

This Week in The Journal

● Cellular/Molecular

Lysosomal Proteolysis and Autophagy Do Not Require Presenilins

Xulun Zhang, Krassimira Garbett, Karthikeyan Veeraraghavalu, Brian Wilburn, Reid Gilmore, et al.

(see pages 8633–8648)

Mutations in genes for presenilins (PS1 and PS2) lead to early-onset familial Alzheimer's disease (FAD). It was recently shown that PS1 is required for macroautophagy in mouse blastocysts, and lysosomal proteolysis was proposed as a potential therapeutic target in FAD. Zhang et al. have meticulously tested that hypothesis and found it flawed. The previous work asserted that in cells lacking PS1 (PS1ko-ES), the proton-translocating V0a1 subunit of the vacuolar (H⁺)-ATPase failed to mature and transport to the lysosome; that lysosomes failed to acidify; and that macroautophagy was impaired compared to normal cells. In contrast, Zhang et al. report that vesicular pH and V0a1 maturation and processing were indistinguishable in wild-type and PS1-null cells and brains, and that autophagic processes were robustly intact. Transcriptome analysis, however, showed that gene expression in the Coordinated Lysosomal Expression and Regulation (CLEAR) network was affected by PS1, hinting at a role for PS1 in lysosome biogenesis.

▲ Development/Plasticity/Repair

Transcription Factors Drive Distinct Neural Circuit Proteins

Zhen Guo, Congling Zhao, Menggui Huang, Tianwen Huang, Mingran Fan, et al.

(see pages 8509–8520)

Neurons of the dorsal spinal cord are critical gatekeepers in somatosensory processing, particularly for pain and itch. In addition to receiving both central and peripheral inputs, these neurons are subject to intraspinal modulation by cross talk.

Communication within neuronal circuits depends on the expression of transmitters and peptides and their receptors in complementary sets of neurons. Guo et al. have made gains toward understanding these spinal circuits by cataloging the expression patterns of 78 signal and receptor genes by *in situ* hybridization. The transcription factors *Tlx1/3* and *Ptf1a* fall into a class called “selector genes,” which promote expression of one set of genes while suppressing another, thereby driving cell fate. Whereas *Tlx1/3* directs excitatory glutamatergic neuron differentiation, *Ptf1a* drives the development of GABAergic cells. In addition, the authors now show, these transcription factors direct the expression of a host of modulatory receptor subunits in their respective cell sets by distinct mechanisms.

■ Behavioral/Systems/Cognitive

Scan Reveals Genes of White Matter Integrity and Intelligence

Ming-Chang Chiang, Marina Barysheva, Katie L. McMahon, Greig I. de Zubicaray, Kori Johnson, et al.

(see pages 8732–8745)

The search for genes that affect human intelligence—or even behavior—has been stymied by the sheer magnitude of the task. Chiang et al. have developed a novel approach using diffusion tensor imaging (DTI) and genome-wide scanning in 472 twins and their non-twin siblings. By taking this global approach, they identified genes that clustered into coexpression networks to influence brain connectivity. DTI provides a measure of fractional anisotropy (FA), an estimate of white matter integrity. Through their genome scanning, the authors identified pairs of single nucleotide polymorphisms (SNPs)—and ultimately a SNP network—that influenced FA throughout the brain. Genes at the “hubs” of this network critically influenced brain function in very basic ways, like mediating neuronal development and excitability. Perhaps most intriguing, these same genes also influenced

human intelligence quotient. The network approach allowed identification of these genes that individually have only very small effects on intelligence.

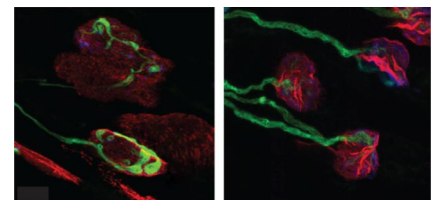
◆ Neurobiology of Disease

Smn Has Important Roles in Both Muscle and Motor Neurons

Tara L. Martinez, Lingling Kong, Xueyong Wang, Melissa A. Osborne, Melissa E. Crowder, et al.

(see pages 8703–8715)

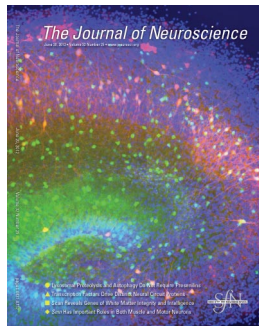
Spinal muscular atrophy (SMA) is characterized by profound muscle weakness, culminating in death. It arises from a homozygous mutation in the gene “survival motor neuron” (*Smn*), which, despite its name, encodes a ubiquitously expressed RNA-processing protein. A mouse model of SMA expresses very low levels of full-length SMN. To address the various roles of SMN, Martinez et al. used mice in which a Cre-inducible *Smn* allele was expressed under the control of promoters specific to either motor neurons or muscle cells. Synaptic integrity and function at both peripheral and central synapses hinged on SMN expression in motor neurons alone, but the protein appeared to have distinct roles at either end of the cell. Interestingly, SMN expression in muscle increased fiber size and survival independent of synaptic function at the neuromuscular junction. The report makes strides toward identifying therapeutic targets in motor neurons, but it also indicates that muscle targets should not be excluded.



In mice lacking *Smn* (left), neurofilament (green) accumulates in presynaptic terminals (blue) at neuromuscular junctions (red), which are partially denervated. Restoring *Smn* expression exclusively in motor neurons (right) rescues this phenotype. See the article by Martinez et al. for details.

