

This Week in The Journal

● Cellular/Molecular

Few Prefrontal Pyramidal Cells Express Dopamine D1 Receptors

Hannah J. Seong and Adam G. Carter

(see pages 10516–10521)

Dopaminergic projections to the prefrontal cortex (PFC) modulate its role in several functions, including attention, working memory, and self-control. The projections terminate predominantly in deep layers, where D1 dopamine receptors (D1DRs) are sparsely distributed. To better understand the distribution and function of D1DRs, Seong and Carter performed whole-cell recordings in PFC slices taken from BAC transgenic mice in which a fluorescent dye was expressed under control of D1DR promoter elements. A small subset of neurons expressed D1DRs, and these were concentrated in deep layers. D1DR-expressing pyramidal neurons in layer 5 differed from nearby pyramidal neurons both morphologically and electrophysiologically: their apical dendrites were shorter and less branched, their resting membrane potentials were more hyperpolarized, they showed minimal activation of hyperpolarization-activated channels, and they were more likely to exhibit burst spiking upon depolarization. A D1 receptor agonist increased the depolarization-induced spiking of D1DR-expressing neurons, and this effect required activation of protein kinase A.

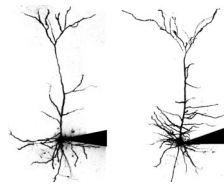
▲ Development/Plasticity/Repair

Adolescent Nicotine Exposure Affects Plasticity in Adult PFC

Natalia A. Goriounova and Huibert D. Mansvelder

(see pages 10484–10493)

Although nicotine has some positive effects, such as enhancing attention in people with cognitive disorders, chronic nicotine use—particularly during adolescence, when prefrontal cortical (PFC) circuits are developing—can produce long-lasting impairments in attention and working memory. In rats, nicotine treatment during adolescence causes attention deficits weeks after nicotine



PFC neurons that express D1DRs (left) have shorter, less-branched apical dendrites than nearby neurons that do not express these receptors (right). See the article by Seong and Carter for details.

treatment has ceased. This deficit results partly from long-term reduction in the expression of metabotropic glutamate receptors (mGluRs), which presynaptically inhibit glutamate release in the PFC. Goriounova and Mansvelder report that nicotine treatment during adolescence also alters spike timing-dependent long-term potentiation (tLTP) in PFC. A protocol that induced tLTP in control adolescent rats often produced long-term depression (LTD) in those that had received nicotine for 10 days. In contrast, adult rats that had received nicotine as adolescents showed enhanced tLTP compared with controls. Age-dependent effects of mGluR agonists and antagonists suggested the effects of adolescent nicotine exposure resulted from short-term upregulation and long-term downregulation of mGluRs.

■ Behavioral/Systems/Cognitive

Active Sensing Alters NTS Responses to Tastes

Andre T. Roussin, Alexandra E. D'Agostino, Andrew M. Fooden, Jonathan D. Victor, and Patricia M. Di Lorenzo

(see pages 10494–10506)

In most studies of sensory processing, stimulus presentation is controlled solely by the experimenter. But in real life, animals shape their own sensory experience by actively looking at, touching, or licking objects. Attentional processes and neural circuitry driving these actions feed into sensory circuits and influence stimulus processing. To fully understand sensory processing, therefore, one must examine sensory system activity during active sensing. By recording from the nucleus of the solitary tract

(NTS)—the target of the gustatory nerve—in freely licking rats, Roussin et al. discovered that taste-responsive cells were more broadly tuned than was determined previously during passive administration of tastes. In fact, many cells responded to all five basic tastes, and few responded exclusively to a single taste. Furthermore, some cells exhibited inhibitory responses, which were not reported previously. The latency of responses to different tastes varied both within and across cells, suggesting tastes are encoded by spatiotemporal patterns of NTS activity.

◆ Neurobiology of Disease

Nrf2 Reduces Pathological Features of Alexander Disease

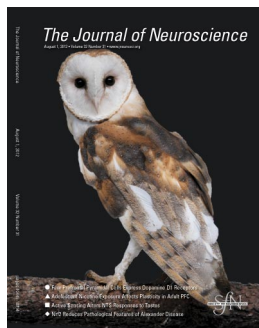
Christine M. LaPash Daniels, Elizabeth V. Austin, Danica E. Rockney, Elizabeth M. Jacka, Tracy L. Hagemann, et al.

(see pages 10507–10515)

Mitochondrial respiration generates reactive oxygen species (ROS) that must be disposed of to prevent oxidative damage to DNA, lipids, and proteins, and subsequent cell death. Overproduction or inefficient removal of ROS contributes to many neurodegenerative diseases. The transcription factor Nrf2 regulates several genes involved in synthesizing free-radical scavengers and, although it functions mainly in astrocytes, its activation protects neurons from oxidative stress. Endogenous Nrf2 is upregulated in Alexander disease, a fatal disease caused by gain-of-function mutations in glial fibrillary acidic protein (GFAP) and characterized by formation of Rosenthal fibers in astrocytes, but Daniels et al. asked whether further Nrf2 elevation would be protective in a mouse model of this disease. Indeed it was—overexpression of Nrf2 reduced both GFAP expression and Rosenthal fiber formation across the brain. Surprisingly, however, Nrf2 overexpression did not increase levels of the free-radical scavenger glutathione, which is thought to underlie the neuroprotective effects of Nrf2 in other disease models.

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Cover legend: A barn owl. These owls are specialized in sound localization. In nature, simultaneous sound sources may excite or inhibit cells in the inferior colliculus depending on the sound source location. For more information, see the article by Wang et al. (pages 10470–10478).

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10794 **Correction:** The article “The RCK2 Domain Uses a Coordination Site Present in Kir Channels to Confer Sodium Sensitivity to Slo2.2 Channels” by Zhe Zhang, Avia Rosenhouse-Dantsker, Qiong-Yao Tang, Sergei Noskov, and Diomedes E. Logothetis appeared on pages 7554–7562 of the June 2, 2010 issue. A correction for that article appears on page 10794.

