

# This Week in The Journal

## ● Cellular/Molecular

### *Release Probability Is Low At Calyx of Held*

Jeannette A. M. Lorteije, Silviu I. Rusu, Christopher Kushmerick, and J. Gerard G. Borst

(see pages 13770–13784)

The calyx of Held synapse between cochlear nucleus neurons and neurons of the medial nucleus of the trapezoid body is an important relay in the sound localization system. Because its large size makes it possible to record presynaptic and postsynaptic action potentials simultaneously, this synapse is useful for studying synaptic mechanisms. Although the calyx synapse has been considered extremely reliable—presynaptic spikes almost always evoke postsynaptic spikes—some studies in slices have suggested that the synapse is unreliable at high frequencies because the readily releasable pool of vesicles is rapidly depleted, causing short-term depression. Lorteije et al. have compared synaptic properties of calyx synapses *in vivo* and in slices, using whole-cell and extracellular recordings. They found that no significant short-term depression occurred *in vivo*, because the probability of release at individual release sites was much lower *in vivo* than in slices. Nonetheless, failures occurred occasionally *in vivo* because of frequency-independent variability in EPSP size and reductions in postsynaptic excitability.

## ▲ Development/Plasticity/Repair

### *Pain-Related Decreases in Gray Matter Are Reversible*

R. Rodriguez-Raecke, A. Niemeier, K. Ihle, W. Ruether, and A. May

(see pages 13746–13750)

Chronic pain, lasting months or years, is sometimes associated with ongoing disease, such as cancer or arthritis, but it can also arise from nerve or muscle injury and persist after the injury heals, and it sometimes develops without any identifiable cause. Chronic pain causes functional reorganiza-

tion of the cortex, so that cortical responses to painful stimuli differ between pain patients and healthy subjects. Decreases in gray matter volume also occur in central pain-processing areas—including cingulate, insular, and prefrontal cortices—of chronic pain patients. To determine whether these changes are reversible, Rodriguez-Raecke et al. measured gray matter in patients with hip pain resulting from osteoarthritis, which can be eliminated by hip replacement. Before surgery, patients had lower gray matter density than controls in several cortical and brain stem regions, but gray matter density increased in patients within two months of surgery, indicating that brain changes resulting from some forms of chronic pain are reversible.

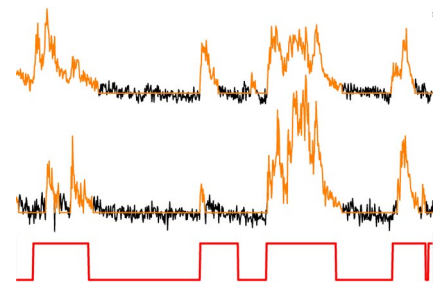
## ■ Behavioral/Systems/Cognitive

### *Functionally Related Neurons Are Clustered in Motor Cortex*

Daniel A. Dombeck, Michael S. Graziano, and David W. Tank

(see pages 13751–13760)

Studying the functional organization of the motor cortex has been limited by the inability to record simultaneously from large numbers of individual neurons in behaving animals. To overcome these problems, Dombeck et al. have developed an apparatus that allows two-photon calcium imaging in head-restrained, unanesthetized mice that can move relatively freely on a spherical treadmill. Using this setup, they recorded the activity of ~80 layer 2/3 motor cortical neurons simultaneously. Segmenting the neuronal population by temporal activity pattern or by correlation with behavior (running or grooming) created similar subsets, and neurons within each subset often were grouped spatially as well as functionally. Moreover, within a given group, neurons with highly correlated activity were likely to be closer to each other than pairs with less correlated activity. These results support the idea of wiring economy, which predicts neurons that are more strongly connected to each other should be positioned close to each other.



Calcium transients (top two traces) in two neurons in mouse motor cortex that were near to each other. Both were active when the mouse was running (bottom trace). See the article by Dombeck et al. for details.

## ◆ Neurobiology of Disease

### *Nanospheres Can Deliver Drugs Across the Blood–Brain Barrier*

H. Karatas, Y. Aktas, Y. Gursoy-Ozdemir, E. Bodur, M. Yemisci, et al.

(see pages 13761–13769)

Many drugs that might be effective in treating neurological diseases have limited clinical use because they do not cross the blood–brain barrier and therefore must be injected intracerebroventricularly. One example is caspase-3 inhibitors, which can decrease secondary damage resulting from ischemia. Karatas et al. have developed a nanoparticle delivery system that efficiently transports caspase-3 inhibitors into the brain. The technique uses nanospheres made of chitosan, a cationic polysaccharide that interacts with negative charges on the brain endothelium. The nanospheres were coated with a specific caspase-3 inhibitor, as well as monoclonal antibodies against a brain-specific transferrin receptor, which facilitates transport across the blood–brain barrier without significant transport into other tissues. When loaded nanoparticles were delivered intravenously to mice, they entered the brain parenchyma within 10 min. Delivery of nanoparticles before or shortly after transient occlusion of the middle cerebral artery significantly reduced the ischemic infarct volume as well as resultant neurological deficits.

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**Cover legend:** Graphical representation of eight colors used by Brouwer and Heeger. Colors are of equal luminance and saturation, and vary only in hue. As depicted in the image, these colors form a circular color space, matching the perception of similarity between these colors of human observers: the organization of the colors form a logical progression through color space, from red, to orange, yellow, green, blue, purple and back to red. Responses to these colors were measured using functional magnetic resonance imaging (fMRI). In visual area V4, these responses reveals a progression through this perceptual color space, with perceptually similar colors evoking the most similar pattern of responses. The image was rendered with Radiance (Larson and Shakespeare, 1997. Rendering with Radiance. San Francisco: Morgan Kaufmann. Oxford UP). For more information, see the article by Brouwer and Heeger in this issue (pages 13992–14003).

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## Brain Gray Matter Decrease in Chronic Pain Is the Consequence and Not the Cause of Pain

Rea Rodriguez-Raecke,<sup>1</sup> Andreas Niemeier,<sup>2</sup> Kristin Ihle,<sup>1</sup> Wolfgang Ruether,<sup>1</sup> and Arne May<sup>1</sup>

Departments of <sup>1</sup>Systems Neuroscience and <sup>2</sup>Orthopaedics, University Medical Center Hamburg Eppendorf, D-20246 Hamburg, Germany

Recently, local morphologic alterations of the brain in areas ascribable to the transmission of pain were reported in patients suffering from chronic pain. Although some authors discussed these findings as damage or loss of brain gray matter, one of the key questions is whether these structural alterations in the cerebral pain-transmitting network precede or succeed the chronicity of pain. We investigated 32 patients with chronic pain due to primary hip osteoarthritis and found a characteristic gray matter decrease in patients compared with controls in the anterior cingulate cortex (ACC), right insular cortex and operculum, dorsolateral prefrontal cortex (DLPFC), amygdala, and brainstem. We then investigated a subgroup of these patients ( $n = 10$ ) 6 weeks and 4 months after total hip replacement surgery, monitoring whole brain structure. After surgery, all 10 patients were completely pain free and we observed a gray matter increase in the DLPFC, ACC, amygdala, and brainstem. As gray matter decrease is at least partly reversible when pain is successfully treated, we suggest that the gray matter abnormalities found in chronic pain do not reflect brain damage but rather are a reversible consequence of chronic nociceptive transmission, which normalizes when the pain is adequately treated.