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Cover legend: A coronal slice of mouse hippocampus that was cultured *in vitro* for 14 d. GFP (green) marks all interneurons expressing glutamic acid decarboxylase 67 (GAD67). Staining against parvalbumin is red and nuclei are labeled with DAPI (blue). Activity deprivation for 2 d with tetrodotoxin reduces the expression of GAD67 and GFP reporter. For more information, see the article by Lau and Murthy (pages 8521–8531).

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Distinct Sensory Requirements for Unimodal and Cross-Modal Homeostatic Synaptic Plasticity

Kaiwen He,^{1,2} Emily Petrus,^{1,2} Nicholas Gammon,^{1,2} and Hey-Kyoung Lee^{1,2}

¹The Solomon H. Snyder Department of Neuroscience, Zanvyl-Krieger Mind/Brain Institute, Johns Hopkins University, Baltimore, Maryland 21218 and

²Department of Biology, University of Maryland, College Park, Maryland 20742

Loss of a sensory modality elicits both unimodal changes in the deprived cortex and cross-modal alterations in the remaining sensory systems. Unimodal changes are proposed to recruit the deprived cortex for processing the remaining senses, while cross-modal changes are thought to refine processing of spared senses. Hence coordinated unimodal and cross-modal changes are likely beneficial. Despite this expectation, we report in mice that losing behaviorally relevant patterned vision is sufficient to trigger cross-modal synaptic changes in the primary somatosensory cortex barrel fields, but is insufficient to drive unimodal synaptic plasticity in visual cortex (V1), which requires a complete loss of visual activity. In addition, cross-modal changes depend on whisker inputs. Our results demonstrate that unimodal and cross-modal synaptic plasticity occur independently of each other and rely on distinct sensory requirements.

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Cannabinoid Receptor-Mediated Regulation of Neuronal Activity and Signaling in Glomeruli of the Main Olfactory Bulb

Ze-Jun Wang, Liqin Sun, and Thomas Heinbockel

Department of Anatomy, Howard University College of Medicine, Washington, DC 20059

Cannabinoid receptors (CB1Rs) are present in glomeruli of the main olfactory bulb. The functions of CB1Rs and their endogenous activators, endocannabinoids, for glomerular signaling are unknown. Glomeruli contain at least three types of neurons: periglomerular (PG), external tufted (ET), and short-axon (SA) cells. PG cells form inhibitory GABAergic dendrodendritic synapses with ET cells. ET cells form excitatory glutamatergic dendrodendritic synapses with PG and SA cells. In mouse brain slices, we used whole-cell patch-clamp recordings to study the role of CB1Rs in regulating PG and ET cells. Cannabinoids displayed strong, direct inhibitory effects on PG cells and weak effects on ET cells. Single pulses or a train of pulses of depolarizing current injected into an ET cell evoked suppression of IPSCs. This suggests retrograde endocannabinoid signaling, namely, depolarization-induced suppression of inhibition (DSI) in ET cells. Our results support the hypothesis that burst firing of ET cells triggers the release of endocannabinoids which in turn directly inhibit PG cells and reduce GABA release from PG cells. This, in turn, can result in a transient reduction of PG cell inhibitory input to ET cells.

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Differing Semaphorin 3A Concentrations Trigger Distinct Signaling Mechanisms in Growth Cone Collapse

Richard P. C. Manns, Geoffrey M. W. Cook, Christine E. Holt, and Roger J. Keynes

Department of Physiology, Development, and Neuroscience, University of Cambridge, Cambridge CB2 3DY, United Kingdom

Semaphorin-3A (Sema3A) is a major guidance cue in the developing nervous system. Previous studies have revealed a dependence of responses to Sema3A on local protein synthesis (PS) in axonal growth cones, but a recent study has called this dependence into question. To understand the basis of this discrepancy we used the growth cone collapse assay on chick dorsal root ganglion neurons. We show that the dependence of growth cone collapse on protein synthesis varies according to Sema3A concentration, from near-total at low concentration (<100 ng/ml) to minimal at high concentration (>625 ng/ml). Further, we show that neuropilin-1 (NP-1) mediates both PS-dependent and PS-independent collapse. Our findings are consistent with the operation of at least two distinct Sema3A signaling pathways: one that is PS-dependent, involving mammalian target of rapamycin, and one that is PS-independent, involving GSK-3 β activation and operative at all concentrations of Sema3A examined. The results provide a plausible explanation for the discrepancy in PS-dependence reported in the literature, and indicate that different signaling pathways activated within growth cones can be modulated by changing the concentration of the same guidance cue.

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Eye Proprioception Used for Visual Localization Only If in Conflict with the Oculomotor Plan

Daniela Balslev,^{1,2} Marc Himmelbach,¹ Hans-Otto Karnath,¹ Svenja Borchers,¹ and Bartholomaeus Odoj^{1,2}

¹Center of Neurology, Division of Neuropsychology, Hertie Institute for Clinical Brain Research, University of Tuebingen, 72076 Tuebingen, Germany, and

²Department of Psychology, University of Copenhagen, DK-1353 Copenhagen, Denmark

Both the corollary discharge of the oculomotor command and eye muscle proprioception provide eye position information to the brain. Two contradictory models have been suggested about how these two sources contribute to visual localization: (1) only the efference copy is used whereas proprioception is a slow recalibrator of the forward model, and (2) both signals are used together as a weighted average. We had the opportunity to test these hypotheses in a patient (R.W.) with a circumscribed lesion of the right postcentral gyrus that overlapped the human eye proprioceptive representation. R.W. was as accurate and precise as the control group ($n = 19$) in locating a lit LED that she viewed through the eye contralateral to the lesion. However, when the task was preceded by a brief (<1 s), gentle push to the closed eye, which perturbed eye position

and stimulated eye proprioceptors in the absence of a motor command, R.W.'s accuracy significantly decreased compared with both her own baseline and the healthy control group. The data suggest that in normal conditions, eye proprioception is not used for visual localization. Eye proprioception is, however, continuously monitored to be incorporated into the eye position estimate when a mismatch with the efference copy of the motor command is detected. Our result thus supports the first model and, furthermore, identifies the limits for its operation.

