

# This Week in The Journal

## ● Cellular/Molecular

### *Myosin Va and Oligodendrocytes*

Jacob A. Sloane and Timothy K. Vartanian

(see pages 11366–11375)

Mutations in myosin Va cause severe neurological abnormalities as manifest in the developmental disorder Griscelli's syndrome type 1 (GSC1). This week, Sloane and Vartanian report that myosin Va-null mice (*dilute-lethal*) have impaired myelination, suggesting a potential role for oligodendrocytes in the pathophysiology of GSC1. Consistent with this idea, myosin 5a was expressed in wild-type cultured oligodendrocytes at all stages of maturation. Oligodendrocytes transfected with dominant-negative myosin Va had smaller lamellar surface areas, and their processes were reduced in length, number, and branching. Loss of myosin Va did not affect oligodendrocyte maturation or cell death. Vesicle-associated membrane protein 2 (VAMP2) associated with myosin Va in the cytosol of developing oligodendrocytes. As oligodendrocytes began to extend processes, VAMP2 abruptly relocated to lamellas and filopodia, a process that required myosin Va. Disruption of VAMP2 also caused similar cellular defects in oligodendrocyte lamellas and processes.

## ▲ Development/Plasticity/Repair

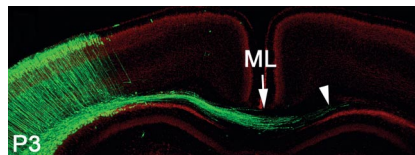
### *Activity Dependence of Callosal Projections*

Chun-Lei Wang, Lei Zhang, Yang Zhou, Jing Zhou, Xiu-Juan Yang, Shu-min Duan, Zhi-Qi Xiong, and Yu-Qiang Ding

(see pages 11334–11342)

That axonal superhighway, the corpus callosum, sends signals whizzing back and forth between the cerebral hemispheres. Turns out it requires neuronal activity to

build and maintain it. Wang et al. labeled these projections by *in utero* electroporation of a fluorescent marker into cells of the dorsolateral ventricular zone. Some of the labeled cells migrated to layer II/III of the somatosensory cortex and sent projections to layer II/III of the contralateral primary somatosensory cortex (S1). The authors "silenced" these pyramidal cells by overexpressing the inwardly rectifying potassium channel Kir2.1. In these cells, projections were delayed, and axons overextended to terminate in layer I. The results were more drastic after expression of tetanus toxin light chain (TeNT-LC), which prevented synaptic transmission. In this case, projections eventually vanished from the somatosensory cortex altogether. The effects of Kir2.1 and TeNT-LC were additive when they were coexpressed.



Labeled axons (green) cross the corpus callosum [midline (ML)] in 3 d postnatal mice after *in utero* electroporation of a fluorescent reporter. See the article by Wang et al. for details.

## ■ Behavioral/Systems/Cognitive

### *Binaural Hearing and Middle Age*

Bernhard Ross, Takako Fujioka, Kelly L. Tremblay, and Terence W. Picton

(see pages 11172–11178)

You might be surprised to learn that changes in central auditory processing as well as in peripheral hearing contribute to sensory deterioration as we age. Central processing is important for comprehension of speech, especially in the presence of background noise. This week, Ross et al. used a binaural hearing task to examine age-related changes in human central auditory processing. The authors measured cortical magnetoencephalographic responses to binaural auditory stimuli that

had changing interaural phase differences (IPD). The auditory-evoked responses to interaural temporal disparity had an upper frequency limit that declined with age. Young adults responded to shifting IPDs for frequencies up to 1225 Hz, whereas performance in middle-aged subjects suffered above 940 Hz and in older subjects was limited to 760 Hz. The decline in binaural hearing performance was noticeable at middle age before age-related declines in hearing sensation.

## ◆ Neurobiology of Disease

### *Histone Methylation and GABAergic Gene Promoters*

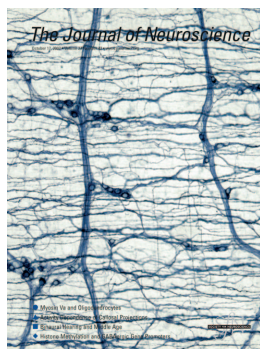
Hsien-Sung Huang, Anouch Matevosian, Catheryne Whittle, Se Young Kim, Armin Schumacher, Stephen P. Baker, and Schahram Akbarian

(see pages 11254–11262)

Prefrontal cortex (PFC) is center stage for those looking at the neurobiology of schizophrenia. In this week's *Journal*, Huang et al. start to build a case for developmental or disease-related changes in the regulation of genes in GABAergic neurons in PFC. The mRNA for the GABA synthetic enzyme GAD1 increased until puberty, as measured in human postmortem brain samples. There was an accompanying change in chromatin remodeling, as indicated by increased methylation of histone H3-lysine 4 in the GAD1 promoter region. In tissue from schizophrenic patients, GAD1 expression and H3K4 trimethylation were reduced, particularly in females. H3K4 methylation of the GAD1 promoter also was downregulated in mice heterozygous for a truncated allele of the mixed-leukemia lineage gene *Mll1*, which encodes a histone methyltransferase expressed in cortical interneurons. In these mice, GAD1 H3K4 trimethylation was increased by the atypical antipsychotic clozapine but not by haloperidol.

# The Journal of Neuroscience

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**Cover legend:** The human enteric nervous system contains ~500 million neurons in 20 functional classes. All of these cells form from a small population of neural crest-derived cells that migrate through the bowel and vigorously proliferate before differentiating and extending neurites. This image shows a whole-mount preparation of the mouse small bowel myenteric plexus after NADPH diaphorase histochemistry. For more information, see the article by Vohra et al. in the August 29, 2007 issue (pages 9458–9468) (<http://www.jneurosci.org/cgi/content/abstract/27/35/9458>).

