

This Week in The Journal

● Cellular/Molecular

Adenylyl Cyclase Is Required for Long-Term Fear

Qiang Shan, Guy C.-K. Chan, and Daniel R. Storm

(see pages 12864–12867)

The hippocampus is required for memory formation, but once formed, long-term memory retention requires the cortex. In mice, contextual fear memory no longer requires hippocampal activity after a few weeks, and instead relies on anterior cingulate cortex. Shan et al. examined the role of a calcium–calmodulin-dependent type 1 adenylyl cyclase (AC1) in long-term (remote) fear memory by examining mice lacking or overexpressing this protein. Contextual fear was induced by delivering a foot shock to mice in a specific chamber. When returned to the chamber, all mice spent a significant amount of time freezing, suggesting that contextual fear learning was not impaired. No difference in freezing between wild-type and mutant mice was measured during the first 5 weeks, but at 11 weeks, mice lacking AC1 froze significantly less often than controls. At 22 weeks, freezing was reduced in wild-type mice, but was significantly more frequent in mice overexpressing AC1, suggesting that AC1 activity enhances remote fear retention.

▲ Development/Plasticity/Repair

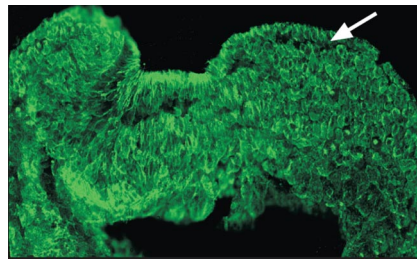
Neogenin Helps Form Neural Tube

Nigel Kee, Nicole Wilson, Melissa De Vries, DanaKai Bradford, Brian Key, and Helen M. Cooper

(see pages 12643–12653)

Development of the nervous system begins when cells on the dorsal surface of the embryo form the neural plate. Next, deep layer cells in the lateral regions of the plate elongate toward the dorsal surface and intercalate with superficial cells, forming neural folds. The neural folds elevate, eventually bending toward the midline

and fusing to form the neural tube. Defects in neural tube closure occur in 1:1000 human pregnancies, causing anencephaly or spina bifida. Kee et al. now report that the receptor protein neogenin is essential in neural fold elevation. In *Xenopus*, knockdown of neogenin, which was expressed laterally in the neural plate, prevented elongation and intercalation of deep cells with superficial cells, likely by disrupting microtubule organization. Although the neural tube eventually formed, loss of neogenin disrupted intracellular interactions. Neuroepithelia cells did not adhere to each other or to the apical or basal surfaces, and therefore were highly disordered.



Knockdown of neogenin on one side of the *Xenopus* embryo (right) disrupted neural fold elevation (arrow). See the article by Kee et al. for details.

■ Behavioral/Systems/Cognitive

Neuropeptide Y Enhances Fear Extinction

Alisa R. Gutman, Yong Yang, Kerry J. Ressler, and Michael Davis

(see pages 12682–12690)

Neuropeptide Y (NPY) is widely expressed in the brain and is thought to moderate animals' response to stress. Reduced levels of NPY have been tied to alcoholism, anxiety, and post-traumatic stress disorder. Experiments reported this week by Gutman et al. suggest that NPY may promote resilience to stress in part by enhancing retention of fear extinction. Sudden acoustic stimuli produce startle responses in rats, and responses are in-

creased when the sound is presented with a conditioned stimulus tied to foot shock. If the conditioned stimulus is repeatedly presented without foot shock, the fear is extinguished, and the conditioned stimulus no longer potentiates acoustic startle responses. Gutman et al. found that infusion of NPY into the basolateral amygdala reduced fear potentiation of startle and accelerated fear extinction. Moreover, NPY enhanced retention of extinction memory across sessions, whereas an NPY receptor antagonist reduced extinction retention, suggesting that NPY is involved in fear extinction learning.

◆ Neurobiology of Disease

Synapse Loss May Be Neuroprotective in HIV Dementia

Hee Jung Kim, Kirill A. Martemyanov, and Stanley A. Thayer

(see pages 12604–12613)

The HIV transcriptional activator Tat is secreted by infected macrophages and glia and causes neurodegeneration and cognitive decline. In the previous issue, we learned that Tat interacts with the NMDA receptor, possibly causing persistent channel activation that results in excitotoxic cell death. Neurons exposed to Tat lose synapses before they die, and because cognitive decline in HIV-associated dementia closely parallels synaptic loss, some treatment strategies have targeted this symptom. But now Kim et al. present evidence that the pathways underlying Tat-mediated synaptic loss diverge from those leading to neurodegeneration, and the former may represent neuronal attempts to limit excitotoxicity. In rat hippocampal cultures, inhibiting nitric oxide synthase prevented cell death, but did not decrease synapse loss. In contrast, preventing proteasomal degradation of the scaffolding protein PSD95 prevented synapse loss but made neurons more susceptible to Tat-induced degeneration. These results indicate that treatments for HIV-associated dementia should target molecules upstream of the pathway divergence.

The Journal of Neuroscience

November 26, 2008 • Volume 28 Number 48 www.jneurosci.org



Cover legend: A schematic representation of the correlation structure in primary visual cortex (V1) of the macaque monkey as measured with 100-electrode implanted arrays. The red dots indicate electrode positions (400 μ m spacing). Each ellipse represents the receptive field size and orientation preference of a neuron in V1. The red lines indicate functional connections between the central neuron and its neighbors, as measured by correlated trial-to-trial response variability in spiking. Correlation is strongest (thickest lines) for neurons that are nearby and for neurons that share a similar orientation preference. This image was created by Ruben Coen Cagli. For more information, see the article by Smith et al. in this issue (pages 12591–12603).

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Activation of an Endogenous Suicide Response after Perturbation of rRNA Synthesis Leads to Neurodegeneration in Mice

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Transcription of rRNA genes is essential for maintaining nucleolar integrity, a hallmark for the healthy state and proliferation rate of a cell. Inhibition of rRNA synthesis leads to disintegration of the nucleolus, elevated levels of p53, and induction of cell suicide, identifying the nucleolus as a critical stress sensor. Whether deregulation of rRNA synthesis is causally involved in neurodegeneration by promoting cell death and/or by inhibiting cellular growth has however not been addressed. The transcription factor TIF-IA plays a central role in mammalian rRNA synthesis, regulating the transcriptional activity of RNA polymerase I. To investigate the consequences of nucleolar perturbation in the nervous system, we have chosen to specifically ablate the gene encoding the transcription factor TIF-IA in two different contexts: neural progenitors and hippocampal neurons. Here, we show that ablation of TIF-IA leads to impaired nucleolar activity and results in increased levels of the proapoptotic transcription factor p53 in both neural progenitors and hippocampal neurons but induces rapid apoptosis only in neural progenitors. Nondividing cells of the adult hippocampus are more refractory to loss of rRNA transcription and face a protracted degeneration. Our study provides an unexploited strategy to initiate neurodegeneration based on perturbation of nucleolar function and underscores a novel perspective to study the cellular and molecular changes involved in the neurodegenerative processes.

The Journal of Neuroscience, November 26, 2008 • 28(48):12759–12764

Renewed Cocaine Exposure Produces Transient Alterations in Nucleus Accumbens AMPA Receptor-Mediated Behavior

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Withdrawal from repeated cocaine is associated with increased synaptic and extrasynaptic AMPA receptor (AMPA) expression in nucleus accumbens (NAc) neurons and enhanced behavioral sensitivity to AMPAR stimulation. Recent studies found that increased membrane expression of AMPARs is reversed or normalized on cocaine reexposure in withdrawal, but the mechanism for this AMPAR plasticity and the behavioral implications are unknown. Here, we examine the effects of renewed cocaine exposure during withdrawal on enhanced NAc AMPAR sensitivity and investigate the underlying mechanisms. Cocaine reexposure transiently reversed enhanced NAc AMPAR-mediated locomotion 1 d later, while enhancing cocaine-induced locomotion. Reversal in AMPAR sensitivity was prohibited by NAc AMPAR blockade with CNQX during cocaine reexposure and mimicked by intra-NAc infusions of AMPA, suggesting that cocaine-induced glutamate stimulation of NAc AMPARs is necessary for reversing AMPAR responsiveness. Similarly, systemic treatment with the dopamine D₁-like agonist SKF 81297 [(±)-6-chloro-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrobromide] reversed AMPAR responsiveness in cocaine withdrawal, but the effect was prevented by local NAc AMPAR blockade in the NAc, and not local D₁-like receptor blockade, suggesting a role for glutamate afferents in the reversal of enhanced AMPAR sensitivity. Together, these findings suggest that cocaine-induced glutamate release in sensitized animals is responsible for dynamic alterations in AMPAR function that contribute to enhanced cocaine sensitivity.