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Rat Claustrum Coordinates But Does Not Integrate Somatosensory and Motor Cortical Information

Jared B. Smith, Harsha Radhakrishnan, and Kevin D. Alloway

Department of Neural and Behavioral Sciences, Center for Neural Engineering, Pennsylvania State University, University Park, Pennsylvania 16802

The function of the claustrum is a fundamental issue in neuroscience. Anatomical data indicate that the rat claustrum is part of an interhemispheric circuit that could be involved in the bilateral coordination of whisker movements. Given that whisking is a somesthetic-guided motor behavior, the goal of the current study was to elucidate the connections of the claustrum with respect to the whisker representations in the primary somatosensory (wSI) and motor (wMI) cortical areas. Anterograde tracer injections showed that wMI projects most densely to the claustrum in the contralateral hemisphere, whereas wSI does not project to the claustrum in either hemisphere. Injections of different retrograde tracers into wMI and wSI of the same animal revealed intermingled populations of labeled neurons in the claustrum, as well as many double-labeled neurons. This indicates that the same part of the claustrum projects to the whisker representations in both SI and MI. Finally, injections of different anterograde tracers in the wMI regions of both hemispheres were combined with a retrograde tracer injection in wSI, and this produced dense terminal labeling around retrogradely labeled neurons in the claustrum of both hemispheres. Although the rodent claustrum is probably involved in the interhemispheric coordination of the MI and SI whisker representations, it does not receive inputs from both of these cortical regions. Hence, the claustrum should not be universally regarded as an integrator of somesthetic and motor information.

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NR2B-Dependent Plasticity of Adult-Born Granule Cells is Necessary for Context Discrimination

Mazen A. Kheirbek,^{1,3} Lindsay Tannenholz,^{2,3} and René Hen^{1,2,3}

¹Departments of Neuroscience and Psychiatry and ²Department of Pharmacology, Columbia University, New York, New York 10032, and ³Division of Integrative Neuroscience, The New York State Psychiatric Institute, New York, New York 10032

Adult-generated granule cells (GCs) in the dentate gyrus (DG) exhibit a period of heightened plasticity 4–6 weeks postmitosis. However, the functional contribution of this critical window of plasticity to hippocampal neurogenesis and behavior remains unknown. Here, we show that deletion of NR2B-containing NMDA receptors from adult-born GCs impairs a neurogenesis-dependent form of LTP in the DG and reduces dendritic complexity of adult-born GCs, but does not impact their survival. Mice in which the NR2B-containing NMDA receptor was deleted from adult-born GCs did not differ from controls in baseline anxiety-like behavior or discrimination of very different contexts, but were impaired in discrimination of highly similar contexts. These results indicate that NR2B-dependent plasticity of adult-born GCs is necessary for fine contextual discrimination and is consistent with their proposed role in pattern separation.

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Wnt7A Identifies Embryonic γ -Motor Neurons and Reveals Early Postnatal Dependence of γ -Motor Neurons on a Muscle Spindle-Derived Signal

Soha Ashrafi,^{1,2} Melanie Lalancette-Hébert,³ Andreas Friesse,^{4,5} Markus Sigrist,^{4,5} Silvia Arber,^{4,5} Neil A. Shneider,³ and Julia A. Kaltschmidt^{1,2,6}

¹Neuroscience Program, Weill Cornell Medical College, New York, New York 10065, ²Developmental Biology Program, Sloan-Kettering Institute, New York, New York 10065, ³Department of Neurology, Center for Motor Neuron Biology and Disease, Columbia University, New York, New York 10032, ⁴Biozentrum, Department of Cell Biology, University of Basel, CH-4056 Basel, Switzerland, ⁵Friedrich Miescher Institute for Biomedical Research, CH-4058 Basel, Switzerland, and ⁶Cell and Developmental Biology Program, Weill Cornell Medical College, New York, New York 10065

Motor pools comprise a heterogeneous population of motor neurons that innervate distinct intramuscular targets. While the organization of motor neurons into motor pools has been well described, the time course and mechanism of motor pool diversification into functionally distinct classes remains unclear. γ -Motor neurons (γ -MNs) and α -motor neurons (α -MNs) differ in size, molecular identity, synaptic input and peripheral target. While α -MNs innervate extrafusal skeletal muscle fibers to mediate muscle contraction, γ -MNs innervate intrafusal fibers of the muscle spindle, and regulate sensitivity of the muscle spindle in response to stretch. In this study, we find that the secreted signaling molecule *Wnt7a* is selectively expressed in γ -MNs in the mouse spinal cord by embryonic day 17.5 and continues to molecularly distinguish γ -from α -MNs into the third postnatal week. Our data demonstrate that *Wnt7a* is the earliest known γ -MN marker, supporting a model of developmental divergence between α - and γ -MNs at embryonic stages. Furthermore, using *Wnt7a* expression as an early marker of γ -MN identity, we demonstrate a previously unknown dependence of γ -MNs on a muscle spindle-derived, GDNF-independent signal during the first postnatal week.

