric EEG activation.

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Steroid Hormones Act Transsynaptically within the Forebrain to Regulate Neuronal Phenotype and Song Stereotypy

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Steroid sex hormones induce dramatic seasonal changes in reproductive related behaviors and their underlying neural substrates in seasonally breeding vertebrates. For example, in adult white-crowned sparrows, increased Spring photoperiod raises circulating testosterone, causing morphological and electrophysiological changes in song-control nuclei, which modify song behavior for the breeding season. We investigated how photoperiod and steroid hormones induce these changes in morphology, electrophysiology, and behavior. Neurons in a song premotor nucleus, the robust nucleus of the arcopallium (RA), show increased intrinsic spontaneous firing rate and soma size when birds are in breeding condition. Using combinations of systemic and unilateral local intracerebral hormonal manipulations, we show that long-day photoperiod accelerates the effects of systemic testosterone on RA neurons via the estradiol-synthesizing enzyme aromatase (CYP19A1); these changes require inputs from the afferent song control nucleus HVC (used as a proper name) and steroid receptor activation within HVC; local coactivation of androgen and estrogen receptors (ARs and ERs, respectively) within HVC, but not RA, is sufficient to cause neuronal changes in RA; activation of ARs in RA is also permissive. Using bilateral local intracerebral hormone-receptor blockade, we found that ARs and ERs in the song-control nucleus HVC mediate systemic testosterone-induced changes in song stereotypy but not rate. This novel transsynaptic effect of gonadal steroids on activity and morphology of RA neurons is part of a concerted change in key premotor nuclei, enabling stereotyped song.

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Gastrin-Releasing Peptide Mediates Light-Like Resetting of the Suprachiasmatic Nucleus Circadian Pacemaker through cAMP Response Element-Binding Protein and *Per1* Activation

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Circadian rhythmicity in the primary mammalian circadian pacemaker, the suprachiasmatic nucleus (SCN) of the hypothalamus, is maintained by transcriptional and translational feedback loops among circadian clock genes. Photic resetting of the SCN pacemaker involves induction of the clock genes *Period1* (*Per1*) and *Period2* (*Per2*) and communication among distinct cell populations. Gastrin-releasing peptide (GRP) is localized to the SCN ventral retinorecipient zone, from where it may communicate photic resetting signals within the SCN network. Here, we tested the putative role of GRP as an intra-SCN light signal at the behavioral and cellular levels, and we also tested whether GRP actions are dependent on activation of the cAMP response element-binding protein (CREB) pathway and *Per1*. *In vivo* microinjections of GRP to the SCN regions of *Per1::green fluorescent protein* (GFP) mice during the late night induced *Per1::GFP* throughout the SCN, including a limited population of arginine vasopressin-immunoreactive (AVP-IR) neurons. Blocking spike-mediated communication with tetrodotoxin did not disrupt overall *Per1::GFP* induction but did reduce induction within AVP-IR neurons. *In vitro* GRP application resulted in persistent increases in the spike frequency of *Per1::GFP*-induced neurons. Blocking endogenous *Per1* with antisense oligodeoxynucleotides inhibited GRP-induced increases in spike frequency. Furthermore, inhibition of CREB-mediated gene activation with decoy oligonucleotides blocked GRP-induced phase shifts of *PER2::luciferase* rhythms in SCN slices. Altogether, these results indicate that GRP communicates phase resetting signals within the SCN network via both spike-dependent and spike-independent mechanisms, and that activation of the CREB pathway and *Per1* are key steps in mediating downstream events in GRP resetting of SCN neurons.

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The Role of Kisspeptin–GPR54 Signaling in the Tonic Regulation and Surge Release of Gonadotropin-Releasing Hormone/Luteinizing Hormone

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The *Kiss1* gene codes for kisspeptin, which binds to GPR54, a G-protein-coupled receptor. Kisspeptin and GPR54 are expressed in discrete regions of the forebrain, and they have been implicated in the neuroendocrine regulation of reproduction. *Kiss1*-expressing neurons are thought to regulate the secretion of gonadotropin-releasing hormone (GnRH) and thus coordinate the estrous cycle in rodents; however, the precise role of kisspeptin–GPR54 signaling in the regulation of gonadotropin secretion is unknown. In this study, we used female mice with deletions in the *GPR54* gene [*GPR54* knock-outs (KOs)] to test the hypothesis that kisspeptin–GPR54 signaling provides the drive necessary for tonic GnRH/luteinizing hormone (LH) release. We predicted that tonic GnRH/LH secretion would be disrupted in *GPR54* KOs and that such animals would be incapable of showing a compensatory rise in LH secretion after ovariectomy. As predicted, we found that *GPR54* KO mice do not exhibit a postovariectomy rise in LH, suggesting that tonic GnRH secretion is disrupted in the absence of kisspeptin–GPR54 signaling. We also postulated that kisspeptin–GPR54 signaling is critical for the generation of the estradiol (E)-induced GnRH/LH surge and thus E should be incapable of inducing an LH surge in the absence of GPR54. However, we found that E induced Fos expression in GnRH neurons and produced a GnRH-dependent LH surge in *GPR54* KOs. Thus, in mice, kisspeptin–GPR54 signaling is required for the tonic stimulation of GnRH/LH secretion but is not required for generating the E-induced GnRH/LH surge.