The Journal of Neuroscience, November 26, 2008 • 28(48):12808–12814

Disruption of *Nectin-Like 1* Cell Adhesion Molecule Leads to Delayed Axonal Myelination in the CNS

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Nectin-like 1 (*Necl-1*) is a neural-specific cell adhesion molecule that is expressed in both the CNS and PNS. Previous *in vitro* studies suggested that *Necl-1* expression is essential for the axon-glia interaction and myelin sheath formation in the PNS. To investigate the *in vivo* role of *Necl-1* in axonal myelination of the developing nervous system, we generated the *Necl-1* mutant mice by replacing exons 2–5 with the LacZ reporter gene. Expression studies revealed that *Necl-1* is exclusively expressed by neurons in the CNS. Disruption of *Necl-1* resulted in developmental delay of axonal myelination in the optic nerve and spinal cord, suggesting that *Necl-1* plays an important role in the initial axon-oligodendrocyte recognition and adhesion in CNS myelination.

The Journal of Neuroscience, November 26, 2008 • 28(48):12815–12819

A Neural Mechanism Underlying Memory Failure in Older Adults

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Older adults have reduced memory, primarily for recall, but also for recognition (Craik and McDowd, 1987), particularly for unfamiliar faces (Bartlett et al., 1989). Behavioral studies have shown that age-related memory declines are due in part to distraction from impaired inhibition of task-irrelevant input during encoding (Healey et al., 2008). Functional magnetic resonance imaging (fMRI) has been used to uncover the sources of memory deficits associated with aging. To date, this work has focused on successful encoding, while the neural correlates of unsuccessful encoding are unknown. Here, we provide novel evidence of a neural mechanism underlying memory failures exclusively affecting older adults. Whereas both younger and older adults showed reduced activation of brain regions important for encoding (e.g., hippocampus) during unsuccessful encoding, only older adults showed increased activity in brain regions mediating distraction (e.g., auditory cortex) and in left prefrontal cortex. Further, these regions were functionally connected with medial parietal areas, previously identified as default mode regions (Raichle and Snyder, 2007), which may reflect environmental monitoring. Our results suggest that increased distraction from task-irrelevant input (auditory in this case), associated with the unfamiliar and noisy fMRI environment, may increase environmental monitoring. This in turn could hinder suppression of default mode processing, resulting in memory failures in older adults. These findings provide novel evidence of a brain mechanism underlying the behavioral evidence that impaired inhibition of extraneous input during encoding leads to memory failure in older adults and may have implications for the ubiquitous use of fMRI for investigating neurocognitive aging.

The Journal of Neuroscience, November 26, 2008 • 28(48):12820–12824

CO₂-Sensitive Preinspiratory Neurons of the Parafacial Respiratory Group Express Phox2b in the Neonatal Rat

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Phox2b protein is a specific marker for neurons in the parafacial region of the ventral medulla, which are proposed to play a role in central chemoreception and postnatal survival. Mutations of *PHOX2B* cause congenital central hypoventilation syndrome. However, there have been no reports concerning electrophysiological characteristics of these Phox2b-expressing neurons in the parafacial region of the neonate immediately after birth. This region overlaps with the parafacial respiratory group (pFRG) composed predominantly of preinspiratory (Pre-I) neurons that are involved in respiratory rhythm generation. We studied (1) whether pFRG neurons are Phox2b immunoreactive or not and (2) whether they show intrinsic CO₂ chemosensitivity. We found that most pFRG/Pre-I neurons were Phox2b immunoreactive and depolarized upon increase in CO₂ concentration under condition of action potential-dependent synaptic transmission blockade by tetrodotoxin. We also confirmed that these pFRG neurons expressed neurokinin-1 receptor. They were tyrosine hydroxylase negative and presumed to be glutamatergic. Our findings suggest that Phox2b-expressing parafacial neurons play a role in respiratory rhythm generation as well as central chemoreception and thus are essential for postnatal survival.

The Journal of Neuroscience, November 26, 2008 • 28(48):12845–12850

Type 1 Adenylyl Cyclase Is Essential for Maintenance of Remote Contextual Fear Memory

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Although molecular mechanisms for hippocampus-dependent memory have been extensively studied, much less is known about signaling events important for remote memory. Here we report that mice lacking type 1 adenylyl cyclase (AC1) are able to establish and retrieve remote contextual memory but unable to sustain it as long as wild-type mice. Interestingly, mice overexpressing AC1 show superior remote contextual memory even though they exhibit normal hippocampus-dependent contextual memory. These data illustrate that calcium coupling to cAMP contributes to the stability of remote memory and identifies AC1 as a potential drug target site to improve long-term remote memory.

The Journal of Neuroscience, November 26, 2008 • 28(48):12864–12867

Glutamatergic Transmission Is Sustained at a Later Period of Development of Medial Nucleus of the Trapezoid Body–Lateral Superior Olive Synapses in Circling Mice

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Synaptic transmission between the medial nucleus of the trapezoid body (MNTB) and the lateral superior olive (LSO) was investigated in circling mice, an animal model for inherited deafness, using the voltage-clamp technique. In postnatal day 9 (P9)–P11 homozygous (*cir/cir*) circling mice, perfusion with 10 μ M DL-APV and 10 μ M CNQX reduced the 10 min average of postsynaptic currents (PSCs) to $8.8 \pm 3.0\%$ compared with controls ($n = 6$). In heterozygous (+/*cir*) mice in the same age range, the 10 min PSCs average was reduced to $87.5 \pm 3.7\%$ compared with controls ($n = 7$). In P0–P2 homozygous (*cir/cir*) and heterozygous (+/*cir*) mice, the 10 min PSCs averages were

11.0 ± 2.6% ($n = 9$) and 84.1 ± 4.6% ($n = 11$), respectively. The effects of a glutamate antagonist mixture were almost the same in single fiber stimulation of P9–P11 mice, reducing mean PSCs to 5.2 ± 3.1% (homozygous *cir/cir* mice, $n = 8$) and 78.3 ± 4.3% (heterozygous *+/cir* mice, $n = 12$). Immunohistochemical study revealed that glycine receptor (GlyR) immunoreactivity in heterozygous *+/cir* mice was more prominent than in homozygous *cir/cir* mice, while immunoreactivities of NR1 and NR2A-type NMDAR of P16 homozygous *cir/cir* mice were more prominent than in heterozygous *+/cir* mice of the same age. No significant difference was found in the immunoreactivity of NR2B-type NMDAR. These results indicate that glutamatergic transmission is sustained at a later period of developing MNTB–LSO synapses in homozygous *cir/cir* mice.

The Journal of Neuroscience, November 26, 2008 • 28(48):13003–13007

Antagonistic Effects of Doublecortin and MARK2/Par-1 in the Developing Cerebral Cortex

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Abnormal neuronal migration is manifested in brain malformations such as lissencephaly. The impairment in coordinated cell motility likely reflects a faulty mechanism of cell polarization or coupling between polarization and movement. Here we report on the relationship between the polarity kinase MARK2/Par-1 and its substrate, the well-known lissencephaly-associated gene doublecortin (*DCX*), during cortical radial migration. We have previously shown using *in utero* electroporation that reduced MARK2 levels resulted in multipolar neurons stalled at the intermediate zone border, similar to the phenotype observed in the case of *DCX* silencing. However, whereas reduced MARK2 stabilized microtubules, we show here that knock-down of *DCX* increased microtubule dynamics. This led to the hypothesis that simultaneous reduction may alleviate the phenotype. Coreduction of MARK2 and *DCX* resulted in a partial restoration of the normal neuronal migration phenotype *in vivo*. The kinetic behavior of the centrosomes reflected the different molecular mechanisms activated when either protein was reduced. In the case of reducing MARK2 processive motility of the centrosome was hindered, whereas when *DCX* was reduced, centrosomes moved quickly but bidirectionally. Our results stress the necessity for successful coupling between the polarity pathway and cytoplasmic dynein-dependent activities for proper neuronal migration.

The Journal of Neuroscience, November 26, 2008 • 28(48):13008–13013

Articles

CELLULAR/MOLECULAR

Interleukin-18-Mediated Microglia/Astrocyte Interaction in the Spinal Cord Enhances Neuropathic Pain Processing after Nerve Injury

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Interleukin (IL)-18 is an important regulator of innate and acquired immune responses. Here we show that both the IL-18 and IL-18 receptor (IL-18R), which are induced in spinal dorsal horn, are crucial for tactile allodynia after nerve injury. Nerve injury induced a striking increase in IL-18 and IL-18R expression in the dorsal horn, and IL-18 and IL-18R were upregulated in hyperactive microglia and astrocytes, respectively. The functional inhibition of IL-18 signaling pathways suppressed injury-induced tactile allodynia and decreased the phosphorylation of nuclear factor κ B in spinal astrocytes and the induction of astroglial markers. Conversely, intrathecal injection of IL-18 induced behavioral, morphological, and biochemical changes similar to those observed after nerve injury. Our results indicate that IL-18-mediated microglia/astrocyte interactions in the spinal cord have a substantial role in the generation of tactile allodynia. Thus, blocking IL-18 signaling in glial cells might provide a fruitful strategy for treating neuropathic pain.