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Hyperpolarizing GABAergic Transmission Requires the KCC2 C-Terminal ISO Domain

Brooke A. Acton,¹ Vivek Mahadevan,¹ Adrianna Mercado,^{2,3} Pavel Uvarov,⁴ Yanli Ding,² Jessica Pressey,¹ Matti S. Airaksinen,⁴ David B. Mount,^{2,5} and Melanie A. Woodin¹

¹Department of Cell and Systems Biology, University of Toronto, Toronto, Ontario, Canada M5S 3G5, ²Renal Division, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts 02115, ³Departamento de Nefrología, Instituto Nacional de Cardiología Ignacio Chávez, 14080 Mexico City, Mexico, ⁴Neuroscience Center and Institute of Biomedicine, University of Helsinki, FIN-00014 Helsinki, Finland, and ⁵Renal Division, Veterans Affairs Boston Healthcare System, Harvard Medical School, West Roxbury, Massachusetts 02132

KCC2 is the neuron-specific member of the K^+-Cl^- cotransporter gene family. It is also the only member of its family that is active under physiologically normal conditions, in the absence of osmotic stress. By extruding Cl^- from the neuron under isotonic conditions, this transporter maintains a low concentration of neuronal Cl^- , which is essential for fast inhibitory synaptic transmission by GABA and glycine in the mature nervous system. The other members of this K^+-Cl^- cotransporter gene family are exclusively swelling-activated. Here we demonstrate that a 15 aa region near the end of the C terminus, unique to KCC2 (termed the ISO domain), is required for KCC2 to cotransport K^+ and Cl^- out of the neuron under isotonic conditions. We made this discovery by overexpressing chimeric KCC2-KCC4 cDNA constructs in cultured hippocampal neurons prepared from Sprague Dawley rat embryos and assaying neuronal Cl^- through gramicidin perforated patch-clamp recordings. We found that when neurons had been transfected with a chimeric KCC2 that lacked the unique ISO domain, hyperpolarizing responses to GABA were abolished. This finding indicates that the ISO domain is required for neuronal Cl^- regulation. Furthermore, we discovered that when KCC2 lacks the ISO domain, it still retains swelling-activated transport, which demonstrates that there are exclusive molecular determinants of isotonic and swelling-induced K^+-Cl^- cotransport in neurons.

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Articles

CELLULAR/MOLECULAR

Neuronal Hypoxia Induces Hsp40-Mediated Nuclear Import of Type 3 Deiodinase As an Adaptive Mechanism to Reduce Cellular Metabolism

Sungro Jo,¹ Imre Kalló,^{4,5} Zsuzsanna Bardóczi,⁴ Rafael Arrojo e Drigo,¹ Anikó Zeöld,⁴ Zsolt Liposits,^{4,5} Anthony Oliva,⁴ Vance P. Lemmon,² John L. Bixby,^{2,3} Balázs Gereben,⁴ and Antonio C. Bianco¹

¹Division of Endocrinology, Diabetes and Metabolism, ²Miami Project to Cure Paralysis, Department of Neurological Surgery, and ³Department of Molecular and Cellular Pharmacology, University of Miami Miller School of Medicine, Miami FL 33136, ⁴Department of Endocrine Neurobiology, Institute of Experimental Medicine, Hungarian Academy of Sciences, 1450 Budapest, Hungary, and ⁵Department of Neuroscience, Faculty of Information Technology, Pázmány Péter Catholic University, 1083 Budapest, Hungary

In neurons, the type 3 deiodinase (D3) inactivates thyroid hormone and reduces oxygen consumption, thus creating a state of cell-specific hypothyroidism. Here we show that hypoxia leads to nuclear import of D3 in neurons, without which thyroid hormone signaling and metabolism cannot be reduced. After unilateral hypoxia in the rat brain, D3 protein level is increased predominantly in the nucleus of the neurons in the pyramidal and granular ipsilateral layers, as well as in the hilus of the dentate gyrus of the hippocampal formation. In hippocampal neurons in culture as well as in a human neuroblastoma cell line (SK-N-AS), a 24 h hypoxia period redirects active D3 from the endoplasmic reticulum to the nucleus via the cochaperone Hsp40 pathway. Preventing nuclear D3 import by Hsp40 knockdown resulted in an almost doubling in the thyroid hormone-dependent glycolytic rate and quadrupling the transcription of thyroid hormone target gene *ENPP2*. In contrast, Hsp40 overexpression increased nuclear import of D3 and minimized thyroid hormone effects in cell metabolism. In conclusion, ischemia/hypoxia induces an Hsp40-mediated translocation of D3 to the nucleus, facilitating thyroid hormone inactivation proximal to the thyroid hormone receptors. This adaptation decreases thyroid hormone signaling and may function to reduce ischemia-induced hypoxic brain damage.

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Tonic Inhibition in Principal Cells of the Amygdala: A Central Role for $\alpha 3$ Subunit-Containing GABA_A Receptors

Anne Marowsky,¹ Uwe Rudolph,² Jean-Marc Fritschy,¹ and Michael Arand¹

¹Institute of Pharmacology and Toxicology, University of Zurich, CH-8057 Zurich, Switzerland, and ²Laboratory of Genetic Neuropharmacology, McLean Hospital, Harvard University Medical School, Belmont, Massachusetts 02478