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## An Ion Channel Essential for Sensing Chemical Damage

Lindsey J. Macpherson,<sup>1\*</sup> Bailong Xiao,<sup>1\*</sup> Kelvin Y. Kwan,<sup>2\*</sup> Matt J. Petrus,<sup>3</sup> Adrienne E. Dubin,<sup>1</sup> SunWook Hwang,<sup>4</sup> Benjamin Cravatt,<sup>1</sup> David P. Corey,<sup>2</sup> and Ardem Patapoutian<sup>1,3</sup>

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Tissue damage and its downstream consequences are experimentally assayed by formaldehyde application, which indiscriminately modifies proteins and is presumed to cause pain through broadly acting mechanisms. Here we show that formaldehyde activates the ion channel TRPA1 and that TRPA1-deficient mice exhibit dramatically reduced formaldehyde-induced pain responses. 4-Hydroxynonenal, a reactive chemical produced endogenously during oxidative stress, and other related aldehydes also activate TRPA1 *in vitro*. Furthermore, painful responses to iodoacetamide, a nonspecific cysteine-alkylating compound, are abolished in TRPA1-deficient mice. Therefore, although these reactive chemicals modify many proteins, the associated pain appears mainly dependent on a single ion channel.

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## Articles

### CELLULAR/MOLECULAR

## Spinal Astrocyte Glutamate Receptor 1 Overexpression after Ischemic Insult Facilitates Behavioral Signs of Spasticity and Rigidity

Michael P. Hefferan,<sup>1</sup> Karolina Kucharova,<sup>1,4</sup> Kiyohiko Kinjo,<sup>1</sup> Osamu Kakinohana,<sup>1</sup> Gabriella Sekerkova,<sup>2</sup> Seiya Nakamura,<sup>1,3</sup> Tatsuya Fuchigami,<sup>1,3</sup> Zoltan Tomori,<sup>5</sup> Tony L. Yaksh,<sup>1</sup> Neil Kurtz,<sup>6</sup> and Martin Marsala<sup>1,4</sup>

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Using a rat model of ischemic paraplegia, we examined the expression of spinal AMPA receptors and their role in mediating spasticity and rigidity. Spinal ischemia was induced by transient occlusion of the descending aorta combined with systemic hypotension. Spasticity/rigidity were identified by simultaneous measurements of peripheral muscle resistance (PMR) and electromyography (EMG) before and during ankle flexion. In addition, Hoffman reflex (H-reflex) and motor evoked potentials (MEPs) were recorded from the gastrocnemius muscle. Animals were implanted with intrathecal catheters for drug delivery and injected with the AMPA receptor antagonist NGX424 (tezampanel), glutamate receptor 1 (GluR1) antisense, or vehicle. Where intrathecal vehicle had no effect, intrathecal NGX424 produced a dose-dependent suppression of PMR [ED<sub>50</sub> of 0.44  $\mu$ g (0.33–0.58)], as well as tonic and ankle flexion-evoked EMG activity. Similar suppression of MEP and H-reflex were also seen. Western blot analyses of lumbar spinal cord tissue from spastic animals showed a significant increase in GluR1 but decreased GluR2 and GluR4 proteins. Confocal and electron microscopic analyses of spinal cord sections from spastic animals revealed increased GluR1 immunoreactivity in reactive astrocytes. Selective GluR1 knockdown by intrathecal antisense treatment resulted in a potent reduction of spasticity and rigidity and concurrent downregulation of neuronal/astrocytic GluR1 in the lumbar spinal cord. Treatment of rat astrocyte cultures with AMPA led to dose-dependent glutamate release, an effect blocked by NGX424. These data suggest that an AMPA/kainate receptor antagonist can represent a novel therapy in modulating spasticity/rigidity of spinal origin and that astrocytes may be a potential target for such treatment.

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## Conditional Knock-Out of K<sub>ir</sub>4.1 Leads to Glial Membrane Depolarization, Inhibition of Potassium and Glutamate Uptake, and Enhanced Short-Term Synaptic Potentiation

Biljana Djukic,<sup>1</sup> Kristen B. Casper,<sup>1</sup> Benjamin D. Philpot,<sup>2</sup> Lih-Shen Chin,<sup>3</sup> and Ken D. McCarthy<sup>1</sup>

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During neuronal activity, extracellular potassium concentration ( $[K^+]_{out}$ ) becomes elevated and, if uncorrected, causes neuronal depolarization, hyperexcitability, and seizures. Clearance of  $K^+$  from the extracellular space, termed  $K^+$  spatial buffering, is considered to be an important function of astrocytes. Results from a number of studies suggest that maintenance of  $[K^+]_{out}$  by astrocytes is mediated by  $K^+$  uptake through the inward-rectifying K<sub>ir</sub>4.1 channels. To study the role of this channel in astrocyte physiology and neuronal excitability, we generated a conditional knock-out (cKO) of K<sub>ir</sub>4.1 directed to astrocytes via the human glial fibrillary acidic protein promoter *gfa2*. K<sub>ir</sub>4.1 cKO mice die prematurely and display severe ataxia and stress-induced seizures. Electrophysiological recordings revealed severe depolarization of both passive astrocytes and complex glia in K<sub>ir</sub>4.1 cKO hippocampal slices. Complex cell depolarization appears to be a direct consequence of K<sub>ir</sub>4.1 removal, whereas

passive astrocyte depolarization seems to arise from an indirect developmental process. Furthermore, we observed a significant loss of complex glia, suggestive of a role for  $K_{ir}4.1$  in astrocyte development.  $K_{ir}4.1$  cKO passive astrocytes displayed a marked impairment of both  $K^+$  and glutamate uptake. Surprisingly, membrane and action potential properties of CA1 pyramidal neurons, as well as basal synaptic transmission in the CA1 stratum radiatum appeared unaffected, whereas spontaneous neuronal activity was reduced in the  $K_{ir}4.1$  cKO. However, high-frequency stimulation revealed greatly elevated posttetanic potentiation and short-term potentiation in  $K_{ir}4.1$  cKO hippocampus. Our findings implicate a role for glial  $K_{ir}4.1$  channel subunit in the modulation of synaptic strength.