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Cognitive Signals in the Primate Motor Thalamus Predict Saccade Timing

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We often generate movements without any external event that immediately triggers them. How the brain decides the timing of self-initiated movements remains unclear. Previous studies suggest that the basal ganglia–thalamocortical pathways play this role, but the subcortical signals that determine movement timing have not been identified. The present study reports that a subset of thalamic neurons predicts the timing of self-initiated saccadic eye movements. When monkeys made a saccade in response to the fixation point (FP) offset in the traditional memory saccade task, neurons in the ventrolateral and the ventroanterior nuclei of the thalamus exhibited a gradual buildup of activity that peaked around the most probable time of the FP offset; however, neither the timing nor the magnitude of neuronal activity correlated with saccade latencies, suggesting that the brain is unlikely to have used this information to decide the times of saccades in the traditional memory saccade task. In contrast, when monkeys were required to make a self-timed saccade within a fixed time interval after an external cue, the same neurons again exhibited a strong buildup of activity that preceded saccades by several hundred milliseconds, showing a close correlation between the times of neuronal activity and the times of self-initiated saccades. The results suggest that neurons in the motor thalamus carry subjective time information, which is used by cortical networks to determine the timing of self-initiated saccades.

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NEUROBIOLOGY OF DISEASE

Diffusion Tensor Imaging Reliably Detects Experimental Traumatic Axonal Injury and Indicates Approximate Time of Injury

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Traumatic axonal injury (TAI) may contribute greatly to neurological impairments after traumatic brain injury, but it is difficult to assess with conventional imaging. We quantitatively compared diffusion tensor imaging (DTI) signal abnormalities with histological and electron microscopic characteristics of pericontusional TAI in a mouse model. Two DTI parameters, relative anisotropy and axial diffusivity, were significantly reduced 6 h to 4 d after trauma, corresponding to relatively isolated axonal injury. One to 4 weeks after trauma, relative anisotropy remained decreased, whereas axial diffusivity “pseudo-normalized” and radial diffusivity increased. These changes corresponded to demyelination, edema, and persistent axonal injury. At every time point, DTI was more sensitive to injury than conventional magnetic resonance imaging, and relative anisotropy distinguished injured from control mice with no overlap between groups. Remarkably, DTI changes strongly predicted the approximate time since trauma. These results provide an important validation of DTI for pericontusional TAI and suggest novel clinical and forensic applications.

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Neural Stem Cells Improve Memory in an Inducible Mouse Model of Neuronal Loss

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Neuronal loss is a major pathological outcome of many common neurological disorders, including ischemia, traumatic brain injury, and Alzheimer disease. Stem cell-based approaches have received considerable attention as a potential means of treatment, although it remains to be determined whether stem cells can ameliorate memory dysfunction, a devastating component of these disorders. We generated a transgenic mouse model in which the tetracycline-off system is used to regulate expression of diphtheria toxin A chain. After induction, we find progressive neuronal loss primarily within the hippocampus, leading to specific impairments in memory. We find that neural stem cells transplanted into the brain after neuronal ablation survive, migrate, differentiate and, most significantly, improve memory. These results show that stem cells may have therapeutic value in diseases and conditions that result in memory loss.

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More Is Not Always Better: Increased Fractional Anisotropy of Superior Longitudinal Fasciculus Associated with Poor Visuospatial Abilities in Williams Syndrome

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We used diffusion tensor imaging to examine white matter integrity in the dorsal and ventral streams among individuals with Williams syndrome (WS) compared with two control groups (typically developing and developmentally delayed) and using three separate analysis methods (whole brain, region of interest, and fiber tractography). All analysis methods consistently showed that fractional anisotropy (FA; a measure of microstructural integrity) was higher in the right superior longitudinal fasciculus (SLF) in WS compared with both control groups. There was a significant association with deficits in visuospatial construction and higher FA in WS individuals. Comparable increases in FA across analytic methods were not observed in the left SLF or the bilateral inferior longitudinal fasciculus in WS subjects. Together, these findings suggest a specific role of right SLF abnormality in visuospatial construction deficits in WS.

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