GABAergic inhibition in the amygdala is essential in regulating fear and anxiety. Although fast “phasic” inhibition arising through the activation of postsynaptic GABA_A receptors (GABA_ARs) has been well described in the amygdala, much less is known about extrasynaptic GABA_ARs mediating persistent or tonic inhibition and regulating neuronal excitability. Here, we recorded tonic currents in the basolateral (BLA) nucleus and the lateral (LA) nucleus of the amygdala. While all BLA principal cells expressed a robust GABAergic tonic current, only 70% of LA principal cells showed a tonic current. Immunohistochemical stainings revealed that the $\alpha 3$ GABA_AR subunit is expressed moderately in the LA and strongly throughout the BLA nucleus, where it is located mostly at extrasynaptic sites. In $\alpha 3$ subunit KO mice, tonic currents are significantly reduced in BLA principal cells yet not in LA principal cells. Moreover, the $\alpha 3$ GABA_AR-selective benzodiazepine site agonist and anxiolytic compound TP003 increases tonic

currents and dampens excitability markedly in wild-type BLA principal cells but fails to do so in $\alpha 3$ KO BLA cells. Interneurons of the LA and BLA nuclei also express a tonic current, but TP003-induced potentiation is seen in only a small fraction of these cells, suggesting that primarily other GABA_AR variants underlie tonic inhibition in this cell type. Together, these studies demonstrate that $\alpha 3$ GABA_AR-mediated tonic inhibition is a central component of the inhibitory force in the amygdala and that tonically activated $\alpha 3$ GABA_ARs present an important target for anxiolytic or fear-reducing compounds.

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A Role for Presenilins in Autophagy Revisited: Normal Acidification of Lysosomes in Cells Lacking *PSEN1* and *PSEN2*

Xulun Zhang,¹ Krassimira Garbett,² Karthikeyan Veeraraghavalu,¹ Brian Wilburn,¹ Reid Gilmore,³ Karoly Mirnics,² and Sangram S. Sisodia¹

¹Department of Neurobiology, The University of Chicago, Chicago, Illinois 60637, ²Department of Psychiatry, Vanderbilt University, Nashville, Tennessee 37232, and ³Department of Biochemistry and Molecular Pharmacology, University of Massachusetts Medical School, Worcester, Massachusetts 01605

Presenilins 1 and 2 (PS1 and PS2) are the catalytic subunits of the γ -secretase complex, and genes encoding mutant PS1 and PS2 variants cause familial forms of Alzheimer's disease. Lee et al. (2010) recently reported that loss of PS1 activity lead to impairments in autophagosomal function as a consequence of lysosomal alkalinization, caused by failed maturation of the proton translocating V0a1 subunit of the vacuolar (H⁺)-ATPase and targeting to the lysosome. We have reexamined these issues in mammalian cells and in brains of mice lacking PS (PScdko) and have been unable to find evidence that the turnover of autophagic substrates, vesicle pH, V0a1 maturation, or lysosome function is altered compared with wild-type counterparts. Collectively, our studies fail to document a role for presenilins in regulating cellular autophagosomal function. On the other hand, our transcriptome studies of PScdko mouse brains reveal, for the first time, a role for PS in regulating lysosomal biogenesis.

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A Nociceptive Signaling Role for Neuromedin B

Santosh K. Mishra, Sarah Holzman, and Mark A. Hoon

Molecular Genetics Unit, Laboratory of Sensory Biology, National Institute of Dental and Craniofacial Health, National Institutes of Health, Bethesda MD 20892

Here we used an array-based differential screen to uncover the expression of the neuropeptide neuromedin B (NMB) in the trigeminal ganglia of mice. Double-labeling experiments reveal NMB is expressed in a subset of sensory neurons that colabel with calcitonin gene-related peptide and TRPV1 suggestive of a role for NMB in nociception. Indeed, administration of NMB antagonist greatly attenuates edema and nerve sensitization following stimulation of peripheral nerves with mustard oil, demonstrating that NMB contributes to neurogenic inflammation. Moreover, direct injection of NMB causes local swelling and nociceptive sensitization. Interestingly, we also find that the receptor for NMB is expressed in interneurons in the superficial layers of the dorsal horn. We used NMB-saporin to specifically eliminate NMBR-expressing neurons and determined they are required in responses to noxious heat, but not for reaction to mechanical and pruritic stimuli. Thus, NMB may be a neurotransmitter that is selectively involved in the perception of thermal stimuli.

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Snapin is Critical for Presynaptic Homeostatic Plasticity

Dion K. Dickman, Amy Tong, and Graeme W. Davis

Department of Biochemistry and Biophysics, University of California, San Francisco, San Francisco, California 94158

The molecular mechanisms underlying the homeostatic modulation of presynaptic neurotransmitter release are largely unknown. We have previously used an electrophysiology-based forward genetic screen to assess the function of >400 neuronally expressed genes for a role in the homeostatic control of synaptic transmission at the neuromuscular junction of *Drosophila melanogaster*. This screen identified a critical function for *dysbindin*, a gene linked to schizophrenia in humans (Dickman and Davis, 2009). Biochemical studies in other systems have shown that Snapin interacts with Dysbindin, prompting us to test whether Snapin might be involved in the mechanisms of synaptic homeostasis. Here, we demonstrate that loss of *snapin* blocks the homeostatic modulation of presynaptic vesicle release following inhibition of postsynaptic glutamate receptors. This is true for both the rapid induction of synaptic homeostasis induced by pharmacological inhibition of postsynaptic glutamate receptors, and the long-term expression of synaptic homeostasis induced by the genetic deletion of the muscle-specific *GluRIIA* glutamate receptor subunit. Loss of *snapin* does not alter baseline synaptic transmission, synapse morphology, synapse growth, or the number or density of active zones, indicating that the block of synaptic homeostasis is not a secondary consequence of impaired synapse development. Additional genetic evidence suggests that *snapin* functions in concert with *dysbindin* to modulate vesicle release and possibly homeostatic plasticity. Finally, we provide genetic evidence that the interaction of Snapin with SNAP25, a component of the SNARE complex, is also involved in synaptic homeostasis.