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## Myosin Va Controls Oligodendrocyte Morphogenesis and Myelination

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A product of myosin Va mutations, Griscelli's syndrome type 1 (GS1) is characterized by several neurologic deficits including quadraparesis, mental retardation, and seizures. Although multiple studies have not clearly established a cause for the neurologic deficits linked with GS1, a few reports suggest that GS1 is associated with abnormal myelination, which could cause the neurologic deficits seen with GS1. In this report, we investigate whether myosin Va is critical to oligodendrocyte morphology and to myelination *in vivo*. We found that myosin Va-null mice exhibit significantly impaired myelination of the brain, optic nerve, and spinal cord. Oligodendrocytes express myosin Va and loss of myosin Va function resulted in significantly smaller lamellas and decreased process number, length, and branching of oligodendrocytes. Loss of myosin Va function also blocked distal localization of vesicle-associated membrane protein 2 (VAMP2), which is known to associate with myosin Va. When VAMP2 function was disrupted, oligodendrocytes exhibited similar morphologic deficits to what is seen with functional ablation of myosin Va. Our findings establish a role for both myosin Va and VAMP2 in oligodendrocyte function as it relates to myelination.

The Journal of Neuroscience, October 17, 2007 • 27(42):11366–11375

## DEVELOPMENT/PLASTICITY/REPAIR

## The Long Form of Fas Apoptotic Inhibitory Molecule Is Expressed Specifically in Neurons and Protects Them against Death Receptor-Triggered Apoptosis

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Death receptors (DRs) and their ligands are expressed in developing nervous system. However, neurons are generally resistant to death induction through DRs and rather their activation promotes neuronal outgrowth and branching. These results suppose the existence of DRs antagonists expressed in the nervous system. Fas apoptosis inhibitory molecule (FAIM<sub>s</sub>) was first identified as a Fas antagonist in B-cells. Soon after, a longer alternative spliced isoform with unknown function was identified and named FAIM<sub>L</sub>. FAIM<sub>s</sub> is widely expressed, including the nervous system, and we have shown previously that it promotes neuronal differentiation but it is not an anti-apoptotic molecule in this system. Here, we demonstrate that FAIM<sub>L</sub> is expressed specifically in neurons, and its expression is regulated during the development. Expression could be induced by NGF through the extracellular regulated kinase pathway in PC12 (pheochromocytoma cell line) cells. Contrary to FAIM<sub>s</sub>, FAIM<sub>L</sub> does not increase the neurite outgrowth induced by neurotrophins and does not interfere with nuclear factor  $\kappa$ B pathway activation as FAIM<sub>s</sub> does. Cells overexpressing FAIM<sub>L</sub> are resistant to apoptotic cell death induced by DRs such as Fas or tumor necrosis factor R1. Reduction of endogenous expression by small interfering RNA shows that endogenous FAIM<sub>L</sub> protects primary neurons from DR-induced cell death. The detailed analysis of this antagonism shows that FAIM<sub>L</sub> can bind to Fas receptor and prevent the activation of the initiator caspase-8 induced by Fas. In conclusion, our results indicate that FAIM<sub>L</sub> could be responsible for maintaining initiator caspases inactive after receptor engagement protecting neurons from the cytotoxic action of death ligands.

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## Tyrosine Phosphorylation Sites in ephrinB2 Are Required for Hippocampal Long-Term Potentiation But Not Long-Term Depression

Farima Bouzioukh,<sup>1</sup> George A. Wilkinson,<sup>1</sup> Giselind Adelmann,<sup>3</sup> Michael Frotscher,<sup>3</sup> Valentin Stein,<sup>2</sup> and Rüdiger Klein<sup>1</sup>

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Long-lasting changes in synaptic function are thought to be the cellular basis for learning and memory and for activity-dependent plasticity during development. Long-term potentiation (LTP) and long-term depression (LTD) are two opposing forms of synaptic plasticity that help fine tune neural connections and possibly serve to store information in the brain. Eph receptor tyrosine kinases and their transmembrane ligands, the ephrinBs, have essential roles in certain forms of synaptic plasticity. At the

CA3–CA1 hippocampal synapse, EphB2 and EphA4 receptors are critically involved in long-term plasticity independent of their cytoplasmic domains, suggesting that ephrinBs are the active signaling partners. In cell-based assays, ephrinB reverse signaling was previously shown to involve phosphotyrosine-dependent and postsynaptic density-95/Discs large/zona occludens-1 (PDZ) domain interaction-dependent pathways. Which reverse signaling mode is required at hippocampal synapses is unknown. To address this question, we used knock-in mice expressing mutant isoforms of ephrinB2 that are deficient in specific aspects of reverse signaling. Our analysis revealed that tyrosine phosphorylation sites in ephrinB2 are required to mediate normal hippocampal LTP, but not for LTD. Conversely, ephrinB2 lacking the C-terminal PDZ interaction site, but competent to undergo tyrosine phosphorylation, cannot mediate either form of long-term plasticity. Our results provide the first evidence for phosphotyrosine-dependent ephrinB reverse signaling in a neuronal network and for differential ephrinB2 reverse signaling in two forms of synaptic plasticity.

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## Rapid Activation of Antioxidant Defenses by Nerve Growth Factor Suppresses Reactive Oxygen Species during Neuronal Apoptosis: Evidence for a Role in Cytochrome *c* Redistribution

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Depriving mouse sympathetic neurons of nerve growth factor (NGF) causes their apoptotic death. A Bax-dependent increase of mitochondrial-derived reactive oxygen species (ROS) begins in these cells soon after NGF withdrawal. We investigated the effects on these ROS of adding NGF to cultures of NGF-deprived neurons. ROS levels were monitored with the fluorescent, redox-sensitive dyes CM-H<sub>2</sub>DCFDA and MitoSOX Red. The intensity of the former dye increases when it is oxidized by H<sub>2</sub>O<sub>2</sub> and free radicals downstream of H<sub>2</sub>O<sub>2</sub>. MitoSOX Red is relatively insensitive to oxidation by H<sub>2</sub>O<sub>2</sub> but is sensitive to oxidation by superoxide (O<sub>2</sub><sup>•−</sup>). Withdrawing NGF increased CM-H<sub>2</sub>DCFDA intensity, indicating elevated H<sub>2</sub>O<sub>2</sub>-associated ROS. Re-exposure of cells deprived of NGF to NGF resulted in rapid suppression of these ROS. Neurons deprived of NGF also had increased MitoSOX Red intensities. Readdition of NGF had no effect on MitoSOX Red fluorescence. The suppression of CM-H<sub>2</sub>DCFDA-detected ROS by NGF was caused by a rapid activation of glutathione redox cycling. The most likely explanation for these findings is that mitochondria increased O<sub>2</sub><sup>•−</sup> production after NGF withdrawal. The O<sub>2</sub><sup>•−</sup> was converted to H<sub>2</sub>O<sub>2</sub> by dismutation, and the H<sub>2</sub>O<sub>2</sub> was detoxified by accelerated glutathione redox cycling. Our previous work shows that H<sub>2</sub>O<sub>2</sub> induces cytochrome *c* to be released from mitochondria in NGF-supported sympathetic neurons, whereas antioxidants that detoxify H<sub>2</sub>O<sub>2</sub> block cytochrome *c* redistribution in NGF-deprived neurons. Readdition of NGF also immediately inhibits cytochrome *c* release. We present evidence that this inhibition is mediated by the rapid activation of glutathione redox cycling by NGF.