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### Articles

#### CELLULAR/MOLECULAR

## Reliability and Precision of the Mouse Calyx of Held Synapse

Jeannette A. M. Lorteije,<sup>1\*</sup> Silviu I. Rusu,<sup>1\*</sup> Christopher Kushmerick,<sup>2</sup> and J. Gerard G. Borst<sup>1</sup>

<sup>1</sup>Department of Neuroscience, Erasmus MC, University Medical Center Rotterdam, 3015 GE Rotterdam, The Netherlands, and <sup>2</sup>Departamento de Fisiologia e Biofísica, Instituto de Ciências Biológicas, Universidade Federal de Minas Gerais, 31270-901 Minas Gerais, Brazil

Traditionally, the calyx of Held synapse is viewed as a highly reliable relay in the sound localization circuit of the auditory brainstem, with every presynaptic action potential triggering a postsynaptic action potential *in vivo*. However, this view is at odds with slice recordings that report large short-term depression (STD). To investigate the reliability and precision of this synapse, we compared slice and *in vivo* recordings from medial nucleus of the trapezoid body neurons of young adult mice. We show that the extracellularly recorded complex waveform can be used to estimate both presynaptic release and postsynaptic excitability. Whereas under standard slice conditions the synapse underwent large STD, both extracellular and whole-cell recordings indicated that *in vivo* the size of the EPSPs was independent of recent history. The estimated quantal content was typically  $<20$  *in vivo*, much lower than in the resting synapse under standard slice conditions. However, due to the large quantal size and summation of EPSPs, the safety factor of this synapse was generally still sufficiently large and postsynaptic failures were observed only infrequently *in vivo*. When present, failures were typically due to stochastic fluctuations in EPSP size or postsynaptic spike depression. *In vivo*, the calyx of Held synapse thus functions as a tonic synapse. The price it pays for its low release probability is an increase in jitter and synaptic latency and occasional postsynaptic failures.

The Journal of Neuroscience, November 4, 2009 • 29(44):13770–13784

## Neuroigin-2 Deletion Selectively Decreases Inhibitory Synaptic Transmission Originating from Fast-Spiking but Not from Somatostatin-Positive Interneurons

Jay R. Gibson,<sup>1</sup> Kimberly M. Huber,<sup>1</sup> and Thomas C. Südhof<sup>1,2,3,4</sup>

<sup>1</sup>Department of Neuroscience and <sup>2</sup>Howard Hughes Medical Institute, University of Texas Southwestern Medical Center, Dallas, Texas 75390, and

<sup>3</sup>Department of Molecular and Cellular Physiology and <sup>4</sup>Howard Hughes Medical Institute, Stanford University School of Medicine, Palo Alto, California 94304

Neuroigins are cell adhesion molecules involved in synapse formation and/or function. Neurons express four neuroigins (NL1–NL4), of which NL1 is specific to excitatory and NL2 to inhibitory synapses. Excitatory and inhibitory synapses include numerous subtypes. However, it is unknown whether NL1 performs similar functions in all excitatory and NL2 in all inhibitory synapses, or whether they regulate the formation and/or function of specific subsets of synapses. To address this central question, we performed paired recordings in primary somatosensory cortex of mice lacking NL1 or NL2. Using this system, we examined neocortical microcircuits formed by reciprocal synapses between excitatory neurons and two subtypes of inhibitory interneurons, namely, fast-spiking and somatostatin-positive interneurons. We find that the NL1 deletion had little effect on inhibitory synapses, whereas the NL2 deletion decreased (40–50%) the unitary (cell-to-cell) IPSC amplitude evoked from single fast-spiking interneurons. Strikingly, the NL2 deletion had no effect on IPSC amplitude evoked from single somatostatin-positive inhibitory interneurons. Moreover, the frequency of unitary synaptic connections between individual fast-spiking and somatostatin-positive interneurons and excitatory neurons was unchanged. The decrease in unitary IPSC amplitude originating from fast-spiking interneurons in NL2-deficient mice was due to a multiplicative and uniform downscaling of the amplitude distribution, which in

turn was mediated by a decrease in both synaptic quantal amplitude and quantal content, the latter inferred from an increase in the coefficient of variation. Thus, NL2 is not necessary for establishing unitary inhibitory synaptic connections but is selectively required for “scaling up” unitary connections originating from a subset of interneurons. The Journal of Neuroscience, November 4, 2009 • 29(44):13883–13897

## Autocrine and Paracrine Roles for ATP and Serotonin in Mouse Taste Buds

Yijen A. Huang,<sup>1</sup> Robin Dando,<sup>1</sup> and Stephen D. Roper<sup>1,2</sup>

<sup>1</sup>Department of Physiology and Biophysics and <sup>2</sup>Program in Neuroscience, University of Miami School of Medicine, Miami, Florida 33136

Receptor (type II) taste bud cells secrete ATP during taste stimulation. In turn, ATP activates adjacent presynaptic (type III) cells to release serotonin (5-hydroxytryptamine, or 5-HT) and norepinephrine (NE). The roles of these neurotransmitters in taste buds have not been fully elucidated. Here we tested whether ATP or 5-HT exert feedback onto receptor (type II) cells during taste stimulation. Our previous studies showed NE does not appear to act on adjacent taste bud cells, or at least on receptor cells. Our data show that 5-HT released from presynaptic (type III) cells provides negative paracrine feedback onto receptor cells by activating 5-HT<sub>1A</sub> receptors, inhibiting taste-evoked Ca<sup>2+</sup> mobilization in receptor cells, and reducing ATP secretion. The findings also demonstrate that ATP exerts positive autocrine feedback onto receptor (type II) cells by activating P2Y1 receptors and enhancing ATP secretion. These results begin to sort out how purinergic and aminergic transmitters function within the taste bud to modulate gustatory signaling in these peripheral sensory organs.

The Journal of Neuroscience, November 4, 2009 • 29(44):13909–13918

## Transgenic Expression of *Glud1* (Glutamate Dehydrogenase 1) in Neurons: *In Vivo* Model of Enhanced Glutamate Release, Altered Synaptic Plasticity, and Selective Neuronal Vulnerability

Xiaodong Bao,<sup>1,2</sup> Ranu Pal,<sup>1,2,3</sup> Kevin N. Hascup,<sup>4</sup> Yongfu Wang,<sup>5</sup> Wen-Tung Wang,<sup>6</sup> Wenhao Xu,<sup>8</sup> Dongwei Hui,<sup>1</sup> Abdulbaki Agbas,<sup>1,2</sup> Xinkun Wang,<sup>1,2,3</sup> Mary L. Michaelis,<sup>1,2</sup> In-Young Choi,<sup>5,6,7</sup> Andrei B. Belousov,<sup>5</sup> Greg A. Gerhardt,<sup>4</sup> and Elias K. Michaelis<sup>1,2,3</sup>

<sup>1</sup>Higuchi Biosciences Center, <sup>2</sup>Department of Pharmacology and Toxicology, and <sup>3</sup>Life Span Studies Institute, University of Kansas, Lawrence, Kansas 66047, <sup>4</sup>Anatomy and Neurobiology, Center for Microelectrode Technology, Morris K. Udall Parkinson's Disease Research Center of Excellence, University of Kentucky, College of Medicine, Lexington, Kentucky 40536, <sup>5</sup>Department of Molecular and Integrative Physiology, <sup>6</sup>Hoglund Brain Imaging Center, and <sup>7</sup>Department of Neurology, University of Kansas Medical Center, Kansas City, Kansas 66160, and <sup>8</sup>Department of Microbiology, University of Virginia Health System, Charlottesville, Virginia 22908

The effects of lifelong, moderate excess release of glutamate (Glu) in the CNS have not been previously characterized. We created a transgenic (Tg) mouse model of lifelong excess synaptic Glu release in the CNS by introducing the gene for glutamate dehydrogenase 1 (*Glud1*) under the control of the neuron-specific enolase promoter. *Glud1* is, potentially, an important enzyme in the pathway of Glu synthesis in nerve terminals. Increased levels of GLUD protein and activity in CNS neurons of hemizygous Tg mice were associated with increases in the *in vivo* release of Glu after neuronal depolarization in striatum and in the frequency and amplitude of miniature EPSCs in the CA1 region of the hippocampus. Despite overexpression of *Glud1* in all neurons of the CNS, the Tg mice suffered neuronal losses in select brain regions (e.g., the CA1 but not the CA3 region). In vulnerable regions, Tg mice had decreases in MAP2A labeling of dendrites and in synaptophysin labeling of presynaptic terminals; the decreases in neuronal numbers and dendrite and presynaptic terminal labeling increased with advancing age. In addition, the Tg mice exhibited decreases in long-term potentiation of synaptic activity and in spine density in dendrites of CA1 neurons. Behaviorally, the Tg mice were significantly more resistant than wild-type mice to induction and duration of anesthesia produced by anesthetics that suppress Glu neurotransmission. The *Glud1* mouse might be a useful model for the effects of lifelong excess synaptic Glu release on CNS neurons and for age-associated neurodegenerative processes.