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Tlx1/3 and Ptf1a Control the Expression of Distinct Sets of Transmitter and Peptide Receptor Genes in the Developing Dorsal Spinal Cord

Zhen Guo,¹ Congling Zhao,² Menggui Huang,² Tianwen Huang,² Mingran Fan,² Zhiqin Xie,¹ Ying Chen,¹ Xiaolin Zhao,² Guannan Xia,¹ Junlan Geng,² and Leping Cheng²

¹Institute of Biochemistry and Cell Biology, and ²Institute of Neuroscience and State Key Laboratory of Neuroscience, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, Shanghai 200031, China

Establishing the pattern of expression of transmitters and peptides as well as their receptors in different neuronal types is crucial for understanding the circuitry in various regions of the brain. Previous studies have demonstrated that the transmitter and peptide phenotypes in mouse dorsal spinal cord neurons are determined by the transcription factors *Tlx1/3* and *Ptf1a*. Here we show that these transcription factors also determine the expression of two distinct sets of transmitter and peptide receptor genes in this region. We have screened the expression of 78 receptor genes in the spinal dorsal horn by *in situ* hybridization. We found that receptor genes *Gabra1*, *Gabra5*, *Gabrb2*, *Gria3*, *Grin3a*, *Grin3b*, *Galr1*, and *Npy1r* were preferentially expressed in *Tlx3*-expressing glutamatergic neurons and their derivatives, and deletion of *Tlx1* and *Tlx3* resulted in the loss of expression of these receptor genes. Furthermore, we obtained genetic evidence that *Tlx3* uses distinct pathways to control the expression of receptor genes. We also found that receptor genes *Grm3*, *Grm4*, *Grm5*, *Grik1*, *Grik2*, *Grik3*, and *Sstr2* were mainly expressed in *Pax2*-expressing GABAergic neurons in the spinal dorsal horn, and their expression in this region was abolished or markedly reduced in *Ptf1a* and *Pax2* deletion mutant mice. Together, our studies indicate that *Tlx1/3* and *Ptf1a*, the key transcription factors for fate determination of glutamatergic and GABAergic neurons in the dorsal spinal cord, are also responsible for controlling the expression of two distinct sets of transmitter and peptide receptor genes.

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Activity-Dependent Regulation of Inhibition via GAD67

C. Geoffrey Lau and Venkatesh N. Murthy

Department of Molecular and Cellular Biology and Center for Brain Science, Harvard University, Cambridge, Massachusetts 02138

Persistent alterations in network activity trigger compensatory changes in excitation and inhibition that restore neuronal firing rate to an optimal range. One example of such synaptic homeostasis is the downregulation of inhibitory transmission by chronic inactivity, in part through the reduction of vesicular transmitter content. The enzyme glutamic acid decarboxylase 67 (GAD67) is critical for GABA synthesis, but its involvement in homeostatic plasticity is unclear. We explored the role of GAD67 in activity-dependent synaptic plasticity using a mouse line (*Gad1*^{−/−}) in which GAD67 expression is disrupted by genomic insertion of the green fluorescent protein (GFP). Homozygous deletion of *Gad1* significantly reduced miniature inhibitory postsynaptic current (mIPSC) amplitudes and GABA levels in cultured hippocampal neurons. The fractional block of mIPSC amplitude by a low affinity, competitive GABA_A receptor antagonist was higher in GAD67-lacking neurons, suggesting that GABA concentration in the synaptic cleft is lower in knockout animals. Chronic suppression of activity by the application of tetrodotoxin (TTX) reduced mIPSC amplitudes and the levels of GAD67 and GABA. Moreover, TTX reduced GFP levels in interneurons, suggesting that GAD67 gene expression is a key regulatory target of activity. These *in vitro* experiments were corroborated by *in vivo* studies in which olfactory deprivation reduced mIPSC amplitudes and GFP levels in glomerular neurons in the olfactory bulb. Importantly, TTX-induced downregulation of mIPSC was attenuated in *Gad1*^{−/−} neurons. Altogether, these findings indicate that activity-driven expression of GAD67 critically controls GABA synthesis and, thus, vesicular filling of the transmitter.

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Lack of Brain-Derived Neurotrophic Factor Hampers Inner Hair Cell Synapse Physiology, But Protects against Noise-Induced Hearing Loss

Annalisa Zuccotti,¹ Stephanie Kuhn,² Stuart L. Johnson,² Christoph Franz,¹ Wibke Singer,¹ Dietmar Hecker,³ Hyun-Soon Geisler,¹ Iris Köpschall,¹ Karin Rohbock,¹ Katja Gutsche,⁴ Julia Dlugaczky,³ Bernhard Schick,³ Walter Marcotti,² Lukas Rüttiger,¹ Thomas Schimmang,⁴ and Marlies Knipper¹

¹Department of Otolaryngology, Head and Neck Surgery, Hearing Research Centre Tübingen, Molecular Physiology of Hearing, University of Tübingen, 72076 Tübingen, Germany, ²Department of Biomedical Science, University of Sheffield, S10 2TN, Sheffield, United Kingdom, ³Department of Otorhinolaryngology, Saarland University Hospital, 66421 Homburg/Saar, Germany, ⁴Instituto de Biología y Genética Molecular, Universidad de Valladolid y Consejo Superior de Investigaciones Científicas, 47003 Valladolid, Spain