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The Resting Transducer Current Drives Spontaneous Activity in Prehearing Mammalian Cochlear Inner Hair Cells

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Spontaneous Ca^{2+} -dependent electrical activity in the immature mammalian cochlea is thought to instruct the formation of the tonotopic map during the differentiation of sensory hair cells and the auditory pathway. This activity occurs in inner hair cells (IHCs) during the first postnatal week, and the pattern differs along the cochlea. During the second postnatal week, which is before the onset of hearing in most rodents, the resting membrane potential for IHCs is apparently more hyperpolarized (approximately -75 mV), and it remains unclear whether spontaneous action potentials continue to occur. We found that when mouse IHC hair bundles were exposed to the estimated *in vivo* endolymphatic Ca^{2+} concentration (0.3 mM) present in the immature cochlea, the increased open probability of the mechanotransducer channels caused the cells to depolarize to around the action potential threshold (approximately -55 mV). We propose that, *in vivo*, spontaneous Ca^{2+} action potentials are intrinsically generated by IHCs up to the onset of hearing and that they are likely to influence the final sensory-independent refinement of the developing cochlea.

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D1 Receptor Modulation of Action Potential Firing in a Subpopulation of Layer 5 Pyramidal Neurons in the Prefrontal Cortex

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Dopamine modulation in the prefrontal cortex is important for cognitive processing and disrupted in diverse neuropsychiatric diseases. Activation of D1 receptors is thought to enable working memory by enhancing the firing properties of pyramidal neurons. However, these receptors are only sparsely expressed in the prefrontal cortex, and how they impact individual neurons remains unknown. Here we study D1 receptor modulation of layer 5 pyramidal neurons in acute slices of the mouse prefrontal cortex. Using whole-cell recordings and two-photon microscopy, we show that neurons expressing D1 receptors have unique morphological and physiological properties. We then demonstrate that activation of these receptors selectively enhances the firing of these neurons by signaling via the protein kinase A pathway. This finding of robust D1 receptor modulation in only a subpopulation of neurons has important implications for cognitive function and disease.

The Journal of Neuroscience, August 1, 2012 • 32(31):10516–10521

Articles

CELLULAR/MOLECULAR

Live-Cell Imaging Evidence for the Ciliary Transport of Rod Photoreceptor Opsin by Heterotrimeric Kinesin-2

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Primary cilia detect extracellular signals through membrane receptors and channels. The outer segment of a vertebrate photoreceptor cell represents the most elaborate of all primary cilia, containing extraordinarily large amounts of the visual receptor protein, opsin. Because of its high abundance, opsin represents a potential model system for the study of ciliary membrane receptors, including their transport. Here, we have analyzed the movement of ciliary opsin to test whether the highly conserved intraflagellar transport (IFT), as driven by heterotrimeric kinesin-2, is required. Results show that opsin can enter and move along the primary cilium of a nonphotoreceptor cell (an hTERT-RPE1 epithelial cell), suggesting that it can co-opt the basic anterograde motor system of cilia. Fluorescence recovery after photobleaching analysis of cilia of hTERT-RPE1 cells showed that the movement of ciliary opsin was comparable to that of the IFT protein, IFT88. Moreover, the movement of opsin in these cilia, as well as in cilia of mouse rod photoreceptor cells, was reduced significantly when KIF3A, the obligate motor subunit of heterotrimeric kinesin-2, was deficient. These studies therefore provide evidence from live-cell analysis that the conserved heterotrimeric kinesin-2 is required for the normal transport of opsin along the ciliary plasma membrane.

The Journal of Neuroscience, August 1, 2012 • 32(31):10587–10593

A New Concept: $A\beta_{1-42}$ Generates a Hyperfunctional Proteolytic NCX3 Fragment That Delays Caspase-12 Activation and Neuronal Death

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Although the amyloid- β_{1-42} ($A\beta_{1-42}$) peptide involved in Alzheimer's disease is known to cause a dysregulation of intracellular Ca^{2+} homeostasis, its molecular mechanisms still remain unclear. We report that the extracellular-dependent early increase (30 min) in intracellular calcium concentration ($[Ca^{2+}]_i$), following $A\beta_{1-42}$ exposure, caused the activation of calpain that in turn elicited a cleavage of the Na^+/Ca^{2+} exchanger isoform NCX3. This cleavage generated a hyperfunctional form of the antiporter and increased NCX currents (I_{NCX}) in the reverse mode of operation. Interestingly, this NCX3 calpain-dependent cleavage was essential for the $A\beta_{1-42}$ -dependent I_{NCX} increase. Indeed, the calpain inhibitor calpeptin and the removal of the calpain-cleavage recognition sequence, via site-directed mutagenesis, abolished this effect. Moreover, the enhanced NCX3 activity was paralleled by an increased Ca^{2+} content in the endoplasmic reticulum (ER) stores. Remarkably, the silencing in PC-12 cells or the knocking-out in mice of the *ncx3* gene prevented the enhancement of both I_{NCX} and Ca^{2+} content in ER stores, suggesting that NCX3 was involved in the increase of ER Ca^{2+} content stimulated by $A\beta_{1-42}$. By contrast, in the late phase (72 h), when the NCX3 proteolytic cleavage abruptly ceased, the occurrence of a parallel reduction in ER Ca^{2+} content triggered ER stress, as revealed by caspase-12 activation. Concomitantly, the late increase in $[Ca^{2+}]_i$ coincided with neuronal death. Interestingly, NCX3 silencing caused an earlier activation of $A\beta_{1-42}$ -induced caspase-12. Indeed, in NCX3-silenced neurons, $A\beta_{1-42}$ exposure hastened caspase-dependent apoptosis, thus reinforcing neuronal cell death. These results suggest that $A\beta_{1-42}$, through Ca^{2+} -dependent calpain activation, generates a hyperfunctional form of NCX3 that, by increasing Ca^{2+} content into ER, delays caspase-12 activation and thus neuronal death.

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Interaction Between α CaMKII and GluN2B Controls ERK-Dependent Plasticity

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Understanding how brief synaptic events can lead to sustained changes in synaptic structure and strength is a necessary step in solving the rules governing learning and memory. Activation of ERK1/2 (extracellular signal regulated protein kinase 1/2) plays a key role in the control of functional and structural synaptic plasticity. One of the triggering events that activates ERK1/2 cascade is an NMDA receptor (NMDAR)-dependent rise in free intracellular Ca^{2+} concentration. However the mechanism by which a short-lasting rise in Ca^{2+} concentration is transduced into long-lasting ERK1/2-dependent plasticity remains unknown. Here we demonstrate that although synaptic activation in mouse cultured cortical neurons induces intracellular Ca^{2+} elevation via both GluN2A and GluN2B-containing NMDARs, only GluN2B-containing NMDAR activation leads to a long-lasting ERK1/2 phosphorylation. We show that α CaMKII, but not β CaMKII, is critically involved in this GluN2B-dependent activation of ERK1/2 signaling, through a direct interaction between GluN2B and α CaMKII. We then show that interfering with GluN2B/ α CaMKII interaction prevents synaptic activity from inducing ERK-dependent increases in synaptic AMPA receptors and spine volume. Thus, in a developing circuit model, the brief activity of synaptic GluN2B-containing receptors and the interaction between GluN2B and α CaMKII have a role in long-term plasticity via the control of ERK1/2 signaling. Our findings suggest that the roles that these major molecular elements have in learning and memory may operate through a common pathway.