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## Inositol 1,4,5-Trisphosphate 3-Kinase A Functions As a Scaffold for Synaptic Rac Signaling

Il Hwan Kim,<sup>1</sup> Soon Kwon Park,<sup>3</sup> Soon Taek Hong,<sup>1</sup> Yong Sang Jo,<sup>2</sup> Eun Joo Kim,<sup>2</sup> Eun Hye Park,<sup>2</sup> Seung Baek Han,<sup>1</sup> Hee-Sup Shin,<sup>4</sup> Woong Sun,<sup>1</sup> Hyun Taek Kim,<sup>2</sup> Scott H. Soderling,<sup>5,6</sup> and Hyun Kim<sup>1</sup>

<sup>1</sup>Department of Anatomy, College of Medicine, Korea University, Brain Korea 21, Seoul 136-705, Korea, <sup>2</sup>Department of Psychology, Korea University, Seoul 136-701, Korea, <sup>3</sup>School of Alternative Medicine and Health Science, Jeonju University, Jeonju 520-759, Korea, <sup>4</sup>Center for Neural Science, Korea Institute of Science and Technology, Seoul 136-791, Korea, and Departments of <sup>5</sup>Cell Biology and <sup>6</sup>Neurobiology, Duke University Medical School, Durham, North Carolina 27710

Activity-dependent alterations of synaptic contacts are crucial for synaptic plasticity. The formation of new dendritic spines and synapses is known to require actin cytoskeletal reorganization specifically during neural activation phases. Yet the site-specific and time-dependent mechanisms modulating actin dynamics in mature neurons are not well understood. In this study, we show that actin dynamics in spines is regulated by a Rac anchoring and targeting function of inositol 1,4,5-trisphosphate 3-kinase A (IP<sub>3</sub>K-A), independent of its kinase activity. On neural activation, IP<sub>3</sub>K-A bound directly to activated Rac1 and recruited it to the actin cytoskeleton in the postsynaptic area. This focal targeting of activated Rac1 induced spine formation through actin dynamics downstream of Rac signaling. Consistent with the scaffolding role of IP<sub>3</sub>K-A, IP<sub>3</sub>K-A knock-out mice exhibited defects in accumulation of PAK1 by long-term potentiation-inducing stimulation. This deficiency resulted in a reduction in the reorganization of actin cytoskeletal structures in the synaptic area of dentate gyrus. Moreover, IP<sub>3</sub>K-A knock-out mice showed deficits of synaptic plasticity in perforant

path and in hippocampal-dependent memory performances. These data support a novel model in which IP<sub>3</sub>K-A is critical for the spatial and temporal regulation of spine actin remodeling, synaptic plasticity, and learning and memory via an activity-dependent Rac scaffolding mechanism.

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## DEVELOPMENT/PLASTICITY/REPAIR

# Retinotopic Mapping Requires Focal Adhesion Kinase-Mediated Regulation of Growth Cone Adhesion

Stephanie Woo,<sup>1</sup> Daniel J. Rowan,<sup>2</sup> and Timothy M. Gomez<sup>2</sup>

<sup>1</sup>Department of Biochemistry and Biophysics, University of California, San Francisco, California 94158, and <sup>2</sup>Department of Anatomy and Program in Cellular and Molecular Biology, University of Wisconsin, Madison, Wisconsin 53706

Adhesion controls growth cone motility, yet the effects of axon guidance cues on adhesion site dynamics are poorly understood. Here we show that ephrin-A1 reduces retinal ganglion cell (RGC) axon outgrowth by stabilizing existing adhesions and inhibiting new adhesion assembly. Ephrin-A1 activates focal adhesion kinase (FAK) in an integrin- and Src-dependent manner and the effects of ephrin-A1 on growth cone motility require FAK activation. We also find that FAK is expressed in a high temporal to low nasal gradient in RGCs, similar to EphA receptors, and that balanced FAK activation is necessary for optimal axon outgrowth. Last, we find that FAK is required for proper topographic positioning of retinal axons along the anterior–posterior axis of the optic tectum in both *Xenopus* and zebrafish, a guidance decision mediated in part by A-type ephrins. Together, our data suggest that ephrin-A1 controls growth cone advance by modulating adhesive point contacts through FAK activation and that graded FAK signaling is an important component of ephrin-A-mediated retinotopic mapping.

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## BEHAVIORAL/SYSTEMS/COGNITIVE

# Functional Clustering of Neurons in Motor Cortex Determined by Cellular Resolution Imaging in Awake Behaving Mice

Daniel A. Dombbeck,<sup>1,3</sup> Michael S. Graziano,<sup>2,3</sup> and David W. Tank<sup>1,3</sup>

Departments of <sup>1</sup>Molecular Biology and <sup>2</sup>Psychology, and <sup>3</sup>Princeton Neuroscience Institute, Princeton University, Princeton, New Jersey 08544

Macroscopic (millimeter scale) functional clustering is a hallmark characteristic of motor cortex spatial organization in awake behaving mammals; however, almost no information is known about the functional micro-organization (~100 μm scale). Here, we optically recorded intracellular calcium transients of layer 2/3 neurons with cellular resolution over ~200-μm-diameter fields in the forelimb motor cortex of mobile, head-restrained mice during two distinct movements (running and grooming). We showed that the temporal correlation between neurons was statistically larger the closer the neurons were to each other. We further explored this correlation by using two separate methods to spatially segment the neurons within each imaging field: K-means clustering and correlations between single neuron activity and mouse movements. The two methods segmented the neurons similarly and led to the conclusion that the origin of the inverse relationship between correlation and distance seen statistically was twofold: clusters of highly temporally correlated neurons were often spatially distinct from one another, and (even when the clusters were spatially intermingled) within the clusters, the more correlated the neurons were to each other, the shorter the distance between them. Our results represent a direct observation of functional clustering within the microcircuitry of the awake mouse motor cortex.

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## From Neurons to Circuits: Linear Estimation of Local Field Potentials

Malte Rasch,<sup>4,5</sup> Nikos K. Logothetis,<sup>5</sup> and Gabriel Kreiman<sup>1,2,3</sup>

<sup>1</sup>Department of Ophthalmology and Neuroscience, Children's Hospital Boston, Harvard Medical School, Boston, Massachusetts 02115, <sup>2</sup>Center for Brain Science and <sup>3</sup>Swartz Center for Theoretical Neuroscience, Harvard University, Cambridge, Massachusetts 02138, <sup>4</sup>Graz University of Technology, A8010 Graz, Austria, and <sup>5</sup>Max Planck Institute for Biological Cybernetics, D-72072 Tübingen, Germany

Extracellular physiological recordings are typically separated into two frequency bands: local field potentials (LFPs) (a circuit property) and spiking multiunit activity (MUA). Recently, there has been increased interest in LFPs because of their correlation with functional magnetic resonance imaging blood oxygenation level-dependent measurements and the possibility of studying local processing and neuronal synchrony. To further understand the biophysical origin of LFPs, we asked whether it is possible to estimate their time course based on the spiking activity from the same electrode or nearby electrodes. We used “signal estimation theory” to show that a linear filter operation on the activity of one or a few neurons can explain a significant fraction of the LFP time course in the macaque monkey primary visual cortex. The linear filter used to estimate the LFPs had a stereotypical shape characterized by a sharp downstroke at negative time lags and a slower positive upstroke for positive time lags. The filter was similar across different neocortical regions and behavioral conditions, including spontaneous activity and visual stimulation. The estimations had a spatial resolution of ~1 mm and a temporal resolution of ~200 ms. By considering a causal filter, we observed a temporal asymmetry such that the positive time lags in the filter contributed more to the LFP estimation than the negative time lags. Additionally, we showed that spikes occurring within ~10 ms of spikes from nearby neurons yielded better

estimation accuracies than nonsynchronous spikes. In summary, our results suggest that at least some circuit-level local properties of the field potentials can be predicted from the activity of one or a few neurons.