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## Activity-Dependent Development of Callosal Projections in the Somatosensory Cortex

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The corpus callosum is the largest commissural system in the mammalian brain, but the mechanisms underlying its development are not well understood. Here we report that neuronal activity is necessary for the normal development and maintenance of callosal projections in the mouse somatosensory cortex. We labeled a subpopulation of layer II/III callosal neurons via *in utero* electroporation and traced their axons in the contralateral cortex at different postnatal stages. Callosal axons displayed region- and layer-specific projection patterns within the first 2 weeks postnatally. Prenatal suppression of neuronal excitation was achieved via electroporation-induced overexpression of the inward rectifying potassium channel Kir2.1 in layer II/III cortical neurons. This resulted in abnormal callosal projections with many axons extending beyond layers II–III to terminate in layer I. Others failed to terminate at the border between the primary and secondary somatosensory cortices. Blocking synaptic transmission via expression of the tetanus toxin light chain (TeNT-LC) in these axons produced a more pronounced reduction in the projections to the border region, and the eventual disappearance of callosal projections over the entire somatosensory cortex. When Kir2.1 and TeNT-LC were coexpressed, callosal axon targeting exhibited a more severe phenotype that appeared to represent the addition of the effects produced by individual expression of Kir2.1 and TeNT-LC. These results underscore the importance of activity in regulating the developing neural connections and suggest that neuronal and synaptic activities are involved in regulating different aspects of the development of callosal projection.

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## The Marginal Zone/Layer I as a Novel Niche for Neurogenesis and Gliogenesis in Developing Cerebral Cortex

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The cellular diversity of the cerebral cortex is thought to arise from progenitors located in the ventricular zone and subventricular zone in the telencephalon. Here we describe a novel source of progenitors located outside these two major germinative zones of the mouse cerebral cortex that contributes to neurogenesis and gliogenesis. Proliferating cells first appear in the preplate of the embryonic cerebral cortex and further increase in the marginal zone during mid and late neurogenesis. The embryonic

marginal zone progenitors differ in their molecular characteristics as well as the size and identity of their clonal progeny from progenitors isolated from the ventricular zone and subventricular zone. Time-lapse video microscopy and clonal analysis *in vitro* revealed that the marginal zone progenitor pool contains a large fraction of oligodendrocyte or astrocyte progenitors, as well as neuronal and bipotent progenitors. Thus, marginal zone progenitors are heterogeneous in regard to their fate specification, as well as in regard to their region of origin (pallial and subpallial) as revealed by *in vivo* fate mapping. The local environment in the marginal zone tightly regulates the size of this novel progenitor pool, because both basement membrane defects in laminin  $\gamma 1^{-/-}$  mice or alterations in the cellular composition of the marginal zone in Pax6 *Small Eye* mutant mice lead to an increase in the marginal zone progenitor pool. In conclusion, we have identified a novel source of neuronal and glial progenitors in the marginal zone of the developing cerebral cortex with properties notably distinct from those of ventricular zone and subventricular zone progenitors.

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## Role of Kinase Suppressor of Ras-1 in Neuronal Survival Signaling by Extracellular Signal-Regulated Kinase 1/2

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Scaffolding proteins including kinase suppressor of Ras-1 (KSR1) determine specificity of signaling by extracellular signal-regulated kinase 1/2 (ERK1/2), enabling it to couple diverse extracellular stimuli to various cellular responses. The scaffolding protein(s) that contributes to ERK1/2-mediated neuronal survival has not yet been identified. In cultured rat cortical neurons, BDNF activates ERK1/2 to enhance neuronal survival by suppressing DNA damage- or trophic deprivation-induced apoptosis. Here we report that in this system, BDNF increased KSR1 association with activated ERK1/2, whereas KSR1 knockdown with a short hairpin (sh) RNA reduced BDNF-mediated activation of ERK1/2 and protection against a DNA-damaging drug, camptothecin (CPT). In contrast, BDNF suppression of trophic deprivation-induced apoptosis was unaffected by shKSR1 although blocked by shERK1/2. Also, overexpression of KSR1 enhanced BDNF protection against CPT. Therefore, KSR1 is specifically involved in antigenotoxic activation of ERK1/2 by BDNF. To test whether KSR1 contributes to ERK1/2 activation by other neuroprotective stimuli, we used a cAMP-elevating drug, forskolin. In cortical neurons, ERK1/2 activation by forskolin was protein kinase A (PKA) dependent but TrkB (receptor tyrosine kinase B) independent and was accompanied by the increased association between KSR1 and active ERK1/2. Forskolin suppressed CPT-induced apoptosis in a KSR1 and ERK1/2-dependent manner. Inhibition of PKA abolished forskolin protection, whereas selective PKA activation resulted in an ERK1/2- and KSR1-mediated decrease in apoptosis. Hence, KSR1 is critical for the antiapoptotic activation of ERK1/2 by BDNF or cAMP/PKA signaling. In addition, these novel data indicate that stimulation of cAMP signaling is a candidate neuroprotective strategy to intervene against neurotoxicity of DNA-damaging agents.