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DEVELOPMENT/PLASTICITY/REPAIR

Nicotine Exposure during Adolescence Leads to Short- and Long-Term Changes in Spike Timing-Dependent Plasticity in Rat Prefrontal Cortex

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Adolescence is a critical period of brain development during which maturation of areas involved in cognitive functioning, such as the medial prefrontal cortex (mPFC), is still ongoing. Tobacco smoking during this age can compromise the normal course of prefrontal development and lead to cognitive impairments in later life. Recently, we reported that nicotine exposure during adolescence results in a short-term increase and lasting reduction in synaptic mGluR2 levels in the rat mPFC, causing attention deficits during adulthood. It is unknown how changed synaptic mGluR2 levels after adolescent nicotine exposure affect the ability of mPFC synapses to undergo long-term synaptic plasticity. Here, we addressed this question. To model nicotine exposure, adolescent (P34–P43) or adult (P60–P69) rats were treated with nicotine injections three times per day for 10 d. We found that, both during acute activation of nicotinic receptors in the adolescent mPFC as well as immediately following nicotine treatment during adolescence, long-term plasticity in response to timed presynaptic and postsynaptic activity (tLTP) was strongly reduced. In contrast, in the mPFC of adult rats 5 weeks after they received nicotine treatment during adolescence, but not during adulthood, tLTP was increased. Short- and long-term adaptation of mPFC synaptic plasticity after

adolescent nicotine exposure could be explained by changed mGluR2 signaling. Blocking mGluR2s augmented tLTP, whereas activating mGluR2s reduced tLTP. Our findings suggest neuronal mechanisms by which exposure to nicotine during adolescence alters the rules for spike timing-dependent plasticity in prefrontal networks that may explain the observed deficits in cognitive performance in later life.

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Regulation of p27^{Kip1} by Sox2 Maintains Quiescence of Inner Pillar Cells in the Murine Auditory Sensory Epithelium

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Sox2 plays critical roles in cell fate specification during development and in stem cell formation; however, its role in postmitotic cells is largely unknown. Sox2 is highly expressed in supporting cells (SCs) of the postnatal mammalian auditory sensory epithelium, which unlike non-mammalian vertebrates remains quiescent even after sensory hair cell damage. Here, we induced the ablation of Sox2, specifically in SCs at three different postnatal ages (neonatal, juvenile and adult) in mice. In neonatal mice, Sox2-null inner pillar cells (IPCs, a subtype of SCs) proliferated and generated daughter cells, while other SC subtypes remained quiescent. Furthermore, p27^{Kip1}, a cell cycle inhibitor, was absent in Sox2-null IPCs. Similarly, upon direct deletion of p27^{Kip1}, p27^{Kip1}-null IPCs also proliferated but retained Sox2 expression. Interestingly, cell cycle control of IPCs by Sox2-mediated expression of p27^{Kip1} gradually declined with age. In addition, deletion of Sox2 or p27^{Kip1} did not cause a cell fate change. Finally, chromatin immunoprecipitation with Sox2 antibodies and luciferase reporter assays with the p27^{Kip1} promoter support that Sox2 directly activates p27^{Kip1} transcription in postmitotic IPCs. Hence, in contrast to the well known activity of Sox2 in promoting proliferation and cell fate determination, our data demonstrate that Sox2 plays a novel role as a key upstream regulator of p27^{Kip1} to maintain the quiescent state of postmitotic IPCs. Our studies suggest that manipulating Sox2 or p27^{Kip1} expression is an effective approach to inducing proliferation of neonatal auditory IPCs, an initial but necessary step toward restoring hearing in mammals.

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Experience-Dependent Switch in Sign and Mechanisms for Plasticity in Layer 4 of Primary Visual Cortex

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Neural circuits are extensively refined by sensory experience during postnatal development. How the maturation of recurrent cortical synapses may contribute to events regulating the postnatal refinement of neocortical microcircuits remains controversial. Here we show that, in the main input layer of rat primary visual cortex, layer 4 (L4), recurrent excitatory synapses are endowed with multiple, developmentally regulated mechanisms for induction and expression of excitatory synaptic plasticity. Maturation of L4 synapses and visual experience lead to a sharp switch in sign and mechanisms for plasticity at recurrent excitatory synapses in L4 at the onset of the critical period for visual cortical plasticity. The state of maturation of excitatory pyramidal neurons allows neurons to engage different mechanisms for plasticity in response to the same induction paradigm. Experience is determinant for the maturation of L4 synapses, as well as for the transition between forms of plasticity and the mechanisms they may engage. These results indicate a tight correlation between the effects of sensory drive and maturation on cortical neurons and provide a new set of cellular mechanisms engaged in the postnatal refinement of cortical circuits.

The Journal of Neuroscience, August 1, 2012 • 32(31):10562–10573

The *stat3/socs3a* Pathway Is a Key Regulator of Hair Cell Regeneration in Zebrafish *stat3/socs3a* Pathway: Regulator of Hair Cell Regeneration

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All nonmammalian vertebrates studied can regenerate inner ear mechanosensory receptors (i.e., hair cells) (Corwin and Cotanche, 1988; Lombarte et al., 1993; Baird et al., 1996), but mammals possess only a very limited capacity for regeneration after birth (Roberson and Rubel, 1994). As a result, mammals experience permanent deficiencies in hearing and balance once their inner ear hair cells are lost. The mechanisms of hair cell regeneration are poorly understood. Because the inner ear sensory epithelium is highly conserved in all vertebrates (Fritzsche et al., 2007), we chose to study hair cell regeneration mechanism in adult zebrafish, hoping the results would be transferrable to inducing hair cell regeneration in mammals. We defined the comprehensive network of genes involved in hair cell regeneration in the inner ear of adult zebrafish with the powerful transcriptional profiling technique digital gene expression, which leverages the power of next-generation sequencing (t'Hoen et al., 2008). We also identified a key pathway, *stat3/socs3*, and demonstrated its role in promoting hair cell regeneration through stem cell activation, cell division, and differentiation. In addition, transient pharmacological inhibition of *stat3* signaling accelerated hair cell regeneration without overproducing cells. Taking other published datasets into account (Sano et al., 1999;