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## Dynamic Range Adaptation to Sound Level Statistics in the Auditory Nerve

**Bo Wen,<sup>1,2</sup> Grace I. Wang,<sup>1,2,3</sup> Isabel Dean,<sup>4</sup> and Bertrand Delgutte<sup>1,2</sup>**

<sup>1</sup>Eaton-Peabody Laboratory, Massachusetts Eye and Ear Infirmary, Boston, Massachusetts 02114, <sup>2</sup>Research Laboratory of Electronics and <sup>3</sup>Department of Electrical Engineering and Computer Science, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, and <sup>4</sup>Ear Institute, University College London, London WC1X 8EE, United Kingdom

The auditory system operates over a vast range of sound pressure levels (100–120 dB) with nearly constant discrimination ability across most of the range, well exceeding the dynamic range of most auditory neurons (20–40 dB). Dean et al. (2005) have reported that the dynamic range of midbrain auditory neurons adapts to the distribution of sound levels in a continuous, dynamic stimulus by shifting toward the most frequently occurring level. Here, we show that dynamic range adaptation, distinct from classic firing rate adaptation, also occurs in primary auditory neurons in anesthetized cats for tone and noise stimuli. Specifically, the range of sound levels over which firing rates of auditory nerve (AN) fibers grows rapidly with level shifts nearly linearly with the most probable levels in a dynamic sound stimulus. This dynamic range adaptation was observed for fibers with all characteristic frequencies and spontaneous discharge rates. As in the midbrain, dynamic range adaptation improved the precision of level coding by the AN fiber population for the prevailing sound levels in the stimulus. However, dynamic range adaptation in the AN was weaker than in the midbrain and not sufficient (0.25 dB/dB, on average, for broadband noise) to prevent a significant degradation of the precision of level coding by the AN population above 60 dB SPL. These findings suggest that adaptive processing of sound levels first occurs in the auditory periphery and is enhanced along the auditory pathway.

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## Reference Frame of the Ventriloquism Aftereffect

**Norbert Kopčo,<sup>1,2,3</sup> I-Fan Lin,<sup>2</sup> Barbara G. Shinn-Cunningham,<sup>2</sup> and Jennifer M. Groh<sup>1</sup>**

<sup>1</sup>Center for Cognitive Neuroscience, Duke University, Durham, North Carolina 27708, <sup>2</sup>Hearing Research Center, Department of Cognitive and Neural Systems, Boston University, Boston, Massachusetts 02215, and <sup>3</sup>Department of Cybernetics and Artificial Intelligence, Technical University of Košice, 04001 Košice, Slovakia

Seeing the image of a newscaster on a television set causes us to think that the sound coming from the loudspeaker is actually coming from the screen. How images capture sounds is mysterious because the brain uses different methods for determining the locations of visual versus auditory stimuli. The retina senses the locations of visual objects with respect to the eyes, whereas differences in sound characteristics across the ears indicate the locations of sound sources referenced to the head. Here, we tested which reference frame (RF) is used when vision recalibrates perceived sound locations. Visually guided biases in sound localization were induced in seven humans and two monkeys who made eye movements to auditory or audiovisual stimuli. On audiovisual (training) trials, the visual component of the targets was displaced laterally by 5–6°. Interleaved auditory-only (probe) trials served to evaluate the effect of experience with mismatched visual stimuli on auditory localization. We found that the displaced visual stimuli induced ventriloquism aftereffect in both humans (~50% of the displacement size) and monkeys (~25%), but only for locations around the trained spatial region, showing that audiovisual recalibration can be spatially specific. We tested the reference frame in which the recalibration occurs. On probe trials, we varied eye position relative to the head to dissociate head- from eye-centered RFs. Results indicate that both humans and monkeys use a mixture of the two RFs, suggesting that the neural mechanisms involved in ventriloquism occur in brain region(s) using a hybrid RF for encoding spatial information.

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## The Responses of Visual Neurons in the Frontal Eye Field Are Biased for Saccades

**Bonnie M. Lawrence<sup>1</sup> and Lawrence H. Snyder<sup>2</sup>**

<sup>1</sup>Department of Psychology, Case Western Reserve University, Cleveland, Ohio 44106, and <sup>2</sup>Department of Anatomy and Neurobiology, Washington University School of Medicine, St. Louis, Missouri 63110

Previous research suggests that visually responsive neurons in the frontal eye field (FEF) respond to visual targets even when they are not the goal of a saccadic eye movement. These results raise the possibility that these neurons respond to visual targets independent of the effector that is to be used to acquire the target locations. In the present study, we examined whether a plan to execute a saccade or a reach to a visual target influenced the response to and the representation of targets in the FEF. We recorded single unit responses to the onset of the target, during the delay period, and around the time of the movement, on interleaved saccade and reach trials of a delayed-response task. We found that the responses of approximately equal percentages of visual, visuomovement, and movement neurons (50%, 58%, and 58%, respectively) were greater on saccade trials than on reach trials in at least one interval of the delayed-response task. Converse biases, in favor of reaches, were much less frequent (13%, 10%, and 19%, in visual, visuomovement, and movement neurons respectively). Thus, although visual neurons may not be directly involved in triggering saccadic eye movements, they are nonetheless highly saccade-biased, with percentages comparable to neurons that are directly involved in triggering saccadic eye movements.

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# Correlating Stimulus-Specific Adaptation of Cortical Neurons and Local Field Potentials in the Awake Rat

Wolfgang von der Behrens, Peter Bauerle, Manfred Kossel, and Bernhard H. Gaese

Institute for Cell Biology and Neuroscience, Department of Biological Sciences, Goethe University, D-60323 Frankfurt am Main, Germany

Changes in the sensory environment are good indicators for behaviorally relevant events and strong triggers for the reallocation of attention. In the auditory domain, violations of a pattern of repetitive stimuli precipitate in the event-related potentials as mismatch negativity (MMN). Stimulus-specific adaptation (SSA) of single neurons in the auditory cortex has been proposed to be the cellular substrate of MMN (Nelken and Ulanovsky, 2007). However, until now, the existence of SSA in the awake auditory cortex has not been shown. In the present study, we recorded single and multiunits in parallel with evoked local field potentials (eLFPs) in the primary auditory cortex of the awake rat. Both neurons and eLFPs in the awake animal adapted in a stimulus-specific manner, and SSA was controlled by stimulus probability and frequency separation. SSA of isolated units was significant during the first stimulus-evoked “on” response but not in the following inhibition and rebound of activity. The eLFPs exhibited SSA in the first negative deflection and, to a lesser degree, in a slower positive deflection but no MMN. Spike adaptation correlated closely with adaptation of the fast negative deflection but not the positive deflection. Therefore, we conclude that single neurons in the auditory cortex of the awake rat adapt in a stimulus-specific manner and contribute to corresponding changes in eLFP but do not generate a late deviant response component directly equivalent to the human MMN. Nevertheless, the described effect may reflect a certain part of the process needed for sound discrimination.

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# Two Classes of GABAergic Neurons in the Inferior Colliculus

Tetsufumi Ito (伊藤哲史),<sup>1,2</sup> Deborah C. Bishop,<sup>2</sup> and Douglas L. Oliver<sup>2</sup>

<sup>1</sup>Department of Anatomy, Faculty of Medical Sciences, University of Fukui, Fukui 910-1193, Japan, and <sup>2</sup>Department of Neuroscience, University of Connecticut Health Center, Farmington, Connecticut 06030-3401

The inferior colliculus (IC) is unique, having both glutamatergic and GABAergic projections ascending to the thalamus. Although subpopulations of GABAergic neurons in the IC have been proposed, criteria to distinguish them have been elusive and specific types have not been associated with specific neural circuits. Recently, the largest IC neurons were found to be recipients of somatic terminals containing vesicular glutamate transporter 2 (VGLUT2). Here, we show with electron microscopy that VGLUT2-positive (VGLUT2<sup>+</sup>) axonal terminals make axosomatic synapses on IC neurons. These terminals contain only VGLUT2 even though others in the IC have VGLUT1 or both VGLUT1 and 2. We demonstrate that there are two types of GABAergic neurons: larger neurons with VGLUT2<sup>+</sup> axosomatic endings and smaller neurons without such endings. Both types are present in all subdivisions of the IC, but larger GABAergic neurons with VGLUT2<sup>+</sup> axosomatic terminals are most prevalent in the central nucleus. The GABAergic tectothalamic neurons consist almost entirely of the larger cells surrounded by VGLUT2<sup>+</sup> axosomatic endings. Thus, two types of GABAergic neurons in the IC are defined by different synaptic organization and neuronal connections. Larger tectothalamic GABAergic neurons are covered with glutamatergic axosomatic synapses that could allow them to fire rapidly and overcome a slow membrane time constant; their axons may be the largest in the brachium of the IC. Thus, large GABAergic neurons could deliver IPSPs to the medial geniculate body before EPSPs from glutamatergic IC neurons firing simultaneously.