The precision of sound information transmitted to the brain depends on the transfer characteristics of the inner hair cell (IHC) ribbon synapse and its multiple contacting auditory fibers. We found that brain derived neurotrophic factor (BDNF) differentially influences IHC characteristics in the intact and injured cochlea. Using conditional knock-out mice (BDNF^{Pax2} KO) we found that resting membrane potentials, membrane capacitance and resting linear leak conductance of adult BDNF^{Pax2} KO IHCs showed a normal maturation. Likewise, in BDNF^{Pax2} KO membrane capacitance (ΔC_m) as a function of inward calcium current (I_{Ca}) follows the linear relationship typical for normal adult IHCs. In contrast the maximal ΔC_m , but not the maximal size of the calcium current, was significantly reduced by 45% in basal but not in apical cochlear turns in BDNF^{Pax2} KO IHCs. Maximal ΔC_m correlated with a loss of IHC ribbons in these cochlear turns and a reduced activity of the auditory nerve (auditory brainstem response wave I). Remarkably, a noise-induced loss of IHC ribbons, followed by reduced activity of the auditory nerve and reduced centrally generated wave II and III observed in

control mice, was prevented in equally noise-exposed BDNF^{Pax2} KO mice. Data suggest that BDNF expressed in the cochlea is essential for maintenance of adult IHC transmitter release sites and that BDNF upholds opposing afferents in high-frequency turns and scales them down following noise exposure.
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Disrupted ERK Signaling during Cortical Development Leads to Abnormal Progenitor Proliferation, Neuronal and Network Excitability and Behavior, Modeling Human Neuro-Cardio-Facial-Cutaneous and Related Syndromes

Joanna Pucilowska, Pavel A. Puzerey, J. Colleen Karlo, Roberto F. Galán, and Gary E. Landreth

Department of Neurosciences, Case Western Reserve University, Cleveland, Ohio 44106-4928

Genetic disorders arising from copy number variations in the ERK (extracellular signal-regulated kinase) MAP (mitogen-activated protein) kinases or mutations in their upstream regulators that result in neuro-cardio-facial-cutaneous syndromes are associated with developmental abnormalities, cognitive deficits, and autism. We developed murine models of these disorders by deleting the ERKs at the beginning of neurogenesis and report disrupted cortical progenitor generation and proliferation, which leads to altered cytoarchitecture of the postnatal brain in a gene-dose-dependent manner. We show that these changes are due to ERK-dependent dysregulation of cyclin D1 and p27^{Kip1}, resulting in cell cycle elongation, favoring neurogenic over self-renewing divisions. The precocious neurogenesis causes premature progenitor pool depletion, altering the number and distribution of pyramidal neurons. Importantly, loss of ERK2 alters the intrinsic excitability of cortical neurons and contributes to perturbations in global network activity. These changes are associated with elevated anxiety and impaired working and hippocampal-dependent memory in these mice. This study provides a novel mechanistic insight into the basis of cortical malformation which may provide a potential link to cognitive deficits in individuals with altered ERK activity.

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BEHAVIORAL/SYSTEMS/COGNITIVE

Anterior Prefrontal Cortex Contributes to Action Selection through Tracking of Recent Reward Trends

Christopher K. Kovach,^{1,2*} Nathaniel D. Daw,^{3*} David Rudrauf,⁴ Daniel Tranel,⁴ John P. O'Doherty,¹ and Ralph Adolphs¹

¹Division of Humanities and Social Sciences, California Institute of Technology, Pasadena, California 91125, Departments of ²Neurosurgery and

⁴Neurology, University of Iowa Hospitals and Clinics, Iowa City, Iowa 52242, and ³Center for Neural Science and Department of Psychology, New York University, New York, New York 10003

The functions of prefrontal cortex remain enigmatic, especially for its anterior sectors, putatively ranging from planning to self-initiated behavior, social cognition, task switching, and memory. A predominant current theory regarding the most anterior sector, the frontopolar cortex (FPC), is that it is involved in exploring alternative courses of action, but the detailed causal mechanisms remain unknown. Here we investigated this issue using the lesion method, together with a novel model-based analysis. Eight patients with anterior prefrontal brain lesions including the FPC performed a four-armed bandit task known from neuroimaging studies to activate the FPC. Model-based analyses of learning demonstrated a selective deficit in the ability to extrapolate the most recent trend, despite an intact general ability to learn from past rewards. Whereas both brain-damaged and healthy controls used comparisons between the two most recent choice outcomes to infer trends that influenced their decision about the next choice, the group with anterior prefrontal lesions showed a complete absence of this component and instead based their choice entirely on the cumulative reward history. Given that the FPC is thought to be the most evolutionarily recent expansion of primate prefrontal cortex, we suggest that its function may reflect uniquely human adaptations to select and update models of reward contingency in dynamic environments.

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Predictive Top-Down Integration of Prior Knowledge during Speech Perception

Ediz Sohoglu, Jonathan E. Peelle, Robert P. Carlyon, and Matthew H. Davis

Medical Research Council Cognition and Brain Sciences Unit, Cambridge CB2 7EF, United Kingdom

A striking feature of human perception is that our subjective experience depends not only on sensory information from the environment but also on our prior knowledge or expectations. The precise mechanisms by which sensory information and prior knowledge are integrated remain unclear, with longstanding disagreement concerning whether integration is strictly feedforward or whether higher-level knowledge influences sensory processing through feedback connections. Here we used concurrent EEG and MEG recordings to determine how sensory information and prior knowledge are integrated in the brain during speech perception. We manipulated listeners' prior knowledge of speech content by presenting matching, mismatching, or neutral written text before a degraded (noise-vocoded) spoken word. When speech conformed to prior knowledge, subjective perceptual clarity was enhanced. This enhancement in clarity was associated with a spatiotemporal profile of brain activity uniquely consistent with a feedback process: activity in the inferior frontal gyrus was modulated by prior knowledge before activity in lower-level sensory regions of the superior temporal gyrus. In parallel, we parametrically varied the level of speech degradation, and therefore the amount of sensory detail, so that changes in neural responses attributable to sensory information and prior knowledge could be directly compared. Although sensory detail and prior knowledge both enhanced speech clarity, they had an opposite influence

on the evoked response in the superior temporal gyrus. We argue that these data are best explained within the framework of predictive coding in which sensory activity is compared with top-down predictions and only unexplained activity propagated through the cortical hierarchy.
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Precise Feature Based Time Scales and Frequency Decorrelation Lead to a Sparse Auditory Code