Schebesta et al., 2006; Dierssen et al., 2008; Riehle et al., 2008; Zhu et al., 2008; Qin et al., 2009), we propose that the *stat3/socs3* pathway is a key response in all tissue regeneration and thus an important therapeutic target for a broad application in tissue repair and injury healing.
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Purinergic Modulation of Neuronal Activity in Developing Auditory Brainstem

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In the developing nervous system, spontaneous neuronal activity arises independently of experience or any environmental input. This activity may play a major role in axonal pathfinding, refinement of topographic maps, dendritic morphogenesis, and the segregation of axonal terminal arbors. In the auditory system, endogenously released ATP in the cochlea activates inner hair cells to trigger bursts of action potentials (APs), which are transferred to the central auditory system. Here we show the modulatory role of purinergic signaling beyond the cochlea, i.e., the developmentally regulated and cell-type-specific depolarizing effects on auditory brainstem neurons of Mongolian gerbil. We assessed the effects of P2X receptors (P2XRs) on neuronal excitability from prehearing to early stages of auditory signal processing. Our results demonstrate that in neurons expressing P2XRs, extracellular ATP can evoke APs in sync with Ca^{2+} signals. In cochlear nucleus (CN) bushy cells, ATP increases spontaneous and also acoustically evoked activity *in vivo*, but these effects diminish with maturity. Moreover, ATP not only augmented glutamate-driven firing, but it also evoked APs in the absence of glutamatergic transmission. *In vivo* recordings also revealed that endogenously released ATP in the CN contributes to neuronal firing activity by facilitating AP generation and prolonging AP duration. Given the enhancing effect of ATP on AP firing and confinement of P2XRs to certain auditory brainstem nuclei, and to distinct neurons within these nuclei, it is conceivable that purinergic signaling plays a specific role in the development of neuronal brainstem circuits.

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BEHAVIORAL/SYSTEMS/COGNITIVE

Activation of Dorsal Raphe Serotonin Neurons Is Necessary for Waiting for Delayed Rewards

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The forebrain serotonergic system is a crucial component in the control of impulsive behaviors. We previously reported that the activity of serotonin neurons in the midbrain dorsal raphe nucleus increased when rats performed a task that required them to wait for delayed rewards. However, the causal relationship between serotonin neural activity and the tolerance for the delayed reward remained unclear. Here, we test whether the inhibition of serotonin neural activity by the local application of the 5-HT_{1A} receptor agonist 8-hydroxy-2-(di-*n*-propylamino) tetralin in the dorsal raphe nucleus impairs rats' tolerance for delayed rewards. Rats performed a sequential food-water navigation task that required them to visit food and water sites alternately via a tone site to get rewards at both sites after delays. During the short (2 s) delayed reward condition, the inhibition of serotonin neural activity did not significantly influence the numbers of reward choice errors (nosepoke at an incorrect reward site following a conditioned reinforcer tone), reward wait errors (failure to wait for the delayed rewards), or total trials (sum of reward choice errors, reward wait errors, and acquired rewards). By contrast, during the long (7–11 s) delayed reward condition, the number of wait errors significantly increased while the numbers of total trials and choice errors did not significantly change. These results indicate that the activation of dorsal raphe serotonin neurons is necessary for waiting for long delayed rewards and suggest that elevated serotonin activity facilitates waiting behavior when there is the prospect of forthcoming rewards.

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A Widely Distributed Spectral Signature of Task-Negative Electrocorticography Responses Revealed during a Visuomotor Task in the Human Cortex

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While research of human cortical function has typically focused on task-related increases in neuronal activity, there is a growing interest in the complementary phenomenon—namely, task-induced reductions. Recent human BOLD fMRI studies have associated such reductions with a specific network termed the default mode network (DMN). However, detailed understanding of the spatiotemporal patterns of task-negative responses and particularly how they compare across different cortical networks is lacking. Here we examined this issue in a large-scale electrocorticography study in patients performing a demanding backward masking task. Our results uncovered rapid (<1 s) task-induced reductions in gamma power, often concomitant with power increase in alpha/beta bands. Importantly, these responses were found both in the DMN and sensory-motor networks. Comparing the task-negative responses across these different networks revealed similar spectral signatures and dynamics. We hypothesize

that the task-negative responses may reflect a cortical switching mechanism whose role is to steer activity away from cortical networks, which are inappropriate for the task at hand.

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Population-Wide Bias of Surround Suppression in Auditory Spatial Receptive Fields of the Owl's Midbrain

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The physical arrangement of receptive fields (RFs) within neural structures is important for local computations. Nonuniform distribution of tuning within populations of neurons can influence emergent tuning properties, causing bias in local processing. This issue was studied in the auditory system of barn owls. The owl's external nucleus of the inferior colliculus (ICx) contains a map of auditory space in which the frontal region is overrepresented. We measured spatiotemporal RFs of ICx neurons using spatial white noise. We found a population-wide bias in surround suppression such that suppression from frontal space was stronger. This asymmetry increased with laterality in spatial tuning. The bias could be explained by a model of lateral inhibition based on the overrepresentation of frontal space observed in ICx. The model predicted trends in surround suppression across ICx that matched the data. Thus, the uneven distribution of spatial tuning within the map could explain the topography of time-dependent tuning properties. This mechanism may have significant implications for the analysis of natural scenes by sensory systems.