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# Dynamic Encoding of Movement Direction in Motor Cortical Neurons

Jorn Rickert,<sup>1,2</sup> Alexa Riehle,<sup>4</sup> Ad Aertsen,<sup>1,2</sup> Stefan Rotter,<sup>2,3</sup> and Martin P. Nawrot<sup>2,5</sup>

<sup>1</sup>Neurobiology and Biophysics, Faculty of Biology, <sup>2</sup>Bernstein Center for Computational Neuroscience Freiburg, and <sup>3</sup>Computational Neuroscience, Faculty of Biology, Albert Ludwigs University, 79104 Freiburg, Germany, <sup>4</sup>Mediterranean Institute of Cognitive Neuroscience–Centre National de la Recherche Scientifique and University of Aix-Marseille, 13402 Marseille, France, and <sup>5</sup>Neuroinformatics and Theoretical Neuroscience, Institute of Biology, Freie Universitat Berlin, and Bernstein Center for Computational Neuroscience Berlin, 14195 Berlin, Germany

When we perform a skilled movement such as reaching for an object, we can make use of prior information, for example about the location of the object in space. This helps us to prepare the movement, and we gain improved accuracy and speed during movement execution. Here, we investigate how prior information affects the motor cortical representation of movements during preparation and execution. We trained two monkeys in a delayed reaching task and provided a varying degree of prior information about the final target location. We decoded movement direction from multiple single-unit activity recorded from M1 (primary motor cortex) in one monkey and from PMd (dorsal premotor cortex) in a second monkey. Our results demonstrate that motor cortical cells in both areas exhibit individual encoding characteristics that change dynamically in time and dependent on prior information. On the population level, the information about movement direction is at any point in time accurately represented in a neuronal ensemble of time-varying composition. We conclude that movement representation in the motor cortex is not a static one, but one in which neurons dynamically allocate their computational resources to meet the demands defined by the movement task and the context of the movement. Consequently, we find that the decoding accuracy decreases if the precise task time, or the previous information that was available to the monkey, were disregarded in the decoding process. An optimal strategy for the readout of movement parameters from motor cortex should therefore take into account time and contextual parameters.

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# Selective Targeting of the Dendrites of Corticothalamic Cells by Thalamic Afferents in Area 17 of the Cat

Nuno Maçarico da Costa and Kevan A. C. Martin

Institute for Neuroinformatics, University of Zürich and ETH Zürich, 8057 Zürich, Switzerland

Pyramidal cells of layer 6 in cat visual cortex are the source of the corticothalamic projection, and their recurrent collaterals provide substantially more excitatory synapses in layer 4 than does the thalamic input. They have predominantly simple receptive fields and can be driven monosynaptically by electrically stimulating thalamic relay cells. Layer 6 cells could thus provide a significant disynaptic amplification of the thalamic input to layer 4, particularly since their synapses facilitate, unlike the thalamic afferents whose synapses depress. However, purely geometric considerations of the relation of their dendritic trees to the thalamic input indicate that they should form a far smaller number of synapses with thalamic afferents than do the simple cells of layer 4. We thus analyzed quantitatively the thalamic input to identified corticothalamic cells by labeling the thalamic afferents and corticothalamic cells *in vivo*. We made a correlated light and electron microscopic study of 73 “contacts” between thalamic afferents and five corticothalamic cells. The electron microscope revealed that only 24 of the contacts identified at light microscope level were indeed synapses and, contrary to geometric predictions, virtually all were located on spines on the basal dendrites. Our quantitative estimates indicate that the corticothalamic cells form even fewer synapses with the thalamic afferents than predicted by geometric considerations and only 1/10 as many as do the layer 4 simple cells. These data strongly suggest it is the collective computation of cortical neurons, not the monosynaptic thalamic input, that determines the output of the corticothalamic cells.

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# The Nitric Oxide/cGMP Pathway Tunes the Thermosensitivity of Swimming Motor Patterns in *Xenopus laevis* Tadpoles

R. Meldrum Robertson<sup>1,2</sup> and Keith T. Sillar<sup>2</sup>

<sup>1</sup>Department of Biology, Queen’s University, Kingston, Ontario K7L 3N6, Canada, and <sup>2</sup>School of Biology, University of St. Andrews, Fife KY16 9TS, United Kingdom

We investigated the role of the nitric oxide (NO)/cGMP pathway in setting thresholds for failure and recovery during hyperthermic stress of the swimming central pattern generator of immobilized *Xenopus* tadpoles (stage 42). We recorded swimming motor patterns induced by tail skin stimulation (TS) (1 ms current pulse) or by bath application of 50  $\mu$ M NMDA. Swimming rhythm frequency increased in a linear manner with increasing temperature. In the presence of the NO donor *S*-nitroso-*N*-acetylpenicillamine (SNAP), recovery from hyperthermic failure was greatly slowed, often taking longer than the duration of the experiment. Pharmacological activation of the NO/cGMP pathway using SNAP or 8-bromo-cGMP (1) decreased the duration of TS-evoked swim episodes; (2) decreased the temperature threshold for hyperthermic circuit failure; (3) decreased the temperature at which the circuit recovered; and (4) increased the time taken to recover. Pharmacological inhibition of the NO/cGMP pathway using the NO scavenger CPTIO, the nitric oxide synthase (NOS) inhibitor L-NAME or the guanylyl cyclase inhibitor ODQ (1*H*-[1,2,4]oxadiazolo[4,3-*a*]quinoxalin-1-one) had the opposite effects. NMDA rhythms were more resistant to hyperthermic failure than TS-evoked swim episodes, but the effects of SNAP on the temperature sensitivity of swimming evoked by NMDA were similar to those on TS-evoked swimming, suggesting that drug effects occur on central pattern-generating networks rather than sensory pathways. We conclude that the NO/cGMP pathway is involved in setting the threshold temperatures for hyperthermic failure and subsequent recovery of fictive swimming in tadpoles, and we suggest that this is part of a variable response to prevent overexcitation during abiotic stress under different environmental conditions.

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# Decreased Firing of Striatal Neurons Related to Licking during Acquisition and Overtraining of a Licking Task

Chris C. Tang, David H. Root, Dawn C. Duke, Yun Zhu, Kate Teixeira, Sisi Ma, David J. Barker, and Mark O. West

Department of Psychology, Rutgers University, New Brunswick, New Jersey 08903

Neurons that fire in relation to licking, in the ventral part of the dorsolateral striatum (DLS), were studied during acquisition and performance of a licking task in rats for 14 sessions (2 h/d). Task learning was indicated by fewer errors of omission of licking and improved movement efficiency (i.e., shorter lick duration) over sessions. Number of licks did not change over sessions. Overtraining did not result in habit formation, as indicated by similar reductions of licking responses following devaluation by satiety in both early and late sessions. Twenty-nine lick neurons recorded and tracked over sessions exhibited a significant linear decrease in average firing rate across all neurons over sessions, correlating with concurrent declines in lick duration. Individually, most neurons (86%) exhibited decreased firing rates, while a small proportion (14%) exhibited increased firing rates, during lick movements that were matched over sessions. Reward manipulations did not alter firing patterns over sessions. Aside from the absence of habit formation, striatal processing during unconditioned movements (i.e., licking) was characterized by high activity of movement-related neurons during early performance and decreased activity of the same neurons during overtraining, similar to our previous report of head movement neurons during acquired, skilled, instrumental head movements that ultimately became habitual (Tang et al., 2007). Decreased activity in DLS neurons may reflect a common neural mechanism underlying improvement in movement efficiency with overtraining. Nonetheless, the decreased striatal firing in relation to a movement that did not become habitual demonstrates that not all DLS changes reflect habit formation.