The Journal of Neuroscience, November 26, 2008 • 28(48):12775–12787

Dysregulated Editing of Serotonin 2C Receptor mRNAs Results in Energy Dissipation and Loss of Fat Mass

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RNA editing that converts adenosine to inosine replaces the gene-encoded Ile, Asn, and Ile (INI) of serotonin [5-hydroxytryptamine (5-HT)] receptor 2C (5-HT_{2C}R) with Val, Gly, and Val (VGV). Up to 24 different 5-HT_{2C}R isoforms are detected in different brain regions (Burns et al., 1997; Fitzgerald et al., 1999; Wang et al., 2000). To elucidate the physiological significance of 5-HT_{2C}R mRNA editing, we derived mutant mouse lines harboring a knock-in *INI* or *VGV* allele, resulting in sole expression of one of two

extremely different editing isoforms 5-HT_{2c}R-INI (editing blocked) or -VGV (fully edited). Although *INI* mice grew normally, *VGV* mice had a severely reduced fat mass, despite compensatory hyperphagia, as a result of constitutive activation of the sympathetic nervous system and increased energy expenditure. Furthermore, serotonergic neurotransmission was oversensitized in *VGV* mice, most likely because of the increased cell surface expression of VGV receptors. Melanocortin 4 receptor (MC4R) regulates energy homeostasis (Balthasar et al., 2005; Heisler et al., 2006; Lam et al., 2008), and *Mc4r*^{-/-} mice are obese because of hyperphagia and reduced energy expenditure (Huszar et al., 1997). However, the elevated energy expenditure of *VGV* mice could not be rescued in the *Mc4r*^{-/-} background, indicating the presence of a distinct signaling pathway mediated via 5-HT_{2c}R-VGV that dominates the MC4R-dependent pathway in control of energy expenditure. Our results highlight the importance of regulated 5-HT_{2c}R mRNA editing, because dysregulation could result in the pathological consequences such as growth retardation seen in *VGV* mice.

The Journal of Neuroscience, November 26, 2008 • 28(48):12834–12844

Sequential Generation of Two Distinct Synapse-Driven Network Patterns in Developing Neocortex

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Developing cortical networks generate a variety of coherent activity patterns that participate in circuit refinement. Early network oscillations (ENOs) are the dominant network pattern in the rodent neocortex for a short period after birth. These large-scale calcium waves were shown to be largely driven by glutamatergic synapses albeit GABA is a major excitatory neurotransmitter in the cortex at such early stages, mediating synapse-driven giant depolarizing potentials (GDPs) in the hippocampus. Using functional multineuron calcium imaging together with single-cell and field potential recordings to clarify distinct network dynamics in rat cortical slices, we now report that the developing somatosensory cortex generates first ENOs then GDPs, both patterns coexisting for a restricted time period. These patterns markedly differ by their developmental profile, dynamics, and mechanisms: ENOs are generated before cortical GDPs (cGDPs) by the activation of glutamatergic synapses mostly through NMDARs; cENOs are low-frequency oscillations (~0.01 Hz) displaying slow kinetics and gradually involving the entire network. At the end of the first postnatal week, GABA-driven cortical GDPs can be reliably monitored; cGDPs are recurrent oscillations (~0.1 Hz) that repetitively synchronize localized neuronal assemblies. Contrary to cGDPs, cENOs were unexpectedly facilitated by short anoxic conditions suggesting a contribution of glutamate accumulation to their generation. In keeping with this, alterations of extracellular glutamate levels significantly affected cENOs, which are blocked by an enzymatic glutamate scavenger. Moreover, we show that a tonic glutamate current contributes to the neuronal membrane excitability when cENOs dominate network patterns. Therefore, cENOs and cGDPs are two separate aspects of neocortical network maturation that may be differentially engaged in physiological and pathological processes.

The Journal of Neuroscience, November 26, 2008 • 28(48):12851–12863

Phosphoinositides Regulate P2X₄ ATP-Gated Channels through Direct Interactions

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P2X receptors are ATP-gated nonselective cation channels highly permeable to calcium that contribute to nociception and inflammatory responses. The P2X₄ subtype, upregulated in activated microglia, is thought to play a critical role in the development of tactile allodynia following peripheral nerve injury. Posttranslational regulation of P2X₄ function is crucial to the cellular mechanisms of neuropathic pain, however it remains poorly understood. Here, we show that the phosphoinositides PI(4,5)P₂ (PIP₂) and PI(3,4,5)P₃ (PIP₃), products of phosphorylation by wortmannin-sensitive phosphatidylinositol 4-kinases and phosphatidylinositol 3-kinases, can modulate the function of native and recombinant P2X₄ receptor channels. In BV-2 microglial cells, depleting the intracellular levels of PIP₂ and PIP₃ with wortmannin significantly decreased P2X₄ current amplitude and P2X₄-mediated calcium entry measured in patch clamp recordings and ratiometric ion imaging, respectively. Wortmannin-induced depletion of phosphoinositides in *Xenopus* oocytes decreased the current amplitude of P2X₄ responses by converting ATP into a partial agonist. It also decreased their recovery from desensitization and affected their kinetics. Injection of phosphoinositides in wortmannin-treated oocytes reversed these effects and application of PIP₂ on excised inside-out macropatches rescued P2X₄ currents from rundown. Moreover, we report the direct interaction of phospholipids with the proximal C-terminal domain of P2X₄ subunit (Cys₃₆₀-Val₃₇₅) using an *in vitro* binding assay. These results demonstrate novel regulatory roles of the major signaling phosphoinositides PIP₂ and PIP₃ on P2X₄ function through direct channel-lipid interactions.

The Journal of Neuroscience, November 26, 2008 • 28(48):12938–12945

Polarized Targeting of Neurexins to Synapses Is Regulated by their C-Terminal Sequences

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Two families of cell-adhesion molecules, predominantly presynaptic neurexins and postsynaptic neuroligins, are important for the formation and functioning of synapses in the brain, and mutations in several genes encoding these transmembrane proteins have been found in autism patients. However, very little is known about how neurexins are targeted to synapses and which mechanisms regulate this process. Using various epitope-tagged neurexins in primary hippocampal neurons of wild-type and knock-out

mice *in vitro* and in transgenic animals *in vivo*, we show that neuexins are trafficked throughout neurons via transport vesicles and the plasma membrane insertion of neuexins occurs preferentially in the axonal/synaptic compartment. We also observed that exit of neuexins from the ER/Golgi and correct targeting require their PDZ-binding motif at the C terminus, whereas two presumptive ER retention signals are inactive. The ubiquitous presence of neuexin-positive transport vesicles and absence of bassoon colabeling demonstrate that these carriers are not active zone precursor vesicles, but colocalization with CASK, RIM1 α , and calcium channels suggests that they may carry additional components of the exocytotic machinery. Our data indicate that neuexins are delivered to synapses by a polarized and regulated targeting process that involves PDZ-domain mediated interactions, suggesting a novel pathway for the distribution of neuexins and other synaptic proteins.

The Journal of Neuroscience, November 26, 2008 • 28(48):12969–12981

DEVELOPMENT/PLASTICITY/REPAIR

Glutamatergic Neuronal Differentiation of Mouse Embryonic Stem Cells after Transient Expression of Neurogenin 1 and Treatment with BDNF and GDNF: *In Vitro* and *In Vivo* Studies

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Differentiation of the pluripotent neuroepithelium into neurons and glia is accomplished by the interaction of growth factors and cell-type restricted transcription factors. One approach to obtaining a particular neuronal phenotype is by recapitulating the expression of these factors in embryonic stem (ES) cells. Toward the eventual goal of auditory nerve replacement, the aim of the current investigation was to generate auditory nerve-like glutamatergic neurons from ES cells. Transient expression of Neurog1 promoted widespread neuronal differentiation *in vitro*; when supplemented with brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF), 75% of ES cell-derived neurons attained a glutamatergic phenotype after 5 d *in vitro*. Mouse ES cells were also placed into deafened guinea pig cochleae and Neurog1 expression was induced for 48 h followed by 26 d of BDNF/GDNF infusion. *In vivo* differentiation resulted in 50–75% of ES cells bearing markers of early neurons, and a majority of these cells had a glutamatergic phenotype. This is the first study to report a high percentage of ES cell differentiation into a glutamatergic phenotype and sets the stage for cell replacement of auditory nerve.