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Taste Coding in the Nucleus of the Solitary Tract of the Awake, Freely Licking Rat

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It is becoming increasingly clear that the brain processes sensory stimuli differently according to whether they are passively or actively acquired, and these differences can be seen early in the sensory pathway. In the nucleus of the solitary tract (NTS), the first relay in the central gustatory neuraxis, a rich variety of sensory inputs generated by active licking converge. Here, we show that taste responses in the NTS reflect these interactions. Experiments consisted of recordings of taste-related activity in the NTS of awake rats as they freely licked exemplars of the five basic taste qualities (sweet, sour, salty, bitter, umami). Nearly all taste-responsive cells were broadly tuned across taste qualities. A subset responded to taste with long latencies (>1.0 s), suggesting the activation of extraoral chemoreceptors. Analyses of the temporal characteristics of taste responses showed that spike timing conveyed significantly more information than spike count alone in almost one-half of NTS cells, as in anesthetized rats, but with less information per cell. In addition to taste-responsive cells, the NTS contains cells that synchronize with licks. Since the lick pattern per se can convey information, these cells may collaborate with taste-responsive cells to identify taste quality. Other cells become silent during licking. These latter "antlick" cells show a surge in firing rate predicting the beginning and signaling the end of a lick bout. Collectively, the data reveal a complex array of cell types in the NTS, only a portion of which include taste-responsive cells, which work together to acquire sensory information.

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Traveling Waves on the Organ of Corti of the Chinchilla Cochlea: Spatial Trajectories of Inner Hair Cell Depolarization Inferred from Responses of Auditory-Nerve Fibers

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Spatial magnitude and phase profiles for inner hair cell (IHC) depolarization throughout the chinchilla cochlea were inferred from responses of auditory-nerve fibers (ANFs) to threshold- and moderate-level tones and tone complexes. Firing-rate profiles for frequencies ≤ 2 kHz are bimodal, with the major peak at the characteristic place and a secondary peak at 3–5 mm from the extreme base. Response-phase trajectories are synchronous with peak outward stapes displacement at the extreme cochlear base and accumulate 1.5 period lags at the characteristic places. High-frequency phase trajectories are very similar to the trajectories of basilar-membrane peak velocity toward scala tympani. Low-frequency phase trajectories undergo a polarity flip in a region, 6.5–9 mm from the cochlear base, where traveling-wave phase velocity attains a local minimum and a local maximum and where the onset latencies of near-threshold impulse responses computed from responses to near-threshold white noise exhibit a local minimum. That region is the same where frequency-threshold tuning curves of ANFs undergo a shape transition. Since depolarization of IHCs presumably indicates the mechanical stimulus to their stereocilia, the present results suggest that distinct low-frequency forward waves of organ of Corti vibration are launched simultaneously at the extreme base of the cochlea and at the 6.5–9 mm transition region, from where antiphase reflections arise.

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Unleashing Potential: Transcranial Direct Current Stimulation over the Right Posterior Parietal Cortex Improves Change Detection in Low-Performing Individuals

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The limits of human visual short-term memory (VSTM) have been well documented, and recent neuroscientific studies suggest that VSTM performance is associated with activity in the posterior parietal cortex. Here we show that artificially elevating parietal activity via positively charged electric current through the skull can rapidly and effortlessly improve people's VSTM performance. This artificial improvement, however, comes with an interesting twist: it interacts with people's natural VSTM capability such that low performers who tend to remember less information benefitted from the stimulation, whereas high performers did not. This behavioral dichotomy is explained by event-related potentials around the parietal regions: low performers showed increased waveforms in N2pc and contralateral delay activity (CDA), which implies improvement in attention deployment and memory access in the current paradigm, respectively. Interestingly, these components are found during the presentation of the test array instead of the retention interval, from the parietal sites ipsilateral to the target location, thus suggesting that transcranial direct current stimulation (tDCS) was mainly improving one's ability to suppress no-change distractors located on the irrelevant side of the display during the comparison stage. The high performers, however, did not benefit from tDCS as they showed equally large waveforms in N2pc and CDA, or SPCN (sustained parietal contralateral negativity), before and after the stimulation such that electrical stimulation could not help any further, which also accurately accounts for our behavioral observations. Together, these results suggest that there is indeed a fixed upper limit in VSTM, but the low performers can benefit from neurostimulation to reach that maximum via enhanced comparison processes, and such behavioral improvement can be directly quantified and visualized by the magnitude of its associated electrophysiological waveforms.

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Large-Scale Synchronized Activity during Vocal Deviance Detection in the Zebra Finch Auditory Forebrain

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Auditory systems bias responses to sounds that are unexpected on the basis of recent stimulus history, a phenomenon that has been widely studied using sequences of unmodulated tones (mismatch negativity; stimulus-specific adaptation). Such a paradigm, however, does not directly reflect problems that neural systems normally solve for adaptive behavior. We recorded multiunit responses in the caudomedial auditory forebrain of anesthetized zebra finches (*Taeniopygia guttata*) at 32 sites simultaneously, to contact calls that recur probabilistically at a rate that is used in communication. Neurons in secondary, but not primary, auditory areas respond preferentially to calls when they are unexpected (deviant) compared with the same calls when they are expected (standard). This response bias is predominantly due to sites more often not responding to standard events than to deviant events. When two call stimuli alternate between standard and deviant roles, most sites exhibit a response bias to deviant events of both stimuli. This suggests that biases are not based on a use-dependent decrease in response strength but involve a more complex mechanism that is sensitive to auditory deviance per se. Furthermore, between many secondary sites, responses are tightly synchronized, a phenomenon that is driven by internal neuronal interactions rather than by the timing of stimulus acoustic features. We hypothesize that this deviance-sensitive, internally synchronized network of neurons is involved in the involuntary capturing of attention by unexpected and behaviorally potentially relevant events in natural auditory scenes.

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A Fast and Simple Population Code for Orientation in Primate V1

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Orientation tuning has been a classic model for understanding single-neuron computation in the neocortex. However, little is known about how orientation can be read out from the activity of neural populations, in particular in alert animals. Our study is a first step toward that goal. We recorded from up to 20 well isolated single neurons in the primary visual cortex of alert macaques simultaneously and applied a simple, neurally plausible decoder to read out the population code. We focus on two questions: First, what are the time course and the timescale at which orientation can be read out from the population response? Second, how complex does the decoding mechanism in a downstream neuron have to be to reliably discriminate between visual stimuli with different orientations? We show that the neural ensembles in primary visual cortex of awake macaques represent orientation in a way that facilitates a fast and simple readout mechanism: With an average latency of 30–80 ms, the population code can be read out instantaneously with a short integration time of only tens of milliseconds, and neither stimulus contrast nor correlations need to be taken into account to compute the optimal synaptic weight pattern. Our study shows that—similar to the case of single-neuron computation—the representation of orientation in the spike patterns of neural populations can serve as an exemplary case for understanding the computations performed by neural ensembles underlying visual processing during behavior.