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## BEHAVIORAL/SYSTEMS/COGNITIVE

## Aging in Binaural Hearing Begins in Mid-Life: Evidence from Cortical Auditory-Evoked Responses to Changes in Interaural Phase

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Older adults often have difficulty understanding speech in a noisy environment or with multiple speakers. In such situations, binaural hearing improves the signal-to-noise ratio. How does this binaural advantage change with increasing age? Using magnetoencephalography, we recorded cortical activity evoked by changes in interaural phase differences of amplitude-modulated tones. These responses occurred for frequencies up to 1225 Hz in young subjects but only up to 940 Hz in middle-aged and 760 Hz in older adults. Behavioral thresholds also decreased with increasing age but were more variable, likely because some older adults make effective use of compensatory mechanisms. The reduced frequency range for binaural hearing became significant in middle age, before decline in hearing sensation and the morphology of cortical responses, which became apparent only in the older subjects. This study provides evidence from human physiological data for the early onset of biological aging in binaural hearing.

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## Weber's Law in Decision Making: Integrating Behavioral Data in Humans with a Neurophysiological Model

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Recent single-cell studies in monkeys (Romo et al., 2004) show that the activity of neurons in the ventral premotor cortex covaries with the animal's decisions in a perceptual comparison task regarding the frequency of vibrotactile events. The firing rate response of these neurons was dependent only on the frequency differences between the two applied vibrations, the sign of that difference being the determining factor for correct task performance. We present a biophysically realistic neurodynamical model that can

account for the most relevant characteristics of this decision-making-related neural activity. One of the nontrivial predictions of this model is that Weber's law will underlie the perceptual discrimination behavior. We confirmed this prediction in behavioral tests of vibrotactile discrimination in humans and propose a computational explanation of perceptual discrimination that accounts naturally for the emergence of Weber's law. We conclude that the neurodynamical mechanisms and computational principles underlying the decision-making processes in this perceptual discrimination task are consistent with a fluctuation-driven scenario in a multistable regime. The Journal of Neuroscience, October 17, 2007 • 27(42):11192–11200

## Behavioral Discrimination between Sucrose and Other Natural Sweeteners in Mice: Implications for the Neural Coding of T1R Ligands

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In taste bud cells, two different T1R heteromeric taste receptors mediate signal transduction of sugars (the canonical "sweet" taste receptor, T1R2 + T1R3) and L-amino acids (the T1R1 + T1R3 receptor). The T1R1 + T1R3 receptor is thought to mediate what is considered the fifth basic taste quality "umami." However, a subset of L-amino acids is "sweet tasting" to humans and appears to possess a "sucrose-like" taste quality to nonhuman mammals. This suggests, to varying degrees, that all of these compounds activate a single neural channel that leads to the perception of sweetness.

The experiments detailed here were designed to test the ability of mice to distinguish between sucrose and various other sugars and L-amino acids in operant taste discrimination tasks. Mice had at least some difficulty discriminating sucrose from L-serine, L-threonine, maltose, fructose, and glucose. For example, when concentration effects are taken into consideration, mice discriminated poorly, if at all, sucrose from glucose or fructose and, to a lesser extent maltose, suggesting that sugars generate a unitary perceptual quality. However, mice were able to reliably discriminate sucrose from L-serine and L-threonine. Data gathered using a conditioned taste aversion assay also suggest that, although qualitatively similar to the taste of sucrose, L-serine and L-threonine generate distinctive percepts.

In conclusion, it appears that some signals from taste receptor proteins binding with sugars and some L-amino acids converge somewhere along the gustatory neuraxis. However, the results of these experiments also imply that sweet-tasting L-amino acids may possess qualitative taste characteristics that are distinguishable from the prototypical sweetener sucrose.

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## Intraburst and Interburst Signaling by Climbing Fibers

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Although cerebellar Purkinje cell complex spikes occur at low frequency ( $\sim 1$ /s), each complex spike is often associated with a high-frequency burst ( $\sim 500$ /s) of climbing fiber spikes. We examined the possibility that signals are present within the climbing fiber bursts. By intracellularly recording from depolarized, nonspiking Purkinje cells in anesthetized pigmented rabbits, climbing fiber burst patterns were investigated by determining the number of components in the induced compound EPSPs during spontaneous activity and during visual stimulation. For our sample of 43 cells,  $>70\%$  of all EPSPs were of the compound type composed of two or three EPSPs. During spontaneous activity, the number of components in each compound EPSP was not related to the latency to the succeeding compound EPSP. Conversely, the number of components in each compound EPSP was related to its latency after the preceding compound EPSP. This latency increased from 0.62 s for one-component EPSPs to 1.69 s for compound EPSPs with four or more components. The effect of visual stimulation on the climbing fiber activity was studied in 19 floccular Purkinje cells whose low-frequency interburst climbing fiber response was modulated by movement about the vertical axis. During sinusoidal oscillation (0.1 Hz,  $\pm 10^\circ$ ), compound EPSPs with a larger number of components tended to be more prevalent during movement in the excitatory direction than in the inhibitory direction. Thus, climbing fibers can, in addition to modulation of their low interburst frequency, transmit signals in the form of the number of spikes within each high-frequency burst.

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## Bihemispheric Leftward Bias in a Visuospatial Attention-Related Network

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Asymmetry of spatial attention has long been described in both disease (hemispatial neglect) and healthy (pseudoneglect) states. Although right-hemisphere specialization for spatial attention has been suggested, the exact neural mechanisms of asymmetry have not been deciphered yet. A recent functional magnetic resonance imaging study from our laboratory serendipitously revealed bihemispheric left-hemifield superiority in activation of a visuospatial attention-related network. Nineteen right-handed healthy adult females participated in two experiments of visual half-field presentation. Either facial expressions (experiment 1) or house images (experiment 2) were presented unilaterally and parafoveally for 150 ms while subjects were engaging a central fixation task. Brain regions previously associated with a visuospatial attention network, in both hemispheres, were found to be more robustly activated by left visual field stimuli. The consistency of this finding with manifestations of attention lateralization is discussed, and a revised model based on neural connectivity asymmetry is proposed. Support for the revised model is given by a dynamic causal modeling analysis. Unraveling the basis for attention asymmetry may lead to better understanding of the pathogenesis of attention disorders, followed by improved diagnosis and

treatment. Additionally, the proposed model for asymmetry of visuospatial attention might provide important insights into the mechanisms underlying functional brain lateralization in general.