The Journal of Neuroscience, November 26, 2008 • 28(48):12622–12631

Neogenin and RGMA Control Neural Tube Closure and Neuroepithelial Morphology by Regulating Cell Polarity

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In humans, neural tube closure defects occur in 1:1000 pregnancies. The design of new strategies for the prevention of such common defects would benefit from an improved understanding of the molecular events underlying neurulation. Neural fold elevation is a key morphological process that acts during neurulation to drive neural tube closure. However, to date, the molecular pathways underpinning neural fold elevation have not been elucidated. Here, we use morpholino knock-down technology to demonstrate that Repulsive Guidance Molecule (RGMA)-Neogenin interactions are essential for effective neural fold elevation during *Xenopus* neurulation and that loss of these molecules results in disrupted neural tube closure. We demonstrate that Neogenin and RGMA are required for establishing the morphology of deep layer cells in the neural plate throughout neurulation. We also show that loss of Neogenin severely disrupts the microtubule network within the deep layer cells suggesting that Neogenin-dependent microtubule organization within the deep cells is essential for radial intercalation with the overlying superficial cell layer, thereby driving neural fold elevation. In addition, we show that sustained Neogenin activity is also necessary for the establishment of the apicobasally polarized pseudostratified neuroepithelium of the neural tube. Therefore, our study identifies a novel signaling pathway essential for radial intercalation and epithelialization during neural fold elevation and neural tube morphogenesis.

The Journal of Neuroscience, November 26, 2008 • 28(48):12643–12653

A TrkB/EphrinA Interaction Controls Retinal Axon Branching and Synaptogenesis

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Toward understanding topographically specific branching of retinal axons in their target area, we have studied the interaction between neurotrophin receptors and members of the Eph family. TrkB and its ligand BDNF are uniformly expressed in the retina and tectum, respectively, and exert a branch-promoting activity, whereas EphAs and ephrinAs are expressed in gradients in retina and tectum and can mediate a suppression of axonal branching. We have identified a novel *cis* interaction between

ephrinA5 and TrkB on retinal ganglion cell axons. TrkB interacts with ephrinA5 via its second cysteine-rich domain (CC2), which is necessary and sufficient for binding to ephrinA5. Their functional interaction is twofold: ephrinA5 augments BDNF-promoted retinal axon branching in the absence of its activator EphA7-Fc, whereas EphA7-Fc application abolishes branching in a local and concentration-dependent manner. The importance of TrkB in this process is shown by the fact that overexpression of an isolated TrkB-CC2 domain interfering with the ephrinA/TrkB interaction abolishes this regulatory interplay, whereas knockdown of TrkB via RNA interference diminishes the ephrinA5-evoked increase in branching. The ephrinA/TrkB interaction is neurotrophin induced and specifically augments the PI-3 kinase/Akt pathway generally known to be involved in the promotion of branching. In addition, ephrinAs/TrkB modulate axon branching and also synapse formation of hippocampal neurons. Our findings uncover molecular mechanisms of how spatially restricted axon branching can be achieved by linking globally expressed branch-promoting with differentially expressed branch-suppressing activities. In addition, our data suggest that growth factors and the EphA-ephrinA system interact in a way that affects axon branching and synapse development.

The Journal of Neuroscience, November 26, 2008 • 28(48):12700–12712

Ceruloplasmin Protects Injured Spinal Cord from Iron-Mediated Oxidative Damage

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CNS injury-induced hemorrhage and tissue damage leads to excess iron, which can cause secondary degeneration. The mechanisms that handle this excess iron are not fully understood. We report that spinal cord contusion injury (SCI) in mice induces an “iron homeostatic response” that partially limits iron-catalyzed oxidative damage. We show that ceruloplasmin (Cp), a ferroxidase that oxidizes toxic ferrous iron, is important for this process. SCI in Cp-deficient mice demonstrates that Cp detoxifies and mobilizes iron and reduces secondary tissue degeneration and functional loss. Our results provide new insights into how astrocytes and macrophages handle iron after SCI. Importantly, we show that iron chelator treatment has a delayed effect in improving locomotor recovery between 3 and 6 weeks after SCI. These data reveal important aspects of the molecular control of CNS iron homeostasis after SCI and suggest that iron chelator therapy may improve functional recovery after CNS trauma and hemorrhagic stroke.

The Journal of Neuroscience, November 26, 2008 • 28(48):12736–12747

Serotonergic Transcription of Human *FEV* Reveals Direct GATA Factor Interactions and Fate of *Pet-1*-Deficient Serotonin Neuron Precursors

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Altered expression of the human *FEV* (fifth Ewing variant) ETS transcription factor gene impacts the level of CNS serotonin (5-HT) neuron gene expression and maternal nurturing. However, the regulatory mechanisms that determine *FEV* expression are poorly understood. Here, we investigated the *cis*-regulatory control of *FEV* to begin to identify the upstream transcription factors that restrict *FEV* expression to 5-HT neurons. We find that sequences extending only 275 bp upstream of the *FEV* 5' untranslated region are sufficient to direct *FEV* transgene expression to embryonic 5-HT neurons, although sequences farther upstream are required for maintenance in adult 5-HT neurons. Two highly conserved consensus GATA factor binding sites within the 275 bp region interact with GATA factors *in vitro*. Chromatin immunoprecipitations with embryonic hindbrain demonstrated Gata-2 interactions with the orthologous mouse *Pet-1* ETS *cis*-regulatory region. Mutagenesis of GATA sites revealed that one or the other site is required for serotonergic *FEV* transgene expression. Unexpectedly, *FEV*-LacZ transgenes enabled determination of 5-HT neuron precursor fate in the adult *Pet-1*^{-/-} dorsal and median raphe nuclei and thus provided additional insight into *FEV/Pet-1* function. Comparable numbers of *FEV*-LacZ-positive cells were detected in *Pet-1*^{+/-} and *Pet-1*^{-/-} adult dorsal raphe nuclei, indicating that the majority of mutant serotonergic precursors are not fated to apoptosis. However, B7 dorsal raphe cells were aberrantly distributed, suggesting a role for *FEV/Pet-1* in their midline organization. Our findings identify a direct transcriptional interaction between Gata-2 and *FEV* and a unique marker for new insight into *FEV/Pet-1* function in 5-HT neuron development.

The Journal of Neuroscience, November 26, 2008 • 28(48):12748–12758

A Crucial Role for Primary Cilia in Cortical Morphogenesis

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Primary cilia are important sites of signal transduction involved in a wide range of developmental and postnatal functions. Proteolytic processing of the transcription factor Gli3, for example, occurs in primary cilia, and defects in intraflagellar transport (IFT), which is crucial for the maintenance of primary cilia, can lead to severe developmental defects and diseases. Here we report an essential role of primary cilia in forebrain development. Uncovered by *N*-ethyl-*N*-nitrosourea-mutagenesis, *cobblestone* is a hypomorphic allele of the IFT gene *Ift88*, in which *Ift88* mRNA and protein levels are reduced by 70–80%. *cobblestone* mutants are distinguished by subpial heterotopias in the forebrain. Mutants show both severe defects in the formation of dorsomedial telencephalic structures, such as the choroid plexus, cortical hem and hippocampus, and

also a relaxation of both dorsal-ventral and rostral-caudal compartmental boundaries. These defects phenocopy many of the abnormalities seen in the *Gli3* mutant forebrain, and we show that Gli3 proteolytic processing is reduced, leading to an accumulation of the full-length activator isoform. In addition, we observe an upregulation of canonical Wnt signaling in the neocortex and in the caudal forebrain. Interestingly, the ultrastructure and morphology of ventricular cilia in the *cobblestone* mutants remains intact. Together, these results indicate a critical role for ciliary function in the developing forebrain.

The Journal of Neuroscience, November 26, 2008 • 28(48):12887–12900

Traumatic Brain Injury-Induced Hippocampal Neurogenesis Requires Activation of Early Nestin-Expressing Progenitors

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It is becoming increasingly clear that brain injuries from a variety of causes stimulate neurogenesis within the hippocampus. It remains unclear, however, how robust this response may be and what primary cell types are involved. Here, using a controlled cortical impact model of traumatic brain injury on a previously characterized transgenic mouse line that expresses enhanced green fluorescent protein (eGFP) under the control of the nestin promoter, we demonstrate that it is the earliest type-1 quiescent progenitor cells that are induced to proliferate and migrate outside the subgranular layer of the dentate gyrus. This type-1 cell activation occurs at the same time that we observe adjacent but more differentiated doublecortin-expressing progenitors (type-2 cells) being eliminated. Also, although type-2 cells remain intact in the contralateral (uninjured) dentate gyrus, the type-1 cells there are also activated and result in increased numbers of the doublecortin-expressing type-2 cells. In addition, we have generated a novel mouse transgenic that expresses a modified version of the herpes simplex virus thymidine kinase along with eGFP that allows for the visualization and inducible ablation of early dividing progenitors by exposing them to ganciclovir. Using this transgenic in the context of traumatic brain injury, we demonstrate that these early progenitors are required for injury-induced remodeling to occur. This work suggests that injury-induced hippocampal remodeling following brain injury likely requires sustained activation of quiescent early progenitors.