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Visual Fixation as Equilibrium: Evidence from Superior Colliculus Inactivation

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During visual fixation, the image of an object is maintained within the fovea. Previous studies have shown that such maintenance involves the deep superior colliculus (dSC). However, the mechanisms by which the dSC supports visual fixation remain controversial. According to one view, activity in the rostral dSC maintains gaze direction by preventing neurons in the caudal dSC from issuing saccade commands. An alternative hypothesis proposes that gaze direction is achieved through equilibrium of target position signals originating from the two dSCs. Here, we show in monkeys that artificially reducing activity in the rostral half of one dSC results in a biased estimate of target position during fixation, consistent with the second hypothesis, rather than an inability to maintain gaze fixation as predicted by the first hypothesis. After injection of muscimol at rostral sites in the dSC, fixation became more stable since microsaccade rate was reduced rather than increased. Moreover, the scatter of eye positions was offset relative to preinactivation baselines. The magnitude and the direction of the offsets depended on both the target size and the injected site in the collicular map. Other oculomotor parameters, such as the accuracy of saccades to peripheral targets and the amplitude and velocity of fixational saccades, were largely unaffected. These results suggest that the rostral half of the dSC supports visual fixation through a distributed representation of behaviorally relevant target position signals. The inactivation-induced fixation offset establishes the foveal visual stimulation that is required to restore the balance of activity between the two dSCs.

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Deconstructing the Architecture of Dorsal and Ventral Attention Systems with Dynamic Causal Modeling

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Attentional orientation to a spatial cue and reorientation—after invalid cueing—are mediated by two distinct networks in the human brain. A bilateral dorsal frontoparietal network, comprising the intraparietal sulcus (IPS) and the frontal eye fields (FEF), controls the voluntary deployment of attention and may modulate visual cortex in preparation for upcoming stimulation. In contrast, reorienting attention to invalidly cued targets engages a right-lateralized ventral frontoparietal network comprising the temporoparietal junction (TPJ) and ventral frontal cortex. The present fMRI study investigated the functional architecture of these two attentional systems by characterizing effective connectivity during lateralized orienting and reorienting of attention, respectively. Subjects performed a modified version of Posner's location-cueing paradigm. Dynamic causal modeling (DCM) of regional responses in the dorsal and ventral network, identified in a conventional (SPM) whole-brain analysis, was used to compare different functional architectures. Bayesian model selection showed that top-down connections from left and right IPS to left and right visual cortex, respectively, were modulated by the direction of attention. Moreover, model evidence was highest for a model with directed influences from bilateral IPS to FEF, and reciprocal coupling between right and left FEF. Invalid cueing enhanced forward connections from visual areas to right TPJ, and directed influences from right TPJ to right IPS and IFG (inferior frontal gyrus). These findings shed further light on the functional organization of the dorsal and ventral attentional network and support a context-sensitive lateralization in the top-down (backward) mediation of attentional orienting and the bottom-up (forward) effects of invalid cueing.

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Stepwise Connectivity of the Modal Cortex Reveals the Multimodal Organization of the Human Brain

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How human beings integrate information from external sources and internal cognition to produce a coherent experience is still not well understood. During the past decades, anatomical, neurophysiological and neuroimaging research in multimodal integration have stood out in the effort to understand the perceptual binding properties of the brain. Areas in the human lateral occipitotemporal, prefrontal, and posterior parietal cortices have been associated with sensory multimodal processing. Even though this, rather patchy, organization of brain regions gives us a glimpse of the perceptual convergence, the articulation of the flow of information from modality-related to the more parallel cognitive processing systems remains elusive. Using a method called stepwise functional connectivity analysis, the present study analyzes the functional connectome and transitions from primary sensory cortices to higher-order brain systems. We identify the large-scale multimodal integration network and essential connectivity axes for perceptual integration in the human brain.

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Deciding When to Decide: Time-Variant Sequential Sampling Models Explain the Emergence of Value-Based Decisions in the Human Brain

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The cognitive and neuronal mechanisms of perceptual decision making have been successfully linked to sequential sampling models. These models describe the decision process as a gradual accumulation of sensory evidence over time. The temporal evolution of economic choices, however, remains largely unexplored. We tested whether sequential sampling models help to understand the formation of value-based decisions in terms of behavior and brain responses. We used functional magnetic resonance imaging (fMRI) to measure brain activity while human participants performed a buying task in which they freely decided upon how and when to choose. Behavior was accurately predicted by a time-variant sequential sampling model that uses a decreasing rather than fixed decision threshold to estimate the time point of the decision. Presupplementary motor area, caudate nucleus, and anterior insula activation was associated with the accumulation of evidence over time. Furthermore, at the beginning of the decision process the fMRI signal in these regions accounted for trial-by-trial deviations from behavioral model predictions: relatively high activation preceded relatively early responses. The updating of value information was correlated with signals in the ventromedial prefrontal cortex, left and right orbitofrontal cortex, and ventral striatum but also in the primary motor cortex well before the response itself. Our results support a view of value-based decisions as emerging from sequential sampling of evidence and suggest a close link between the accumulation process and activity in the motor system when people are free to respond at any time.

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Ablation of Retinal Horizontal Cells from Adult Mice Leads to Rod Degeneration and Remodeling in the Outer Retina

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In the brain, including the retina, interneurons show an enormous structural and functional diversity. Retinal horizontal cells represent a class of interneurons that form triad synapses with photoreceptors and ON bipolar cells. At this first retinal synapse, horizontal cells modulate signal transmission from photoreceptors to bipolar cells by feedback and feedforward inhibition. To test how the fully developed retina reacts to the specific loss of horizontal cells, these interneurons were specifically ablated from adult mice using the diphtheria toxin (DT)/DT-receptor system and the *connexin57* promoter. Following ablation, the retinal network responded with extensive remodeling: rods retracted their axons from the outer plexiform layer and partially degenerated, whereas cones survived. Cone pedicles remained in the outer plexiform layer and preserved synaptic contacts with OFF but not with ON bipolar cells. Consistently, the retinal ON pathway was impaired, leading to reduced amplitudes and prolonged latencies in electroretinograms. However, ganglion cell responses showed only slight changes in time course, presumably because ON bipolar cells formed multiple ectopic synapses with photoreceptors, and visual performance, assessed with an optomotor system, was only mildly affected. Thus, the loss of an entire interneuron class can be largely compensated even by the adult retinal network.