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## Neurotoxic Lesions of the Medial Mediodorsal Nucleus of the Thalamus Disrupt Reinforcer Devaluation Effects in Rhesus Monkeys

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The mediodorsal thalamus is a major input to the prefrontal cortex and is thought to modulate cognitive functions of the prefrontal cortex. Damage to the medial, magnocellular part of the mediodorsal thalamus (MDmc) impairs cognitive functions dependent on prefrontal cortex, including memory. The contribution of MDmc to other aspects of cognition dependent on prefrontal cortex has not been determined. The ability of monkeys to adjust their choice behavior in response to changes in reinforcer value, a capacity impaired by lesions of orbital prefrontal cortex, can be tested in a reinforcer devaluation paradigm. In the present study, rhesus monkeys with bilateral neurotoxic MDmc lesions were tested in the devaluation procedure. Monkeys learned visual discrimination problems in which each rewarded object is reliably paired with one of two different food rewards and then were given choices between pairs of rewarded objects, one associated with each food. Selective satiation of one of the food rewards reduces choices of objects associated with that food in normal monkeys. Monkeys with bilateral neurotoxic lesions of MDmc learned concurrently presented visual discrimination problems as quickly as unoperated control monkeys but showed impaired reinforcer devaluation effects. This finding suggests that the neural circuitry for control of behavioral choice by changes in reinforcer value includes MDmc.

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## Cyclooxygenase-1-Derived Prostaglandins in the Periaqueductal Gray Differentially Control C-versus A-Fiber-Evoked Spinal Nociception

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Nonsteroidal anti-inflammatory drugs (NSAIDs) exert analgesic effects by inhibiting peripheral cyclooxygenases (COXs). It is now clear that these drugs also have central actions that include the modulation of descending control of spinal nociception from the midbrain periaqueductal gray (PAG). Descending control is a powerful determinant of the pain experience and is thus a potential target for analgesic drugs, including COX inhibitors. Noxious information from the periphery is conveyed to the spinal cord in A- and C-fiber nociceptors, which convey different qualities of the pain signal and have different roles in chronic pain. This *in vivo* study used different rates of skin heating to preferentially activate A- or C-heat nociceptors to further investigate the actions of COX inhibitors and prostaglandins in the PAG on spinal nociceptive processing. The results significantly advance our understanding of the central mechanisms underlying the actions of NSAIDs and prostaglandins by demonstrating that (1) in the PAG, it is COX-1 and not COX-2 that is responsible for acute antinociceptive effects of NSAIDs *in vivo*; (2) these effects are only evoked from the opioid-sensitive ventrolateral PAG; and (3) prostaglandins in the PAG exert tonic facilitatory control that targets C- rather than A-fiber-mediated spinal nociception. This selectivity of control is of particular significance given the distinct roles of A- and C-nociceptors in acute and chronic pain. Thus, effects of centrally acting prostaglandins are pivotal, we suggest, to both the understanding of nociceptive processing and the development of new analgesic drugs.

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## Top–Down Attentional Deficits in Macaques with Lesions of Lateral Prefrontal Cortex

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Brain imaging, electrical stimulation, and neurophysiological studies have all implicated the prefrontal cortex (PFC) in the top–down control of attention. Specifically, feedback from PFC has been proposed to bias activity in visual cortex in favor of attended stimuli over irrelevant distracters. To identify which attentional functions are critically dependent on PFC, we removed PFC unilaterally in combination with transection of the corpus callosum and anterior commissure in two macaques. In such a preparation, the ipsilesional hemisphere is deprived of top–down feedback from PFC to visual cortex, and the contralesional hemisphere can serve as an intact normal control. Monkeys were trained to fixate a central cue and discriminate the orientation of a colored target grating presented among colored distracter gratings in either the hemifield affected by the PFC lesion or the normal control hemifield. Locations of the targets and distracters were varied, and the color of the central cue specified the color of the target on each trial. The behavioral response was a bar release, and thus attentional impairments could be distinguished from impaired oculomotor control. When the cue was held constant for many trials, task performance in the affected hemifield was nearly normal. However, the monkeys were severely impaired when the cue was switched frequently across trials. The monkeys were unimpaired in a pop-out task with changing targets that did not require top–down attentional control. The PFC thus appears to play a critical role in the ability to flexibly reallocate attention on the basis of changing task demands.

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# Orbital Prefrontal Cortex Is Required for Object-in-Place Scene Memory But Not Performance of a Strategy Implementation Task

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The orbital prefrontal cortex is thought to be involved in behavioral flexibility in primates, and human neuroimaging studies have identified orbital prefrontal activation during episodic memory encoding. The goal of the present study was to ascertain whether deficits in strategy implementation and episodic memory that occur after ablation of the entire prefrontal cortex can be ascribed to damage to the orbital prefrontal cortex. Rhesus monkeys were preoperatively trained on two behavioral tasks, the performance of both of which is severely impaired by the disconnection of frontal cortex from inferotemporal cortex. In the strategy implementation task, monkeys were required to learn about two categories of objects, each associated with a different strategy that had to be performed to obtain food reward. The different strategies had to be applied flexibly to optimize the rate of reward delivery. In the scene memory task, monkeys learned 20 new object-in-place discrimination problems in each session. Monkeys were tested on both tasks before and after bilateral ablation of orbital prefrontal cortex. These lesions impaired new scene learning but had no effect on strategy implementation. This finding supports a role for the orbital prefrontal cortex in memory but places limits on the involvement of orbital prefrontal cortex in the representation and implementation of behavioral goals and strategies.

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# Subsecond Changes in Top–Down Control Exerted by Human Medial Frontal Cortex during Conflict and Action Selection: A Combined Transcranial Magnetic Stimulation–Electroencephalography Study

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Action selection requires choosing one of all the possible conflicting action plans that are available. There is currently a debate as to whether the dorsal medial frontal cortex (dmFC) merely detects or actively resolves response conflict. We used combined on-line transcranial magnetic stimulation and electroencephalographic recording (TMS–EEG) to test whether human dmFC plays a critical causal role in conflict resolution, and whether the mechanism for such a function is via interactions with primary motor cortex. In an Eriksen flanker task, subjects discriminated the direction of the centermost arrow in an array of five, responding with the left or right hand. The lateralized readiness potential (LRP), a measure of relative levels of activity in left and right motor cortices, was also recorded. Reaction times and error rates were higher on incongruent than congruent trials, and incongruent trials produced a positive LRP deflection reflecting initial partial activation of the incorrect response. On one-half of trials, repetitive TMS was applied to left dmFC starting 100 ms before visual stimulus onset and ending 100 ms afterward. TMS disrupted performance by selectively increasing error rates on contralateral (right hand) incongruent trials. TMS also only modulated the LRP on incongruent trials, causing an increased positive deflection (associated with preparation of the incorrect response) starting 180 ms after visual stimulus onset. TMS of a control site did not interfere with behavior or motor cortical activity. dmFC has a direct causal role in resolving conflict during action selection, and the mechanism involves the top–down modulation of primary motor cortical activity.