The Journal of Neuroscience, November 26, 2008 • 28(48):12901–12912

Postnatal Differentiation of Basket Cells from Slow to Fast Signaling Devices

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Gamma frequency (30–100 Hz) oscillations in the mature cortex underlie higher cognitive functions. Fast signaling in GABAergic interneuron networks plays a key role in the generation of these oscillations. During development of the rodent brain, gamma activity appears at the end of the first postnatal week, but frequency and synchrony reach adult levels only by the fourth week. However, the mechanisms underlying the maturation of gamma activity are unclear. Here we demonstrate that hippocampal basket cells (BCs), the proposed cellular substrate of gamma oscillations, undergo marked changes in their morphological, intrinsic, and synaptic properties between postnatal day 6 (P6) and P25. During maturation, action potential duration, propagation time, duration of the release period, and decay time constant of IPSCs decreases by ~30–60%. Thus, postnatal development converts BCs from slow into fast signaling devices. Computational analysis reveals that BC networks with young intrinsic and synaptic properties as well as reduced connectivity generate oscillations with moderate coherence in the lower gamma frequency range. In contrast, BC networks with mature properties and increased connectivity generate highly coherent activity in the upper gamma frequency band. Thus, late postnatal maturation of BCs enhances coherence in neuronal networks and will thereby contribute to the development of cognitive brain functions.

The Journal of Neuroscience, November 26, 2008 • 28(48):12956–12968

Detection of Endogenous Retinoids in the Molluscan CNS and Characterization of the Trophic and Tropic Actions of 9-*cis* Retinoic Acid on Isolated Neurons

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Retinoic acid (RA) is an active metabolite of Vitamin A that plays an important role in the growth and differentiation of many cell types. All-*trans* RA (atRA) is the retinoic acid isomer that has been most widely studied in the nervous system, and can induce and direct neurite outgrowth from both vertebrate and invertebrate preparations. The presence and role of the 9-*cis*-RA isomer in the nervous system is far less well defined. Here, we used high-pressure liquid chromatography (HPLC) and mass spectrometry (MS) to show for the first time, the presence of both atRA and 9-*cis*-RA in the CNS of an invertebrate. We then demonstrated that 9-*cis*-RA was capable of exerting the same neurotrophic and chemotropic effects on cultured neurons as atRA. In this study, significantly more cells showed neurite outgrowth in 9-*cis*-RA versus the EtOH vehicle control, and 9-*cis*-RA significantly increased the number and length of neurites from identified neurons after 4 d in culture. 9-*cis*-RA also extended the duration of time that cells remained electrically excitable in culture. Furthermore, we showed for the first time in any species, that exogenous application of 9-*cis*-RA induced positive growth

cone turning of cultured neurons. This study provides the first evidence for the presence of both atRA and 9-*cis*-RA in an invertebrate CNS and also provides the first direct evidence for a potential physiological role for 9-*cis*-RA in neuronal regeneration and axon pathfinding.

The Journal of Neuroscience, November 26, 2008 • 28(48):13014–13024

BEHAVIORAL/SYSTEMS/COGNITIVE

Spatial and Temporal Scales of Neuronal Correlation in Primary Visual Cortex

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The spiking activity of cortical neurons is correlated. For instance, trial-to-trial fluctuations in response strength are shared between neurons, and spikes often occur synchronously. Understanding the properties and mechanisms that generate these forms of correlation is critical for determining their role in cortical processing. We therefore investigated the spatial extent and functional specificity of correlated spontaneous and evoked activity. Because feedforward, recurrent, and feedback pathways have distinct extents and specificity, we reasoned that these measurements could elucidate the contribution of each type of input. We recorded single unit activity with microelectrode arrays which allowed us to measure correlation in many hundreds of pairings, across a large range of spatial scales. Our data show that correlated evoked activity is generated by two mechanisms that link neurons with similar orientation preferences on different spatial scales: one with high temporal precision and a limited spatial extent (~3 mm), and a second that gives rise to correlation on a slow time scale and extends as far as we were able to measure (10 mm). The former is consistent with common input provided by horizontal connections; the latter likely involves feedback from extrastriate cortex. Spontaneous activity was correlated over a similar spatial extent, but approximately twice as strongly as evoked activity. Visual stimuli thus caused a substantial decrease in correlation, particularly at response onset. These properties and the circuit mechanism they imply provide new constraints on the functional role that correlation may play in visual processing.

The Journal of Neuroscience, November 26, 2008 • 28(48):12591–12603

Fur Seals Display a Strong Drive for Bilateral Slow-Wave Sleep While on Land

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Fur seals (pinnipeds of the family Otariidae) display two fundamentally different patterns of sleep: bilaterally symmetrical slow-wave sleep (BSWS) as seen in terrestrial mammals and slow-wave sleep (SWS) with a striking interhemispheric EEG asymmetry (asymmetrical SWS or ASWS) as observed in cetaceans. We examined the effect of preventing fur seals from sleeping in BSWS on their pattern of sleep. Four northern fur seals (*Callorhinus ursinus*) kept on land were sleep deprived (SD) of BSWS for 3 consecutive days, followed by 1 recovery day. EEG asymmetry was evaluated both visually and by EEG spectral analysis. SD significantly reduced the percentage of high-voltage BSWS (on average to 14% of baseline) and REM sleep (to 60% of baseline) whereas the percentage of low-voltage BSWS was not affected. During the SD period, all seals repeatedly tried to enter BSWS (109–411 attempts per day). SD significantly increased the amount of ASWS in each seal when scored visually (to 116–235% of baseline) and the difference in the EEG slow-wave activity (spectral power in the range of 1.2–4.0 Hz) between the two hemispheres (117–197%) as measured by the asymmetry index. High-voltage BSWS and the amount of SWS in each hemisphere were significantly elevated during the first 4 h of recovery. These data indicate that fur seals display a homeostatic response to the loss of SWS and that alternating SWS in the two hemispheres does not adequately compensate for the absence of BSWS.

The Journal of Neuroscience, November 26, 2008 • 28(48):12614–12621

Discharges in Human Muscle Receptor Afferents during Block Grasping

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Human grasping relies on feedforward control that is monitored and corrected on-line by means of sensory feedback. While much of the sensory mechanisms underpinning hand-object interaction are known, information has been lacking about muscle receptor responses during the phases before and after actual object contact. We therefore let subjects use their thumb and fingers to grasp blocks presented to them while we recorded muscle afferents from the thumb and finger extensor muscles along with wrist and digit kinematics, and electromyographic activity. The kinematics of the task was indistinguishable from “normal” grasping. None of the afferents encoded either object contact or finger apposition. Both primary and secondary afferents were more phase advanced on the parent muscle lengths than expected from previous studies as well as from their responses to imposed length changes of their parent muscles. Thus, the discharges of both primary and secondary afferents were well correlated to the tendon velocity of their parent muscles and that of primary afferents also to acceleration whereas neither appeared to encode muscle length as such. Decoding the velocity of muscle length changes were significantly improved if the discharge of Golgi tendon organ afferents were taken into account along with that of the muscle spindle afferents. We propose that these findings may be explained by the biomechanical properties of contracting muscles. Moreover, we conclude that it seems unlikely that the muscle spindle afferents recorded in this task have any role in providing “proprioceptive” information pertaining to the size of an object grasped.

The Journal of Neuroscience, November 26, 2008 • 28(48):12632–12642

The Smooth Monostratified Ganglion Cell: Evidence for Spatial Diversity in the Y-Cell Pathway to the Lateral Geniculate Nucleus and Superior Colliculus in the Macaque Monkey

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In the primate visual system approximately 20 morphologically distinct pathways originate from retinal ganglion cells and project in parallel to the lateral geniculate nucleus (LGN) and/or the superior colliculus. Understanding of the properties of these pathways and the significance of such extreme early pathway diversity for later visual processing is limited. In a companion study we found that the magnocellular LGN-projecting parasol ganglion cells also projected to the superior colliculus and showed Y-cell receptive field structure supporting the hypothesis that the parasol cells are analogous to the well studied alpha-Y cell of the cat's retina. We here identify a novel ganglion cell class, the smooth monostratified cells, that share many properties with the parasol cells. Smooth cells were retrogradely stained from tracer injections made into either the LGN or superior colliculus and formed inner-ON and outer-OFF populations with narrowly monostratified dendritic trees that surprisingly appeared to perfectly costratify with the dendrites of parasol cells. Also like parasol cells, smooth cells summed input from L- and M-cones, lacked measurable S-cone input, showed high spike discharge rates, high contrast and temporal sensitivity, and a Y-cell type nonlinear spatial summation. Smooth cells were distinguished from parasol cells however by smaller cell body and axon diameters but ~2 times larger dendritic tree and receptive field diameters that formed a regular but lower density mosaic organization. We suggest that the smooth and parasol populations may sample a common presynaptic circuitry but give rise to distinct, parallel achromatic spatial channels in the primate retinogeniculate pathway.