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A Common Neural Mechanism for Preventing and Terminating the Allocation of Attention

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Much is known about the mechanisms by which attention is focused to facilitate perception, but little is known about what happens to attention after perception of the attended object is complete. One possibility is that the focus of attention passively fades. A second possibility is that attention is actively terminated after the completion of perception so that the brain can be prepared for the next target. The present study investigated this issue with event-related potentials in humans, focusing on the N2pc component (a neural measure of attentional deployment) and the Pd component (a neural measure of attentional suppression). We found that active suppression occurred both to prevent the allocation of attention to known distractors and to terminate attention after the perception of an attended object was complete. In addition, the neural measure of active suppression was correlated with a behavioral measure of trial-to-trial variations in the allocation of attention. Active suppression therefore appears to be a general-purpose mechanism that both prevents and terminates the allocation of attention.

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Neural Correlates of the Lombard Effect in Primate Auditory Cortex

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Speaking is a sensory-motor process that involves constant self-monitoring to ensure accurate vocal production. Self-monitoring of vocal feedback allows rapid adjustment to correct perceived differences between intended and produced vocalizations. One important behavior in vocal feedback control is a compensatory increase in vocal intensity in response to noise masking during vocal production, commonly referred to as the Lombard effect. This behavior requires mechanisms for continuously monitoring auditory feedback during speaking. However, the underlying neural mechanisms are poorly understood. Here we show that when marmoset monkeys vocalize in the presence of masking noise that disrupts vocal feedback, the compensatory increase in vocal intensity is accompanied by a shift in auditory cortex activity toward neural response patterns seen during vocalizations under normal feedback condition. Furthermore, we show that neural activity in auditory cortex during a vocalization phrase predicts vocal intensity compensation in subsequent phrases. These observations demonstrate that the auditory cortex participates in self-monitoring during the Lombard effect, and may play a role in the compensation of noise masking during feedback-mediated vocal control.

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Opposing Effects of Aging on Large-Scale Brain Systems for Memory Encoding and Cognitive Control

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Episodic memory declines with advancing age. Neuroimaging studies have associated such decline to age-related changes in general cognitive-control networks as well as to changes in process-specific encoding or retrieval networks. To assess the specific influence of aging on encoding and retrieval processes and associated brain systems, it is vital to dissociate encoding and retrieval from each other and from shared cognitive-control processes. We used multivariate partial-least-squares to analyze functional magnetic resonance imaging data from a large population-based sample ($n = 292$, 25–80 years). The participants performed a face-name paired-associates task and an active baseline task. The analysis revealed two significant network patterns. The first reflected a process-general encoding-retrieval network that included frontoparietal cortices and posterior hippocampus. The second pattern dissociated encoding and retrieval networks. The anterior hippocampus was differentially engaged during encoding. Brain scores, representing whole-brain integrated measures of how strongly an individual recruited a brain network, were correlated with cognitive performance and chronological age. The scores from the general cognitive-control network correlated negatively with episodic memory performance and positively with age. The encoding brain scores, which strongly reflected hippocampal functioning, correlated positively with episodic memory performance and negatively with age. Univariate analyses confirmed that bilateral hippocampus showed the most pronounced activity reduction in older age, and brain structure analyses found that the activity reduction partly related to hippocampus atrophy. Collectively, these findings suggest that age-related structural brain changes underlie age-related reductions in the efficient recruitment of a process-specific encoding network, which cascades into upregulated recruitment of a general cognitive-control network.

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Neural Selectivity and Representation of Gloss in the Monkey Inferior Temporal Cortex

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When we view an object, its appearance depends in large part on specific surface reflectance properties; among these is surface gloss, which provides important information about the material composition of the object and the fine structure of its surface. To study how gloss is represented in the visual cortical areas related to object recognition, we examined the responses of neurons in the inferior temporal (IT) cortex of the macaque monkey to a set of object images exhibiting various combinations of specular reflection, diffuse reflection, and roughness, which are important physical parameters of surface gloss. We found that there are neurons in the lower bank of the superior temporal sulcus that selectively respond to specific gloss. This neuronal selectivity was largely maintained when the shape or illumination of the object was modified and perceived glossiness was unchanged. By contrast, neural responses were significantly altered when the pixels of the images were randomly rearranged, and perceived glossiness was dramatically changed. The stimulus preference of these neurons differed from cell to cell, and, as a population, they systematically represented a variety of surface glosses. We conclude that, within the visual cortex, there are mechanisms operating to integrate local image features and extract information about surface gloss and that this information is systematically represented in the IT cortex, an area playing an important role in object recognition.

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Beneficial Effects of Nrf2 Overexpression in a Mouse Model of Alexander Disease

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Alexander disease is a fatal neurodegenerative disease caused by dominant mutations in glial fibrillary acidic protein (GFAP). The disease is characterized by protein inclusions called Rosenthal fibers within astrocyte cell bodies and processes, and an antioxidant response mediated by the transcription factor Nrf2. We sought to test whether further elevation of Nrf2 would be beneficial in a mouse model of Alexander disease. Forcing overexpression of Nrf2 in astrocytes of R236H GFAP mutant mice decreased GFAP protein in all brain regions examined (olfactory bulb, hippocampus, cerebral cortex, brainstem, cerebellum, and spinal cord) and decreased Rosenthal fibers in olfactory bulb, hippocampus, corpus callosum, and brainstem. Nrf2 overexpression also restored body weights of R236H mice to near wild-type levels. Nrf2 regulates several genes involved in homeostasis of the antioxidant molecule glutathione, and the neuroprotective effects of Nrf2 in other neurological disorders may reflect restoration of glutathione to normal levels. However, glutathione levels in R236H mice were not decreased. Nrf2 overexpression did not change glutathione levels or ratio of reduced to oxidized glutathione (indicative of oxidative stress) in olfactory bulb, where Nrf2 dramatically reduced GFAP. Depletion of glutathione through knock-out of the GCLM (glutamate–cysteine ligase modifier subunit) also did not affect GFAP levels or body weight of R236H mice. These data suggest that the beneficial effects of Nrf2 are not mediated through glutathione.