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# Activations in Visual and Attention-Related Areas Predict and Correlate with the Degree of Perceptual Learning

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Repeated experience with a visual stimulus can result in improved perception of the stimulus, i.e., perceptual learning. To understand the underlying neural mechanisms of this process, we used functional magnetic resonance imaging to track brain activations during the course of training on a contrast discrimination task. Based on their ability to improve on the task within a single scan session, subjects were separated into two groups: “learners” and “nonlearners.” As learning progressed, learners showed progressively reduced activation in both visual cortex, including Brodmann’s areas 18 and 19 and the fusiform gyrus, and several cortical regions associated with the attentional network, namely, the intraparietal sulcus (IPS), frontal eye field (FEF), and supplementary eye field. Among learners, the decrease in brain activations in these regions was highly correlated with the magnitude of performance improvement. Unlike learners, nonlearners showed no changes in brain activations during training. Learners showed stronger activation than nonlearners during the initial period of training in all these brain regions, indicating that one could predict from the initial activation level who would learn and who would not. In addition, over the course of training, the functional connectivity between IPS and FEF in the right hemisphere with early visual areas was stronger for learners than nonlearners. We speculate that sharpened tuning of neuronal representations may cause reduced activation in visual cortex during perceptual learning and that attention may facilitate this process through an interaction of attention-related and visual cortical regions.

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# How Progesterone Impairs Memory for Biologically Salient Stimuli in Healthy Young Women

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Progesterone, or rather its neuroactive metabolite allopregnanolone, modulates amygdala activity and thereby influences anxiety. Cognition and, in particular, memory are also altered by allopregnanolone. In the present study, we investigated whether allopregnanolone modulates memory for biologically salient stimuli by influencing amygdala activity, which in turn may affect neural processes in other brain regions. A single progesterone dose was administered orally to healthy young women in a double-blind, placebo-controlled, crossover design, and participants were asked to memorize and recognize faces while undergoing functional magnetic resonance imaging. Progesterone decreased recognition accuracy without affecting reaction times. The imaging results show that the amygdala, hippocampus, and fusiform gyrus supported memory formation. Importantly, progesterone decreased responses to faces in the amygdala and fusiform gyrus during memory encoding, whereas it increased hippocampal responses. The progesterone-induced decrease in neural activity in the amygdala and fusiform gyrus predicted the decrease in memory performance across subjects. However, progesterone did not modulate the differential activation between subsequently remembered and subsequently forgotten faces in these areas. A similar pattern of results was observed in the fusiform gyrus and prefrontal cortex during memory retrieval. These results suggest that allopregnanolone impairs memory by reducing the recruitment of those brain regions that support memory formation and retrieval. Given the important role of the amygdala in the modulation of memory, these results suggest that allopregnanolone alters memory by influencing amygdala activity, which in turn may affect memory processes in other brain regions.

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# Audiovisual Temporal Correspondence Modulates Human Multisensory Superior Temporal Sulcus Plus Primary Sensory Cortices

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The brain should integrate related but not unrelated information from different senses. Temporal patterning of inputs to different modalities may provide critical information about whether those inputs are related or not. We studied effects of temporal correspondence between auditory and visual streams on human brain activity with functional magnetic resonance imaging (fMRI). Streams of visual flashes with irregularly jittered, arrhythmic timing could appear on right or left, with or without a stream of auditory tones that coincided perfectly when present (highly unlikely by chance), were noncoincident with vision (different erratic, arrhythmic pattern with same temporal statistics), or an auditory stream appeared alone. fMRI revealed blood oxygenation level-dependent (BOLD) increases in multisensory superior temporal sulcus (mSTS), contralateral to a visual stream when coincident with an auditory stream, and BOLD decreases for noncoincidence relative to unisensory baselines. Contralateral primary visual cortex and auditory cortex were also affected by audiovisual temporal correspondence or noncorrespondence, as confirmed in individuals. Connectivity analyses indicated enhanced influence from mSTS on primary sensory areas, rather than vice versa, during audiovisual correspondence. Temporal correspondence between auditory and visual streams affects a network of both multisensory (mSTS) and sensory-specific areas in humans, including even primary visual and auditory cortex, with stronger responses for corresponding and thus related audiovisual inputs.

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# Methamphetamine Self-Administration and Voluntary Exercise Have Opposing Effects on Medial Prefrontal Cortex Gliogenesis

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Psychostimulant abuse produces deficits in prefrontal cortex (PFC) function, whereas physical activity improves PFC-dependent cognition and memory. The present study explored the vulnerability of medial PFC (mPFC) precursor proliferation and survival to methamphetamine self-administration and voluntary exercise, factors that may have opposing effects on mPFC plasticity to facilitate functional consequences. Intermittent 1 h access to methamphetamine (I-ShA) increased, but daily 1 and 6 h access decreased, proliferation and survival, with dose-dependent effects on mature cell phenotypes. All groups showed increased cell death. Voluntary exercise enhanced proliferation and survival but, in contrast to methamphetamine exposure, did not alter cell death or mature phenotypes. Furthermore, enhanced cell survival by I-ShA and voluntary exercise had profound effects on gliogenesis with differential regulation of oligodendrocytes versus astrocytes. In addition, new cells in the adult mPFC stain for the neuronal marker neuronal nuclear protein, although enhanced cell survival by I-ShA and voluntary exercise did not result in increased neurogenesis. Our findings demonstrate that mPFC gliogenesis is vulnerable to psychostimulant abuse and physical activity with distinct underlying mechanisms. The susceptibility of mPFC gliogenesis to even modest doses of methamphetamine could account for the pronounced pathology linked to psychostimulant abuse.