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# Stimulus-Induced and State-Dependent Sustained Gamma Activity Is Tightly Coupled to the Hemodynamic Response in Humans

Stefan P. Koch,<sup>1</sup> Peter Werner,<sup>1</sup> Jens Steinbrink,<sup>1</sup> Pascal Fries,<sup>2</sup> and Hellmuth Obrig<sup>1,3</sup>

<sup>1</sup>Berlin NeuroImaging Center, Charité–Universitätsmedizin Berlin, 10117 Berlin, Germany, <sup>2</sup>Donders Institute for Brain, Cognition, and Behaviour, Radboud University Nijmegen, 6500 HB Nijmegen, The Netherlands, and <sup>3</sup>Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, and Day Clinic of Cognitive Neurology, University of Leipzig, 04103 Leipzig, Germany

A prompt behavioral response to a stimulus depends both on the salience of the stimulus as well as the subject's preparedness. Thus, both stimulus properties and cognitive factors, such as attention, may determine the strength of neuronal synchronization in the gamma range. For a comprehensive investigation of stimulus–response processing through noninvasive imaging, it is, however, a crucial issue whether both kinds of gamma modulation elicit a hemodynamic response. Here, we show that, in the human visual cortex, stimulus strength and internal state modulate sustained gamma activity and hemodynamic response in close correspondence. When participants reported velocity changes of gratings varying in contrast, gamma activity (35–70 Hz) increased systematically with contrast. For stimuli of constant contrast, the amplitude of gamma activity before the behaviorally relevant velocity change was inversely correlated to the behavioral response latency. This indicates that gamma activity also reflects an overall attentive state. For both sources of variance, gamma activity was tightly coupled to the hemodynamic response measured through optical topography. Because of the close relationship between high-frequency neuronal activity and the hemodynamic signal, we conclude that both stimulus-induced and state-dependent gamma activity trigger a metabolic demand and are amenable to vascular-based imaging.

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## Decoding and Reconstructing Color from Responses in Human Visual Cortex

Gijs Joost Brouwer and David J. Heeger

Department of Psychology and Center for Neural Science, New York University, New York, New York 10003

How is color represented by spatially distributed patterns of activity in visual cortex? Functional magnetic resonance imaging responses to several stimulus colors were analyzed with multivariate techniques: conventional pattern classification, a forward model of idealized color tuning, and principal component analysis (PCA). Stimulus color was accurately decoded from activity in V1, V2, V3, V4, and V01 but not L01, L02, V3A/B, or MT+. The conventional classifier and forward model yielded similar accuracies, but the forward model (unlike the classifier) also reliably reconstructed novel stimulus colors not used to train (specify parameters of) the model. The mean responses, averaged across voxels in each visual area, were not reliably distinguishable for the different stimulus colors. Hence, each stimulus color was associated with a unique spatially distributed pattern of activity, presumably reflecting the color selectivity of cortical neurons. Using PCA, a color space was derived from the covariation, across voxels, in the responses to different colors. In V4 and V01, the first two principal component scores (main source of variation) of the responses revealed a progression through perceptual color space, with perceptually similar colors evoking the most similar responses. This was not the case for any of the other visual cortical areas, including V1, although decoding was most accurate in V1. This dissociation implies a transformation from the color representation in V1 to reflect perceptual color space in V4 and V01.

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## Range-Adapting Representation of Economic Value in the Orbitofrontal Cortex

Camillo Padoa-Schioppa

Department of Anatomy and Neurobiology, Washington University in St. Louis, St. Louis, Missouri 63110, and Department of Neurobiology, Harvard University, Boston, Massachusetts 02115

While making economic choices, individuals assign subjective values to the available options. Values computed in different behavioral conditions, however, can vary substantially. The same person might choose some times between goods worth a few dollars, and other times between goods worth thousands of dollars, or more. How does the brain system that computes values—the “valuation system”—handle this large variability? Here we show that the representation of value in the orbitofrontal cortex (OFC), an area implicated in value assignment during economic choice, adapts to the behavioral condition of choice and, more specifically, to the range of values available in any given condition. In the experiments, monkeys chose between different juices and their choice patterns provided a measure of subjective value. Value ranges were varied from session to session and, in each session, OFC neurons encoded values in a linear way. Across the population, the neuronal sensitivity (defined as the change in neuronal activity elicited by the increase in one value unit) was inversely proportional to the value range. Conversely, the neuronal activity range did not depend on the value range. This phenomenon of range adaptation complements that of menu invariance observed in a previous study. Indeed, the activity of each neuron adapts to the range values it encodes but does not depend on other available goods. Our results thus suggest that the representation of value in the OFC is at one time instantiative of preference transitivity (menu invariance) and computationally efficient (range adaptation).

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# Enduring Reversal of Neuropathic Pain by a Single Intrathecal Injection of Adenosine 2A Receptor Agonists: A Novel Therapy for Neuropathic Pain

Lisa C. Loram,<sup>1</sup> Jacqueline A. Harrison,<sup>1</sup> Evan M. Sloane,<sup>1</sup> Mark R. Hutchinson,<sup>1,2</sup> Paige Sholar,<sup>1</sup> Frederick R. Taylor,<sup>1</sup> Debra Berkelhammer,<sup>1</sup> Benjamin D. Coats,<sup>1</sup> Stephen Poole,<sup>3</sup> Erin D. Milligan,<sup>1,4</sup> Steven F. Maier,<sup>1</sup> Jayson Rieger,<sup>5</sup> and Linda R. Watkins<sup>1</sup>

<sup>1</sup>Department of Psychology and Center for Neurosciences, University of Colorado at Boulder, Boulder, Colorado 80309-0345, <sup>2</sup>Discipline of Pharmacology, School of Medical Sciences, University of Adelaide, Adelaide, South Australia 5005, Australia, <sup>3</sup>National Institute of Biological Standards and Control, Potters Bar, South Mimms, Hertfordshire EN6 3QG, United Kingdom, <sup>4</sup>Department of Neurosciences, University of New Mexico, Albuquerque, New Mexico 87131, and <sup>5</sup>PGxHealth, A Division of Clinical Data, Inc., Charlottesville, Virginia 22902

Previous studies of peripheral immune cells have documented that activation of adenosine 2A receptors (A<sub>2A</sub>Rs) decrease proinflammatory cytokine release and increase release of the potent anti-inflammatory cytokine, interleukin-10 (IL-10). Given the growing literature supporting that glial proinflammatory cytokines importantly contribute to neuropathic pain and that IL-10 can suppress such pain, we evaluated the effects of intrathecally administered A<sub>2A</sub>R agonists on neuropathic pain using the chronic constriction injury (CCI) model. A single intrathecal injection of the A<sub>2A</sub>R agonists 4-(3-(6-amino-9-(5-cyclopropylcarbamoyl)-3,4-dihydroxytetrahydrofuran-2-yl)-9H-purin-2-yl)prop-2-ynyl)piperidine-1-carboxylic acid methyl ester (ATL313) or 2-*p*-(2-carboxyethyl)phenethylamino-5'-*N*-ethylcarboxamido adenosine HCl (CGS21680), 10–14 d after CCI versus sham surgery, produced a long-duration reversal of mechanical allodynia and thermal hyperalgesia for at least 4 weeks. Neither drug altered the nociceptive responses of sham-operated controls. An A<sub>2A</sub>R antagonist [ZM241385 (4-(2-[7-amino-2-(2-furyl)(1,2,4)triazolo(2,3-*a*)(1,3,5)triazin-5-ylamino]ethyl)phenol)] coadministered intrathecally with ATL313 abolished the action of ATL313 in rats with neuropathy-induced allodynia but had no effect on allodynia in the absence of the A<sub>2A</sub>R agonist. ATL313 attenuated CCI-induced upregulation of spinal cord activation markers for microglia and astrocytes in the L4–L6 spinal cord segments both 1 and 4 weeks after a single intrathecal ATL313 administration. Neutralizing IL-10 antibodies administered intrathecally transiently abolished the effect of ATL313 on neuropathic pain. In addition, IL-10 mRNA was significantly elevated in the CSF cells collected from the lumbar region. Activation of A<sub>2A</sub>Rs after intrathecal administration may be a novel, therapeutic approach for the treatment of neuropathic pain by increasing IL-10 in the immunocompetent cells of the CNS.