The Journal of Neuroscience, November 26, 2008 • 28(48):12654–12671

δ -Opioid Receptor Expression in the Ventral Tegmental Area Protects Against Elevated Alcohol Consumption

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Alcoholism is a complex and debilitating syndrome affecting ~140 million people worldwide. However, not everyone who consumes ethanol develops abuse, raising the possibility that some individuals have a protective mechanism that inhibits elevated alcohol consumption. We tested the hypothesis that the δ -opioid receptor (DOR) plays such a protective role. Here we show that DOR activity in the ventral tegmental area (VTA) robustly decreases ethanol consumption in rats and that these effects depend on baseline ethanol consumption. Intra-VTA microinjection of the DOR agonist DPDPE decreases drinking, particularly in low-drinking animals. Furthermore, VTA microinjection of the DOR selective antagonist TIPP- Ψ increases drinking in low, but not high, drinkers and this increase is blocked by comicroinjection of the GABA_A antagonist bicuculline. Using electrophysiological techniques we found that in VTA brain slices from drinking rats DPDPE presynaptically inhibits GABA_A receptor mediated IPSCs in low drinkers, but not in high drinkers or naive animals, most likely through activation of DORs on GABA terminals. This DOR-mediated inhibition of IPSCs also correlates inversely with behavioral correlates of anxiety measured in the elevated plus maze. In contrast, presynaptic inhibition of VTA GABA_A IPSCs by the μ -opioid receptor agonist DAMGO is significantly reduced in both high- and low-drinking rats (<30%) compared with age-matched nondrinking controls (>70%). Together, our findings demonstrate the protective nature of VTA DORs and identify an important new target for therapeutic intervention for alcoholism.

The Journal of Neuroscience, November 26, 2008 • 28(48):12672–12681

The Role of Neuropeptide Y in the Expression and Extinction of Fear-Potentiated Startle

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Neuropeptides are a promising target for novel treatments for anxiety and other psychiatric disorders and neuropeptide Y (NPY) has emerged as a key component of anxiolytic circuits in the brain. For this reason, we have evaluated the role of NPY in the expression and extinction of conditioned fear. We found that intracerebroventricular administration of NPY inhibits both baseline acoustic startle and the expression of fear-potentiated startle. Infusion of NPY (10 pmol/side) into the basolateral, but not the medial, nucleus of the amygdala reproduced the intracerebroventricular effect. Central administration of NPY (10 μ g) also enhanced within-session extinction of fear-potentiated startle. This finding, coupled with the growing body of literature correlating NPY with resilience in humans, led us to the hypothesis that NPY may enhance the extinction of conditioned fear. When NPY (10 μ g) is administered intracerebroventricularly before extinction training, extinction retention for both the contextual and cued components of conditioned fear is enhanced when tested 48 h later off drug. Additionally, we found that intra-basolateral amygdala administration of the NPY Y₁ receptor antagonist BIBO 3304 (200 pmol/side) before extinction training led to a profound deficit in extinction retention. This is the first evidence that NPY facilitates and an NPY antagonist blocks the extinction of conditioned fear. We believe that the role of NPY in the extinction of conditioned fear may, at least in part, explain the mechanism underlying the association between NPY and psychobiological resilience in humans.

The Journal of Neuroscience, November 26, 2008 • 28(48):12682–12690

Anticipatory Control of Grasping: Independence of Sensorimotor Memories for Kinematics and Kinetics

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We have recently provided evidence for anticipatory grasp control mechanisms in the kinematic domain by showing that subjects modulate digit placement on an object based on its center of mass (CM) when it can be anticipated (Lukos et al., 2007). This behavior relied on sensorimotor memories about digit contact points and forces required for optimal manipulation. We found that accurate sensorimotor memories depended on the acquisition of implicit knowledge about object properties associated with repeated manipulations of the same object.

Whereas implicit knowledge of object properties is essential for anticipatory grasp control, the extent to which subjects can use explicit knowledge to accurately scale digit forces in an anticipatory manner is controversial. Additionally, it is not known whether subjects are able to use explicit knowledge of object properties for anticipatory control of contact points. We addressed this question by asking subjects to grasp and lift an object while providing explicit knowledge of object CM location as visual or verbal cues. Contact point modulation and object roll, a measure of anticipatory force control, were assessed using blocked and random CM presentations. We found that explicit knowledge of object CM enabled subjects to modulate contact points. In contrast, subjects could not minimize object roll in the random condition to the same extent as in the blocked when provided with a verbal or visual cue. These findings point to a dissociation in the effect of explicit knowledge of object properties on grasp kinematics versus kinetics, thus suggesting independent anticipatory processes for grasping.

The Journal of Neuroscience, November 26, 2008 • 28(48):12765–12774

Experience-Dependent Eye Movements Reflect Hippocampus-Dependent (Aware) Memory

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We investigated the relationship between experience-dependent eye movements, hippocampus-dependent memory, and aware memory. We measured eye movements in young adults, older adults, and memory-impaired patients with damage to the medial temporal lobe as they viewed 120 novel scenes and 120 previously viewed scenes. Participants indicated if each scene was old or new and also gave a confidence rating for the memory judgment. Young adults and older adults explored old scenes less than they explored new scenes, but the patients did not. For the young and older adults, this effect was observed only when participants were aware of the scene's familiar or novel status. In a second experiment, young adults viewed scenes that were either new, had been viewed previously, or had been viewed previously but had been changed (i.e., an object within the scene was either added or removed). The only instructions were to pay attention to the scenes and view each scene as it appeared, and there was no expectation that memory would be tested. Directly after the first altered scene was presented, participants were asked to classify the scene as new, old, or old but changed. Participants who were aware of the manipulation preferentially viewed the changed region, but participants who were unaware did not. These findings suggest that experience-dependent eye movements reflect hippocampus-dependent (and aware) memory, even when participants have no expectation that memory is being tested; and they are consistent with the view that awareness of what is learned is a fundamental characteristic of hippocampus-dependent memory.

The Journal of Neuroscience, November 26, 2008 • 28(48):12825–12833

Modeling a Negative Response Bias in the Human Amygdala by Noradrenergic–Glucocorticoid Interactions

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An emerging theme in the neuroscience of emotion is the question of how acute stress shapes, and distorts, social-emotional behavior. The prevailing neurocircuitry models of social-emotional behavior emphasize the central role of the amygdala. Acute stress leads to increased central levels of norepinephrine (NE) and cortisol (CORT), and evidence suggests that these endogenous neuromodulators synergistically influence amygdala responses to social-emotional stimuli. We therefore hypothesized that amygdala responses to emotional facial expressions would be susceptible to pharmacologically induced increases in central NE and CORT levels. To specifically test this hypothesis, we measured amygdala activation to emotional faces using functional magnetic resonance imaging in 62 healthy subjects under four pharmacological conditions: (1) single oral dose of placebo, (2) 4 mg of the selective NE-reuptake inhibitor reboxetine (RBX), (3) 30 mg of hydrocortisone, or (4) both drugs in combination. We found that a decrease in amygdala activation to positive facial emotion was coupled with an increase in amygdala activation to negative facial emotion in the RBX–CORT combined challenge condition. In conclusion, a pharmacologically induced elevation of central NE and CORT levels in healthy subjects created a negative response bias in the amygdala that did not exist at baseline. Our results implicate a causative role of NE–CORT interactions in the emergence of a negative bias of cognitive and emotional functions which is germane in stress-related affective spectrum disorders.

The Journal of Neuroscience, November 26, 2008 • 28(48):12868–12876

Decoding Trajectories from Posterior Parietal Cortex Ensembles

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High-level cognitive signals in the posterior parietal cortex (PPC) have previously been used to decode the intended endpoint of a reach, providing the first evidence that PPC can be used for direct control of a neural prosthesis (Musallam et al., 2004). Here we expand on this work by showing that PPC neural activity can be harnessed to estimate not only the endpoint but also to continuously control the trajectory of an end effector. Specifically, we trained two monkeys to use a joystick to guide a cursor on a computer screen to peripheral target locations while maintaining central ocular fixation. We found that we could accurately reconstruct the trajectory of the cursor using a relatively small ensemble of simultaneously recorded PPC neurons. Using a goal-based Kalman filter that incorporates target information into the state-space, we showed that the decoded estimate of cursor position could be significantly improved. Finally, we tested whether we could decode trajectories during closed-loop brain control sessions, in which the real-time position of the cursor was determined solely by a monkey's neural activity in PPC. The monkey learned to perform brain control trajectories at 80% success rate (for 8 targets) after just 4–5 sessions. This improvement in behavioral performance was accompanied by a corresponding enhancement in neural tuning properties (i.e., increased tuning depth and coverage of encoding parameter space) as well as an increase in off-line decoding performance of the PPC ensemble.