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## Endogenous Transforming Growth Factor $\beta$ 1 Suppresses Inflammation and Promotes Survival in Adult CNS

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Transforming growth factor  $\beta$ 1 (TGF $\beta$ 1) is a pleiotropic cytokine with potent neurotrophic and immunosuppressive properties that is upregulated after injury, but also expressed in the normal nervous system. In the current study, we examined the regulation of TGF $\beta$ 1 and the effects of TGF $\beta$ 1 deletion on cellular response in the uninjured adult brain and in the injured and regenerating facial motor nucleus. To avoid lethal autoimmune inflammation within 3 weeks after birth in TGF $\beta$ 1-deficient mice, this study was performed on a T- and B-cell-deficient RAG2 $^{-/-}$  background. Compared with wild-type siblings, homozygous deletion of TGF $\beta$ 1 resulted in an extensive inflammatory response in otherwise uninjured brain parenchyma. Astrocytes increased in GFAP and CD44 immunoreactivity; microglia showed proliferative activity, expression of phagocytosis-associated markers [ $\alpha$ X $\beta$ 2, B7.2, and MHC1 (major histocompatibility complex type 1)], and reduced branching. Ultrastructural analysis revealed focal blockade of axonal transport, perinodal damming of axonal organelles, focal demyelination, and myelin debris in granule-rich, phagocytic microglia. After facial axotomy, absence of TGF $\beta$ 1 led to a fourfold increase in neuronal cell death (52 vs 13%), decreased central axonal sprouting, and significant delay in functional recovery. It also interfered with the microglial response, resulting in a diminished expression of early activation markers [ICAM1 (intercellular adhesion molecule 1),  $\alpha$ 6 $\beta$ 1, and  $\alpha$ M $\beta$ 2] and reduced proliferation. In line with axonal and glial findings in the otherwise uninjured CNS, absence of endogenous TGF $\beta$ 1 also caused an  $\sim$ 10% reduction in the number of normal motoneurons, pointing to an ongoing and potent trophic role of this anti-inflammatory cytokine in the normal as well as in the injured brain.

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## The Heat Shock Response and Chaperones/Heat Shock Proteins in Brain Tumors: Surface Expression, Release, and Possible Immune Consequences

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The heat shock response is a highly conserved “stress response” mechanism used by cells to protect themselves from potentially damaging insults. It often involves the upregulated expression of chaperone and heat shock proteins (HSPs) to prevent damage and aggregation at the proteome level. Like most cancers, brain tumor cells often overexpress chaperones/HSPs, probably because of the stressful atmosphere in which tumors reside, but also because of the benefits of HSP cytoprotection. However, the cellular dynamics and localization of HSPs in either stressed or unstressed conditions has not been studied extensively in brain tumor cells. We have examined the changes in HSP expression and in cell surface/extracellular localization of selected brain tumor cell lines under heat shock or normal environments. We herein report that brain tumor cell lines have considerable heat shock responses or already high constitutive HSP levels; that those cells express various HSPs, chaperones, and at least one cochaperone on their cell surfaces; and that HSPs may be released into the extracellular environment, possibly as exosome vesicular content. In studies with a murine astrocytoma cell line, heat shock dramatically reduces tumorigenicity, possibly by an immune mechanism. Additional evidence indicative of an HSP-driven immune response comes from immunization studies using tumor-derived chaperone protein vaccines, which lead to antigen-specific immune responses and reduced tumor burden in treated mice. The heat shock response and HSPs in brain tumor cells may represent an area of vulnerability in our attempts to treat these recalcitrant and deadly tumors.

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## Prefrontal Dysfunction in Schizophrenia Involves Mixed-Lineage Leukemia 1-Regulated Histone Methylation at GABAergic Gene Promoters

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Alterations in GABAergic mRNA expression play a key role for prefrontal dysfunction in schizophrenia and other neurodevelopmental disease. Here, we show that histone H3-lysine 4 methylation, a chromatin mark associated with the transcriptional process, progressively increased at *GAD1* and other GABAergic gene promoters (*GAD2*, *NPY*, *SST*) in human prefrontal cortex (PFC) from prenatal to peripubertal ages and throughout adulthood. Alterations in schizophrenia included decreased *GAD1* expression and H3K4-trimethylation, predominantly in females and in conjunction with a risk haplotype at the 5' end of *GAD1*. Heterozygosity for a truncated, lacZ knock-in allele of mixed-lineage leukemia 1 (*MLL1*), a histone methyltransferase expressed in GABAergic and other cortical neurons, resulted in decreased H3K4 methylation at GABAergic gene promoters. In contrast, *Gad1* H3K4 (tri)methylation and *MLL1* occupancy was increased in cerebral cortex of mice after treatment with the atypical antipsychotic,

clozapine. These effects were not mimicked by haloperidol or genetic ablation of dopamine D<sub>2</sub> and D<sub>3</sub> receptors, suggesting that blockade of D<sub>2</sub>-like signaling is not sufficient for clozapine-induced histone methylation. Therefore, chromatin remodeling mechanisms at GABAergic gene promoters, including MLL1-mediated histone methylation, operate throughout an extended period of normal human PFC development and play a role in the neurobiology of schizophrenia.

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## Aberrant Hippocampal Activity Underlies the Dopamine Dysregulation in an Animal Model of Schizophrenia

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Evidence supports a dysregulation of subcortical dopamine (DA) system function as a common etiology of psychosis; however, the factors responsible for this aberrant DA system responsivity have not been delineated. Here, we demonstrate in an animal model of schizophrenia that a pathologically enhanced drive from the ventral hippocampus (vHipp) can result in aberrant dopamine neuron signaling. Adult rats in which development was disrupted by prenatal methylazoxymethanol acetate (MAM) administration display a significantly greater number of spontaneously firing ventral tegmental DA neurons. This appears to be a consequence of excessive hippocampal activity because, in MAM-treated rats, vHipp inactivation completely reversed the elevated DA neuron population activity and also normalized the augmented amphetamine-induced locomotor behavior. These data provide a direct link between hippocampal dysfunction and the hyper-responsivity of the DA system that is believed to underlie the augmented response to amphetamine in animal models and psychosis in schizophrenia patients.

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