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# Visual Learning Shapes the Processing of Complex Movement Stimuli in the Human Brain

Jan Jastorff,<sup>1,2</sup> Zoe Kourtzi,<sup>3,4</sup> and Martin A. Giese<sup>1</sup>

<sup>1</sup>Section for Computational Sensomotrics, Department of Cognitive Neurology, Hertie Institute of Clinical Brain Research and Center for Integrative Neurosciences, University Clinic Tübingen, 72074 Tübingen, Germany, <sup>2</sup>Laboratorium voor Neuro- en Psychofysiologie, Katholieke Universiteit Leuven Medical School, 3000 Leuven, Belgium, <sup>3</sup>Max Planck Institute for Biological Cybernetics, 72026 Tübingen, Germany, and <sup>4</sup>School of Psychology, University of Birmingham, Edgbaston, Birmingham B15 2TT, United Kingdom

Recognition of actions and complex movements is fundamental for social interactions and action understanding. While the relationship between motor expertise and visual recognition of body movements has received a vast amount of interest, the role of visual learning remains largely unexplored. Combining psychophysics and functional magnetic resonance imaging (fMRI) experiments, we investigated neural correlates of visual learning of complex movements. Subjects were trained to visually discriminate between very similar complex movement stimuli generated by motion morphing that were either compatible (experiments 1 and 2) or incompatible (experiment 3) with human movement execution. Employing an fMRI adaptation paradigm as index of discriminability, we scanned human subjects before and after discrimination training. The results of experiment 1 revealed three different effects as a consequence of training: (1) Emerging fMRI-selective adaptation in general motion-related areas (hMT/V5+, KO/V3b) for the differences between human-like movements. (2) Enhanced of fMRI-selective adaptation already present before training in biological motion-related areas (pSTS, FBA). (3) Changes covarying with task difficulty in frontal areas. Moreover, the observed activity changes were specific to the trained movement patterns (experiment 2). The results of experiment 3, testing artificial movement stimuli, were strikingly similar to the results obtained for human movements. General and biological motion-related areas showed movement-specific changes in fMRI-selective adaptation for the differences between the stimuli after training. These results support the existence of a powerful visual machinery for the learning of complex motion patterns that is independent of motor execution. We thus propose a key role of visual learning in action recognition.

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# Sleep Deprivation Differentially Impairs Cognitive Performance in Abstinent Methylenedioxymethamphetamine (“Ecstasy”) Users

Una D. McCann,<sup>1</sup> Michael J. Wilson,<sup>2</sup> Francis P. Sgambati,<sup>1</sup> and George A. Ricaurte<sup>2</sup>

Departments of <sup>1</sup>Psychiatry and <sup>2</sup>Neurology, The Johns Hopkins School of Medicine, Baltimore, Maryland 21224

Methylenedioxymethamphetamine (MDMA; “Ecstasy”) is a popular recreational drug and brain serotonin (5-HT) neurotoxin. Neuroimaging data indicate that some human MDMA users develop persistent deficits in brain 5-HT neuronal markers. Although the consequences of MDMA-induced 5-HT neurotoxicity are not fully understood, abstinent MDMA users have been found to have subtle cognitive deficits and altered sleep architecture. The present study sought to test the hypothesis that sleep disturbance plays a role in cognitive deficits in MDMA users. Nineteen abstinent MDMA users and 21 control subjects participated in a 5 d inpatient study in a clinical research unit. Baseline sleep quality was measured using the Pittsburgh Sleep Quality Inventory. Cognitive performance was tested three times daily using a computerized cognitive battery. On the third day of admission, subjects began a 40 h sleep deprivation period and continued cognitive testing using the same daily schedule. At baseline, MDMA users performed less accurately than controls on a task of working memory and more impulsively on four of the seven computerized tests. During sleep deprivation,

MDMA users, but not controls, became increasingly impulsive, performing more rapidly at the expense of accuracy on tasks of working and short-term memory. Tests of mediation implicated baseline sleep disturbance in the cognitive decline seen during sleep deprivation. These findings are the first to demonstrate that memory problems in MDMA users may be related, at least in part, to sleep disturbance and suggest that cognitive deficits in MDMA users may become more prominent in situations associated with sleep deprivation.

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## NEUROBIOLOGY OF DISEASE

# A Nanomedicine Transports a Peptide Caspase-3 Inhibitor across the Blood–Brain Barrier and Provides Neuroprotection

Hulya Karatas,<sup>1</sup> Yesim Aktas,<sup>2</sup> Yasemin GURSOY-OZDEMIR,<sup>1</sup> Ebru Bodur,<sup>3</sup> Muge Yemisci,<sup>1</sup> Secil Caban,<sup>2</sup> Atay Vural,<sup>1</sup> Onur Pinarbasli,<sup>2</sup> Yilmaz Capan,<sup>2</sup> Eduardo Fernandez-Megia,<sup>4</sup> Ramon Novoa-Carballal,<sup>4</sup> Ricardo Riguera,<sup>4</sup> Karine Andrieux,<sup>5</sup> Patrick Couvreur,<sup>5</sup> and Turgay Dalkara<sup>1</sup>

<sup>1</sup>Department of Neurology, Faculty of Medicine and Institute of Neurological Sciences and Psychiatry, <sup>2</sup>Department of Pharmaceutical Technology, Faculty of Pharmacy, and <sup>3</sup>Department of Biochemistry, Faculty of Medicine, Hacettepe University, 06100 Ankara, Turkey, <sup>4</sup>Departamento de Química Orgánica, Facultad de Química, and Unidad de Resonancia Magnética Nuclear de Biomoléculas Asociada al Consejo Superior de Investigaciones Científicas, Universidad de Santiago de Compostela, 15782 Santiago de Compostela, Spain, and <sup>5</sup>Physico-Chimie, Pharmacotechnie, Biopharmacie, Faculté de Pharmacie, Université Paris Sud, UMR Centre National de la Recherche Scientifique 8612, 92296 Chatenay Malabry, France

Caspases play an important role as mediators of cell death in acute and chronic neurological disorders. Although peptide inhibitors of caspases provide neuroprotection, they have to be administered intracerebroventricularly because they cannot cross the blood–brain barrier (BBB). Herein, we present a nanocarrier system that can transfer chitosan nanospheres loaded with *N*-benzyloxycarbonyl-Asp(OMe)-Glu(OMe)-Val-Asp(OMe)-fluoromethyl ketone (Z-DEVD-FMK), a relatively specific caspase-3 inhibitor, across BBB. Caspase-3 was chosen as a pharmacological target because of its central role in cell death. Polyethylene glycol-coated nanospheres were conjugated to an anti-mouse transferrin receptor monoclonal antibody (TfRMAB) that selectively recognizes the TfR type 1 on the cerebral vasculature. We demonstrate with intravital microscopy that this nanomedicine is rapidly transported across the BBB without being measurably taken up by liver and spleen. Pre- or post-treatment (2 h) with intravenously injected Z-DEVD-FMK-loaded nanospheres dose dependently decreased the infarct volume, neurological deficit, and ischemia-induced caspase-3 activity in mice subjected to 2 h of MCA occlusion and 24 h of reperfusion, suggesting that they released an amount of peptide sufficient to inhibit caspase activity. Similarly, nanospheres inhibited physiological caspase-3 activity during development in the neonatal mouse cerebellum on postnatal day 17 after closure of the BBB. Neither nanospheres functionalized with TfRMAB but not loaded with Z-DEVD-FMK nor nanospheres lacking TfRMAB but loaded with Z-DEVD-FMK had any effect on either paradigm, suggesting that inhibition of caspase activity and subsequent neuroprotection were due to efficient penetration of the peptide into brain. Thus, chitosan nanospheres open new and exciting opportunities for brain delivery of biologically active peptides that are useful for the treatment of CNS disorders.