The Journal of Neuroscience, November 26, 2008 • 28(48):12913–12926

Corticotropin-Releasing Factor Increases GABA Synaptic Activity and Induces Inward Current in 5-Hydroxytryptamine Dorsal Raphe Neurons

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Stress-related psychiatric disorders such as anxiety and depression involve dysfunction of the serotonin [5-hydroxytryptamine (5-HT)] system. Previous studies have found that the stress neurohormone corticotropin-releasing factor (CRF) inhibits 5-HT neurons in the dorsal raphe nucleus (DRN) *in vivo*. The goals of the present study were to characterize the CRF receptor subtypes (CRF-R1 and -R2) and cellular mechanisms underlying CRF–5-HT interactions. Visualized whole-cell patch-clamp recording techniques in brain slices were used to measure spontaneous or evoked GABA synaptic activity in DRN neurons of rats and CRF effects on these measures. CRF-R1 and -R2-selective agonists were bath applied alone or in combination with receptor-selective antagonists. CRF increased presynaptic GABA release selectively onto 5-HT neurons, an effect mediated by the CRF-R1 receptor. CRF increased postsynaptic GABA receptor sensitivity selectively in 5-HT neurons, an effect to which both receptor subtypes contributed. CRF also had direct effects on DRN neurons, eliciting an inward current in 5-HT neurons mediated by the CRF-R2 receptor and in non-5-HT neurons mediated by the CRF-R1 receptor. These results indicate that CRF has direct membrane effects on 5-HT DRN neurons as well as indirect effects on GABAergic synaptic transmission that are mediated by distinct receptor subtypes. The inhibition of 5-HT DRN neurons by CRF *in vivo* may therefore be primarily an indirect effect via stimulation of inhibitory GABA synaptic transmission. These results regarding the cellular mechanisms underlying the complex interaction between CRF, 5-HT, and GABA systems could contribute to the development of novel treatments for stress-related psychiatric disorders.

The Journal of Neuroscience, November 26, 2008 • 28(48):12927–12937

The Melanocortin-3 Receptor Is Required for Entrainment to Meal Intake

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Entrainment of anticipatory activity and wakefulness to nutrient availability is a poorly understood component of energy homeostasis. Restricted feeding (RF) paradigms with a periodicity of 24 h rapidly induce entrainment of rhythms anticipating food presentation that are independent of master clocks in the suprachiasmatic nucleus (SCN) but do require other hypothalamic structures. Here, we report that the melanocortin system, which resides in hypothalamic structures required for food entrainment, is required for expression of food entrainable rhythms. Food anticipatory activity was assessed in wild-type (WT) and melanocortin-3 receptor-deficient (*Mc3r*^{−/−}) C57BL/J mice by wheel running, spontaneous locomotory movement, and measurement of wakefulness. WT mice housed in wheel cages subject to RF exhibited increased wheel activity during the 2 h preceding meal presentation, which corresponded with an increase in wakefulness around meal time and reduced wakefulness during the dark. WT mice also exhibited increased *x*- and *z*-movements centered around food initiation. The activity-based responses to RF were significantly impaired in mice lacking *Mc3r*. RF also failed to increase wakefulness in the 2 h before food presentation in *Mc3r*^{−/−} mice. Food entrainment requires expression of *Neuronal PAS domain 2* (*Npas2*) and *Period2* (*Per2*) genes, components of the transcriptional machinery maintaining a clock rhythm. Analysis of cortical gene expression revealed severe abnormalities in rhythmic expression of clock genes (*Bmal1*, *Npas2*, *Per2*) under *ad libitum* and RF conditions. In summary, *Mc3r* are required for expression of anticipatory patterns of activity and wakefulness during periods of limited nutrient availability and for normal regulation of cortical clock function.

The Journal of Neuroscience, November 26, 2008 • 28(48):12946–12955

Shared versus Specialized Glycinergic Spinal Interneurons in Axial Motor Circuits of Larval Zebrafish

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The neuronal networks in spinal cord can produce a diverse array of motor behaviors. In aquatic vertebrates such as fishes and tadpoles, these include escape behaviors, swimming across a range of speeds, and struggling. We addressed the question of whether these behaviors are accomplished by a shared set of spinal interneurons activated in different patterns or, instead, involve specialized spinal interneurons that may shape the motor output to produce particular behaviors. We used larval zebrafish because they are capable of several distinct axial motor behaviors using a common periphery and a relatively small set of spinal neurons, easing the task of exploring the extent to which cell types are specialized for particular motor patterns. We performed targeted *in vivo* whole-cell patch recordings in 3 d post fertilization larvae to reveal the activity pattern of four commissural glycinergic interneuron types during escape, swimming and struggling behaviors. While some neuronal classes were shared among different motor patterns, we found others that were active only during a single one. These specialized neurons had morphological and functional properties consistent with a role in shaping key features of the motor behavior in which they were active. Our results, in combination with other evidence from excitatory interneurons, support the idea that patterns of activity in a core network of shared spinal neurons may be shaped by more specialized interneurons to produce an assortment of motor behaviors.

The Journal of Neuroscience, November 26, 2008 • 28(48):12982–12992

NEUROBIOLOGY OF DISEASE

Human Immunodeficiency Virus Protein Tat Induces Synapse Loss via a Reversible Process That Is Distinct from Cell Death

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Human immunodeficiency virus (HIV)-1 infection of the CNS produces changes in dendritic morphology that correlate with cognitive decline in patients with HIV-1 associated dementia (HAD). Here, we investigated the effects of HIV-1 transactivator of transcription (Tat), a protein released by virus-infected cells, on synapses between hippocampal neurons using an imaging-based assay that quantified clusters of the scaffolding protein postsynaptic density 95 fused to green fluorescent protein (PSD95–GFP). Tat (24 h) decreased the number of PSD95–GFP puncta by $50 \pm 7\%$. The decrease was concentration-dependent ($EC_{50} = 6 \pm 2$ ng/ml) and preceded cell death. Tat acted via the low-density lipoprotein receptor-related protein (LRP) because the specific LRP blocker, receptor associated protein (RAP), prevented the Tat-induced decrease in the number of PSD95–GFP puncta. Ca^{2+} influx through the NMDA receptor was necessary for Tat-induced synapse loss. Expression of an ubiquitin ligase inhibitor protected synapses, implicating the ubiquitin–proteasome pathway. In contrast to synapse loss, Tat induced cell death (48 h) required activation of nitric oxide synthase. The ubiquitin ligase-inhibitor nutlin-3 prevented synapse loss but not cell death induced by Tat. Thus, the pathways diverged, consistent with the hypothesis that synapse loss is a mechanism to reduce excess excitatory input rather than a symptom of the neuron's demise. Furthermore, application of RAP to cultures treated with Tat for 16 h reversed synapse loss. These results suggest that the impaired network function and decreased neuronal survival produced by Tat involve distinct mechanisms and that pharmacologic targets, such as LRP, might prove useful in restoring function in HAD patients.

The Journal of Neuroscience, November 26, 2008 • 28(48):12604–12613

A Neonatal Ventral Hippocampal Lesion Causes Functional Deficits in Adult Prefrontal Cortical Interneurons

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Animals with a neonatal ventral hippocampal lesion (NVHL) develop abnormal behaviors during or after adolescence, suggesting that early insults can have delayed consequences. Many of these behaviors depend on the prefrontal cortex (PFC), and we have reported that PFC pyramidal neurons of adult rats with an NVHL respond to stimulation of the ventral tegmental area with an increase in firing instead of the characteristic decrease. As the dopamine modulation of cortical interneurons matures during adolescence, these findings raise the possibility that maturation of local inhibitory circuits within the PFC may have been altered in NVHL rats. Here, we assessed the state of PFC interneurons in NVHL rats with *in situ* hybridization measures of the mRNAs for the calcium binding protein parvalbumin (PV) and the GABA synthesizing enzyme GAD₆₇, as well as with electrophysiological measures of interneuron function. Although no differences were observed with PV or GAD₆₇, whole-cell recordings in slices revealed abnormal responses to the D₂ agonist quinpirole in interneurons from NVHL rats. The loss of D₂ modulation of local inhibition in slices from NVHL rats was also evident in the absence of a lasting component in the D₂ attenuation of excitatory synaptic responses in pyramidal neurons, which in sham treated rats was picrotoxin sensitive. The results suggest that the neonatal lesion causes improper maturation, but not loss, of PFC interneurons during adolescence, a finding consistent with current interpretations of imaging data in schizophrenia that suggest a hyperactive, “noisy” cortex underlying dysfunction in the PFC and other cortical areas.