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Movement-Related Changes in Local and Long-Range Synchronization in Parkinson's Disease Revealed by Simultaneous Magnetoencephalography and Intracranial Recordings

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Functional neurosurgery has afforded the opportunity to assess interactions between populations of neurons in the human cerebral cortex and basal ganglia in patients with Parkinson's disease (PD). Interactions occur over a wide range of frequencies, and the functional significance of those >30 Hz is particularly unclear. Do they improve movement, and, if so, in what way? We acquired simultaneously magnetoencephalography and direct recordings from the subthalamic nucleus (STN) in 17 PD patients. We examined the effect of synchronous and sequential finger movements and of the dopamine prodrug levodopa on induced power in the contralateral primary motor cortex (M1) and STN and on the coherence between the two structures. We observed discrete peaks in M1 and STN power at 60–90 Hz and at 300–400 Hz. All these power peaks increased with movement and levodopa treatment. Only STN activity at 60–90 Hz was coherent with activity in M1. Directionality analysis showed that STN gamma activity at 60–90 Hz tended to drive gamma activity in M1. The effects of levodopa on both local and distant synchronization at 60–90 Hz correlated with the degree of improvement in bradykinesia-rigidity as did local STN activity at 300–400 Hz. Despite this, there were no effects of movement type, nor interactions between movement type and levodopa in the STN, nor in the coherence between STN and M1. We conclude that synchronization at 60–90 Hz in the basal ganglia cortical network is prokinetic but likely through a modulatory effect rather than any involvement in explicit motor processing.

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Strain Background Influences Neurotoxicity and Behavioral Abnormalities in Mice Expressing the Tetracycline Transactivator

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The tet-off system has been widely used to create transgenic models of neurological disorders including Alzheimer's, Parkinson's, Huntington's, and prion disease. The utility of this system lies in the assumption that the tetracycline transactivator (TTA) acts as an inert control element and does not contribute to phenotypes under study. Here we report that neuronal expression of TTA can affect hippocampal cytoarchitecture and behavior in a strain-dependent manner. While studying neurodegeneration in two tet-off Alzheimer's disease models, we unexpectedly discovered neuronal loss within the dentate gyrus of single transgenic TTA controls. Granule neurons appeared most sensitive to TTA exposure during postnatal development, and doxycycline treatment during this period was neuroprotective. TTA-induced degeneration could be rescued by moving the transgene onto a congenic C57BL/6J background and recurred on reintroduction of either CBA or C3H/He backgrounds. Quantitative trait analysis of B6C3 F2 TTA mice identified a region on Chromosome 14 that contains a major modifier of the neurodegenerative phenotype. Although B6 mice were resistant to

degeneration, they were not ideal for cognitive testing. F1 offspring of TTA C57BL/6J and 129X1/SvJ, FVB/NJ, or DBA/1J showed improved spatial learning, but TTA expression caused subtle differences in contextual fear conditioning on two of these backgrounds, indicating that strain and genotype can interact independently under different behavioral settings. All model systems have limitations that should be recognized and mitigated where possible; our findings stress the importance of mapping the effects caused by TTA alone when working with tet-off models.

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Cross-Linking of Cell Surface Amyloid Precursor Protein Leads to Increased β -Amyloid Peptide Production in Hippocampal Neurons: Implications for Alzheimer's Disease

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The accumulation of the β -amyloid peptide ($A\beta$) in Alzheimer's disease (AD) is thought to play a causative role in triggering synaptic dysfunction in neurons, leading to their eventual demise through apoptosis. $A\beta$ is produced and secreted upon sequential cleavage of the amyloid precursor protein (APP) by β -secretases and γ -secretases. However, while $A\beta$ levels have been shown to be increased in the brains of AD patients, little is known about how the cleavage of APP and the subsequent generation of $A\beta$ is influenced, or whether the cleavage process changes over time. It has been proposed that $A\beta$ can bind APP and promote amyloidogenic processing of APP, further enhancing $A\beta$ production. Proof of this idea has remained elusive because a clear mechanism has not been identified, and the promiscuous nature of $A\beta$ binding complicates the task of demonstrating the idea. To work around these problems, we used an antibody-mediated approach to bind and cross-link cell-surface APP in cultured rat primary hippocampal neurons. Here we show that cross-linking of APP is sufficient to raise the levels of $A\beta$ in viable neurons with a concomitant increase in the levels of the β -secretase BACE1. This appears to occur as a result of a sorting defect that stems from the caspase-3-mediated inactivation of a key sorting adaptor protein, namely GGA3, which prevents the lysosomal degradation of BACE1. Together, our data suggest the occurrence of a positive pathogenic feedback loop involving $A\beta$ and APP in affected neurons possibly allowing $A\beta$ to spread to nearby healthy neurons.

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Role of Rhodopsin and Arrestin Phosphorylation in Retinal Degeneration of *Drosophila*

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Arrestins belong to a family of multifunctional adaptor proteins that regulate internalization of diverse receptors including G-protein-coupled receptors (GPCRs). Defects associated with endocytosis of GPCRs have been linked to human diseases. We used enhanced green fluorescent protein-tagged arrestin 2 (Arr2) to monitor the turnover of the major rhodopsin (Rh1) in live *Drosophila*. We demonstrate that during degeneration of *norPA*^{P24} photoreceptors the loss of Rh1 is parallel to the disappearance of rhabdomeres, the specialized visual organelle that houses Rh1. The cause of degeneration in *norPA*^{P24} is the failure to activate CaMKII (Ca²⁺/calmodulin-dependent protein kinase II) and retinal degeneration C (RDGC) because of a loss of light-dependent Ca²⁺ entry. A lack of activation in CaMKII, which phosphorylates Arr2, leads to hypophosphorylated Arr2, while a lack of activation of RDGC, which dephosphorylates Rh1, results in hyperphosphorylated Rh1. We investigated how reversible phosphorylation of Rh1 and Arr2 contributes to photoreceptor degeneration. To uncover the consequence underlying a lack of CaMKII activation, we characterized *ala*¹ flies in which CaMKII was suppressed by an inhibitory peptide, and showed that morphology of rhabdomeres was not affected. In contrast, we found that expression of phosphorylation-deficient Rh1s, which either lack the C terminus or contain Ala substitution in the phosphorylation sites, was able to prevent degeneration of *norPA*^{P24} photoreceptors. This suppression is not due to a loss of Arr2 interaction. Importantly, co-expression of these modified Rh1s offered protective effects, which greatly delayed photoreceptor degeneration. Together, we conclude that phosphorylation of Rh1 is the major determinant that orchestrates its internalization leading to retinal degeneration.

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