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# Estrogen Attenuates Ischemic Oxidative Damage via an Estrogen Receptor $\alpha$ -Mediated Inhibition of NADPH Oxidase Activation

Quan-Guang Zhang,<sup>1\*</sup> Limor Raz,<sup>1\*</sup> Ruimin Wang,<sup>2\*</sup> Dong Han,<sup>1</sup> Liesl De Sevilla,<sup>1</sup> Fang Yang,<sup>2</sup> Ratna K. Vadlamudi,<sup>3</sup> and Darrell W. Brann<sup>1</sup>

<sup>1</sup>Developmental Neurobiology Program, Institute of Molecular Medicine and Genetics, and Department of Neurology, Medical College of Georgia, Augusta, Georgia 30912, <sup>2</sup>Research Center for Molecular Biology, North China Coal Medical University, Tangshan 063000, China, and <sup>3</sup>Department of Obstetrics and Gynecology, University of Texas Health Science Center at San Antonio, San Antonio, Texas 78229

The goal of this study was to elucidate the mechanisms of  $17\beta$ -estradiol ( $E_2$ ) antioxidant and neuroprotective actions in stroke. The results reveal a novel extranuclear receptor-mediated antioxidant mechanism for  $E_2$  during stroke, as well as a hypersensitivity of the CA3/CA4 region to ischemic injury after prolonged hypoestrogenicity.  $E_2$  neuroprotection was shown to involve a profound attenuation of NADPH oxidase activation and superoxide production in hippocampal CA1 pyramidal neurons after stroke, an effect mediated by extranuclear estrogen receptor  $\alpha$  (ER $\alpha$ )-mediated nongenomic signaling, involving Akt activation and subsequent phosphorylation/inactivation of Rac1, a factor critical for activation of NOX2 NADPH oxidase. Intriguingly,  $E_2$  nongenomic signaling, antioxidant action, and neuroprotection in the CA1 region were lost after long-term  $E_2$  deprivation, and this loss was tissue specific because the uterus remained responsive to  $E_2$ . Correspondingly, a remarkable loss of ER $\alpha$ , but not ER $\beta$ , was observed in the CA1 after long-term  $E_2$  deprivation, with no change observed in the uterus. As a whole, the study reveals a novel, membrane-mediated antioxidant mechanism in neurons by  $E_2$  provides support and mechanistic insights for a “critical period” of  $E_2$  replacement in the hippocampus and demonstrates a heretofore unknown hypersensitivity of the CA3/CA4 to ischemic injury after prolonged hypoestrogenicity.

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# Reticulon-4A (Nogo-A) Redistributes Protein Disulfide Isomerase to Protect Mice from SOD1-Dependent Amyotrophic Lateral Sclerosis

Yvonne S. Yang,\* Noam Y. Harel,\* and Stephen M. Strittmatter

Program in Cellular Neuroscience, Neurodegeneration, and Repair, Yale University School of Medicine, New Haven, Connecticut 06510

Amyotrophic lateral sclerosis (ALS) is a fatal motor neuron disease inherited in a small subset of patients. The SOD1(G93A) transgenic mouse models this subset of patients, and studies of this strain have suggested that endoplasmic reticulum (ER) stress and deficits in ER chaperone function are contributors to ALS pathophysiology. Here, we demonstrate that the reticulon family of proteins is a novel regulator of the ER chaperone protein disulfide isomerase (PDI), and that through PDI, reticulon-4A (Nogo-A) can protect mice against the neurodegeneration that characterizes ALS. We show that overexpressing reticulon protein induces a punctate redistribution of PDI intracellularly, both *in vitro* and *in vivo*. Conversely, reduction of endogenous NogoA expression causes a more homogeneous expression pattern *in vivo*. These effects occur without induction of the unfolded protein response. To examine the effect of PDI redistribution on ALS disease progression, we conducted survival and behavior studies of SOD1(G93A) mice. Deletion of a single copy of the NogoA,B gene accelerates disease onset and progression, while deletion of both copies further worsens disease. We conclude that NogoA contributes to the proper function of the ER resident chaperone PDI, and is protective against ALS-like neurodegeneration. Our results provide a novel intracellular role for reticulon proteins and support the hypothesis that modulation of PDI function is a potential therapeutic approach to ALS.

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# Main Immunogenic Region Structure Promotes Binding of Conformation-Dependent Myasthenia Gravis Autoantibodies, Nicotinic Acetylcholine Receptor Conformation Maturation, and Agonist Sensitivity

Jie Luo,<sup>1</sup> Palmer Taylor,<sup>2</sup> Mario Losen,<sup>3</sup> Marc H. de Baets,<sup>3</sup> G. Diane Shelton,<sup>4</sup> and Jon Lindstrom<sup>1</sup>

<sup>1</sup>Department of Neuroscience, University of Pennsylvania Medical School, Philadelphia, Pennsylvania 19104-6074, <sup>2</sup>Department of Pharmacology, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California, San Diego, La Jolla, California 92093-0650, <sup>3</sup>Neuroimmunology Group, Department of Neuroscience, School of Mental Health and Neuroscience, Maastricht University, 6200 MD Maastricht, The Netherlands, and <sup>4</sup>Department of Pathology, School of Medicine, University of California, San Diego, La Jolla, California 92093-0709

The main immunogenic region (MIR) is a conformation-dependent region at the extracellular apex of  $\alpha 1$  subunits of muscle nicotinic acetylcholine receptor (AChR) that is the target of half or more of the autoantibodies to muscle AChRs in human myasthenia gravis and rat experimental autoimmune myasthenia gravis. By making chimeras of human  $\alpha 1$  subunits with  $\alpha 7$  subunits, both MIR epitopes recognized by rat mAbs and by the patient-derived human mAb 637 to the MIR were determined to consist of two discontinuous sequences, which are adjacent only in the native conformation. The MIR, including loop  $\alpha 1$  67–76 in combination with the N-terminal  $\alpha$  helix  $\alpha 1$  1–14, conferred high-affinity binding for most rat mAbs to the MIR. However, an additional sequence corresponding to  $\alpha 1$  15–32 was required for high-affinity binding of human mAb 637. A water soluble chimera of *Aplysia* acetylcholine binding protein with the same  $\alpha 1$  MIR sequences substituted was recognized by a majority of human, feline, and canine myasthenia gravis sera. The presence of the  $\alpha 1$  MIR sequences in  $\alpha 1/\alpha 7$  chimeras greatly promoted AChR expression and significantly altered the sensitivity to activation. This reveals a structural and functional, as well as antigenic, significance of the MIR.

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# Phosphorylation of Ezrin/Radixin/Moesin Proteins by LRRK2 Promotes the Rearrangement of Actin Cytoskeleton in Neuronal Morphogenesis

Loukia Parisiadou,<sup>1</sup> Chengsong Xie,<sup>1</sup> Hyun Jin Cho,<sup>1</sup> Xian Lin,<sup>1</sup> Xing-Long Gu,<sup>1</sup> Cai-Xia Long,<sup>1</sup> Evy Lobbsteal,<sup>2</sup> Veerle Baekelandt,<sup>2</sup> Jean-Marc Taymans,<sup>2</sup> Lixin Sun,<sup>1</sup> and Huaibin Cai<sup>1</sup>

<sup>1</sup>Unit of Transgenesis, Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, Maryland 20892, and <sup>2</sup>Laboratory for Neurobiology and Gene Therapy, Division of Molecular Medicine, Department of Molecular and Cellular Medicine, Faculty of Medicine, Katholieke Universiteit Leuven, B-3000 Leuven, Belgium

Leucine-rich repeat kinase 2 (LRRK2) functions as a putative protein kinase of ezrin, radixin, and moesin (ERM) family proteins. A Parkinson's disease-related G2019S substitution in the kinase domain of LRRK2 further enhances the phosphorylation of ERM proteins. The phosphorylated ERM (pERM) proteins are restricted to the filopodia of growing neurites in which they tether filamentous actin (F-actin) to the cytoplasmic membrane and regulate the dynamics of filopodia protrusion. Here, we show that, in cultured neurons derived from *LRRK2* G2019S transgenic mice, the number of pERM-positive and F-actin-enriched filopodia was significantly increased, and this correlates with the retardation of neurite outgrowth. Conversely, deletion of *LRRK2*, which lowered the pERM and F-actin contents in filopodia, promoted neurite outgrowth. Furthermore, inhibition of ERM phosphorylation or actin polymerization rescued the G2019S-dependent neuronal growth defects. These data support a model in which the G2019S mutation of *LRRK2* causes a gain-of-function effect that perturbs the homeostasis of pERM and F-actin in sprouting neurites critical for neuronal morphogenesis.

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