The Journal of Neuroscience, November 26, 2008 • 28(48):12691–12699

Deranged Calcium Signaling and Neurodegeneration in Spinocerebellar Ataxia Type 3

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Spinocerebellar ataxia type 3 (SCA3), also known as Machado–Joseph disease (MJD), is an autosomal-dominant neurodegenerative disorder caused by a polyglutamine expansion in ataxin-3 (ATX3; MJD1) protein. In biochemical experiments, we demonstrate that mutant ATX3^{exp} specifically associated with the type 1 inositol 1,4,5-trisphosphate receptor (InsP₃R1), an intracellular calcium (Ca²⁺) release channel. In electrophysiological and Ca²⁺ imaging experiments, we show that InsP₃R1 was sensitized to activation by InsP₃ in the presence of mutant ATX3^{exp}. We found that feeding SCA3-YAC-84Q transgenic mice with dantrolene, a clinically relevant stabilizer of intracellular Ca²⁺ signaling, improved their motor performance and prevented neuronal cell loss in pontine nuclei and substantia nigra regions. Our results indicate that deranged Ca²⁺ signaling may play an important role in SCA3 pathology and that Ca²⁺ signaling stabilizers such as dantrolene may be considered as potential therapeutic drugs for treatment of SCA3 patients.

The Journal of Neuroscience, November 26, 2008 • 28(48):12713–12724

Polyglutamine-Modulated Striatal Calpain Activity in YAC Transgenic Huntington Disease Mouse Model: Impact on NMDA Receptor Function and Toxicity

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Huntington disease (HD), caused by CAG expansion in the ubiquitously expressed huntingtin gene, is characterized by early dysfunction and death of striatal medium-sized spiny neurons (MSNs). Previous work has shown MSN-specific alterations in NMDA receptor (NMDAR) expression and cell death signaling. Furthermore, studies in HD human brain tissue and a knock-in mouse model demonstrate increases in calpain activity, which can be stimulated by NMDARs and contribute to excitotoxicity. Here, we report increased calpain activity in MSNs from the yeast artificial chromosome (YAC) transgenic mouse model of HD, expressing human full-length huntingtin with 128 polyglutamine repeats (YAC128), compared with wild type. Moreover, the calpain-cleaved product of NMDAR subunit NR2B is increased early, and NR2B expression levels are reduced, in YAC128 striatum. Although steady-state NMDAR surface expression is similar in wild-type and YAC128 MSNs, the rate of loss of NR2B-containing surface receptors is enhanced in YAC128 MSNs, suggesting that NMDAR forward trafficking to the surface is also faster, as previously reported for YAC72 MSNs. Calpain inhibitor-1 treatment normalized the loss rate of surface NMDARs in YAC128 MSNs to that of wild type, and significantly increased surface NMDAR expression in YAC128, but not in wild type or YAC72. With acute NMDAR overstimulation, the increase in calpain activity correlated with polyglutamine length, and calpain inhibitor treatment reduced NMDA-induced apoptosis in YAC72 and YAC128 MSNs to wild-type levels. Thus, the cumulative effect of increasing huntingtin polyglutamine length is to enhance MSN sensitivity to excitotoxicity at least in part by calpain-mediated cell death signaling.

The Journal of Neuroscience, November 26, 2008 • 28(48):12725–12735

Activated Protein C Promotes Neovascularization and Neurogenesis in Postischemic Brain via Protease-Activated Receptor 1

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Activated protein C (APC) is a serine protease with anticoagulant and direct cytoprotective activities. Early postischemic APC application activates the cellular protein C pathway in brain endothelium and neurons, which is neuroprotective. Whether late APC administration after a transient ischemic attack is neuroprotective and whether APC influences brain repair is not known. Here, we determined safety and efficacy of late APC and tissue-plasminogen activator (tPA) administrations in a mouse model of transient brain ischemia. tPA given at 6 h after onset of ischemia killed all mice within 2 d, whereas APC given at 6 or 24 h after ischemia onset improved significantly functional outcome and reduced spread of the ischemic lesion. At 7 d postischemia, APC multiple dosing (0.8 mg/kg, i.p.) at 6–72 or 72–144 h enhanced comparably cerebral perfusion in the ischemic border by ~40% as shown by *in vivo* lectin-FITC angiography, blocked blood–brain barrier leakage of serum proteins, and increased the number of endothelial replicating cells by 4.5- to 4.7-fold. APC multidosing at 6–72 h or 72–144 h increased proliferation of neuronal progenitor cells in the subventricular zone (SVZ) by 40–50% and migration of newly formed neuroblasts from the SVZ toward the ischemic border by approximately twofold. The effects of APC on neovascularization and neurogenesis were mediated by protease-activated receptor 1 and were independent of the reduction by APC of infarction volume. Our data show that delayed APC administration is neuroprotective and mediates brain repair (i.e., neovascularization and neurogenesis), suggesting a significant extension of the therapeutic window for APC intervention in postischemic brain.

The Journal of Neuroscience, November 26, 2008 • 28(48):12788–12797

Anesthesia-Induced Hyperphosphorylation Detaches 3-Repeat Tau from Microtubules without Affecting Their Stability *In Vivo*

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In Alzheimer's disease, tau is hyperphosphorylated, which is thought to detach it from microtubules (MTs), induce MT destabilization, and promote aggregation. Using a previously described *in vivo* model, we investigated whether hyperphosphorylation impacts tau function in wild-type and transgenic mice. We found that after anesthesia-induced hypothermia, MT-free tau was hyperphosphorylated, which impaired its ability to bind MTs and promote MT assembly. MT-bound tau was more resistant to hyperphosphorylation compared with free tau and tau did not dissociate from MTs in wild-type mice. However, 3-repeat tau detached from MT in the transgenic mice. Surprisingly, dissociation of tau from MTs did not lead to overt depolymerization of tubulin, and there was no collapse, or disturbance of axonal MT networks. These results indicate that, *in vivo*, a subpopulation of tau bound to MTs does not easily dissociate under conditions that extensively phosphorylate tau. Tau remaining on the MTs under these conditions is sufficient to maintain MT network integrity.

The Journal of Neuroscience, November 26, 2008 • 28(48):12798–12807

Loss of LR11/SORLA Enhances Early Pathology in a Mouse Model of Amyloidosis: Evidence for a Proximal Role in Alzheimer's Disease

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Alzheimer's disease (AD) is the most prevalent form of dementia, resulting in progressive neuronal death and debilitating damage to brain loci that mediate memory and higher cognitive function. While pathogenic genetic mutations have been implicated in ~2% of AD cases, the proximal events that underlie the common, sporadic form of the disease are incompletely understood. Converging lines of evidence from human neuropathology, basic biology, and genetics have implicated loss of the multifunctional receptor LR11 (also known as SORLA and SORL1) in AD pathogenesis. Cell-based studies suggest that LR11 reduces the formation of β -amyloid ($A\beta$), the molecule believed to be a primary toxic species in AD. Recently, mutant mice deficient in LR11 were shown to upregulate murine $A\beta$ in mouse brain. In the current study, LR11-deficient mice were crossed with transgenic mice expressing autosomal-dominant human AD genes, presenilin-1 (PS1 Δ E9) and amyloid precursor protein (APP^{swe}). Here, we show that LR11 deficiency in this AD mouse model significantly increases $A\beta$ levels and exacerbates early amyloid pathology in brain, causing a forward shift in disease onset that is LR11 gene dose-dependent. Loss of LR11 increases the processing of the APP holo-molecule into α -, β -, and γ -secretase derived metabolites. We propose that LR11 regulates APP processing and $A\beta$ accumulation *in vivo* and is of proximal importance to the cascade of pathological amyloidosis. The results of the current study support the hypothesis that control of LR11 expression may exert critical effects on Alzheimer's disease susceptibility in humans.

The Journal of Neuroscience, November 26, 2008 • 28(48):12877–12886

Direct Binding with Histone Deacetylase 6 Mediates the Reversible Recruitment of Parkin to the Centrosome

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Histone deacetylase 6 (HDAC6), a microtubule-associated tubulin deacetylase, plays a significant role in the formation of protein aggregates in many neurodegenerative disorders. Parkin, a protein-ubiquitin E3 ligase linked to Parkinson's disease, accumulates at the centrosome in a microtubule-dependent manner in response to proteasome inhibition. Here, we show that the centrosome recruitment of parkin was mediated by its direct binding to HDAC6 through multiple interaction domains. The tubulin deacetylase activity of HDAC6 was required for the accumulation of parkin as well as its dispersion upon the reversal of proteasome inhibition. The bidirectional movements of parkin required intact microtubule network and were dependent on dynein and kinesin 1, respectively. Tubulin deacetylation increases microtubule dynamicity and may thus facilitate microtubule-based trafficking of the parkin-HDAC6 complex. The results suggest that HDAC6 acts as a sensor of proteasome inhibition and directs the trafficking of parkin by using different motor proteins.

The Journal of Neuroscience, November 26, 2008 • 28(48):12993–13002