Chen Chen,¹ Heather L. Read,^{2,3} and Monty A. Escabi^{1,2,3}

Departments of ¹Electrical and Computer Engineering, ²Biomedical Engineering, and ³Psychology, University of Connecticut, Storrs, Connecticut 06269-1157

Sparse redundancy reducing codes have been proposed as efficient strategies for representing sensory stimuli. A prevailing hypothesis suggests that sensory representations shift from dense redundant codes in the periphery to selective sparse codes in cortex. We propose an alternative framework where sparseness and redundancy depend on sensory integration time scales and demonstrate that the central nucleus of the inferior colliculus (ICC) of cats encodes sound features by precise sparse spike trains. Direct comparisons with auditory cortical neurons demonstrate that ICC responses were sparse and uncorrelated as long as the spike train time scales were matched to the sensory integration time scales relevant to ICC neurons. Intriguingly, correlated spiking in the ICC was substantially lower than predicted by linear or nonlinear models and strictly observed for neurons with best frequencies within a “critical band,” the hallmark of perceptual frequency resolution in mammals. This is consistent with a sparse asynchronous code throughout much of the ICC and a complementary correlation code within a critical band that may allow grouping of perceptually relevant cues.

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Medial Prefrontal Cortex Neuronal Activation and Synaptic Alterations after Stress-Induced Reinstatement of Palatable Food Seeking: A Study Using *c-fos*-GFP Transgenic Female Rats

Carlo Cifani,^{1*} Eisuke Koya,^{1*} Brittany M. Navarre,¹ Donna J. Calu,¹ Michael H. Baumann,¹ Nathan J. Marchant,¹ Qing-Rong Liu,¹ Thi Khuc,¹ James Pickel,² Carl R. Lupica,¹ Yavin Shaham,¹ and Bruce T. Hope¹

Intramural Research Program, ¹NIDA/NIH, Baltimore, Maryland 21224, and ²NIMH/NIH, Bethesda, Maryland 20892

Relapse to maladaptive eating habits during dieting is often provoked by stress and there is evidence for a role of ovarian hormones in stress responses and feeding. We studied the role of these hormones in stress-induced reinstatement of food seeking and medial prefrontal cortex (mPFC) neuronal activation in *c-fos*-GFP transgenic female rats, which express GFP in strongly activated neurons. Food-restricted ovariectomized or sham-operated *c-fos*-GFP rats were trained to lever-press for palatable food pellets. Subsequently, lever-pressing was extinguished and reinstatement of food seeking and mPFC neuronal activation was assessed after injections of the pharmacological stressor yohimbine (0.5–2 mg/kg) or pellet priming (1–4 noncontingent pellets). Estrous cycle effects on reinstatement were also assessed in wild-type rats. Yohimbine- and pellet-priming-induced reinstatement was associated with Fos and GFP induction in mPFC; both reinstatement and neuronal activation were minimally affected by ovarian hormones in both *c-fos*-GFP and wild-type rats. *c-fos*-GFP transgenic rats were then used to assess glutamatergic synaptic alterations within activated GFP-positive and nonactivated GFP-negative mPFC neurons following yohimbine-induced reinstatement of food seeking. This reinstatement was associated with reduced AMPA receptor/NMDA receptor current ratios and increased paired-pulse facilitation in activated GFP-positive but not GFP-negative neurons. While ovarian hormones do not appear to play a role in stress-induced relapse of food seeking in our rat model, this reinstatement was associated with unique synaptic alterations in strongly activated mPFC neurons. Our paper introduces the *c-fos*-GFP transgenic rat as a new tool to study unique synaptic changes in activated neurons during behavior.

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NMDARs Mediate the Role of Monoamine Oxidase A in Pathological Aggression

Marco Bortolato,^{1,3,6*} Sean C. Godar,^{1*} Miriam Melis,⁴ Alessio Soggiu,⁴ Paola Roncada,⁸ Angelo Casu,⁴ Giovanna Flore,⁷ Kevin Chen,¹ Roberto Frau,^{5,6} Andrea Urbani,³ M. Paola Castelli,^{4,6} Paola Devoto,^{5,6} and Jean C. Shih^{1,2}

Departments of ¹Pharmacology and Pharmaceutical Sciences, and ²Cell and Neurobiology, University of Southern California, Los Angeles, California 90089, ³Santa Lucia Foundation-IRCCS (Istituto Di Ricovero e Cura a Carattere Scientifico), 00143 Rome, Italy, ⁴Department of Neuroscience “Bernard B. Brodie,” ⁵“Guy Everett” Laboratory, Department of Neuroscience “Bernard B. Brodie,” ⁶Tourette Syndrome Center, and ⁷Department of Cardiovascular and Neurological Sciences, University of Cagliari, 09124 Cagliari, Italy, and ⁸Istituto Sperimentale Italiano “Lazzaro Spallanzani,” 20134 Milan, Italy

Converging evidence shows that monoamine oxidase A (MAO A), the key enzyme catalyzing serotonin (5-hydroxytryptamine; 5-HT) and norepinephrine (NE) degradation, is a primary factor in the pathophysiology of antisocial and aggressive behavior. Accordingly, male MAO A-deficient humans and mice exhibit an extreme predisposition to aggressive outbursts in response to stress. As NMDARs regulate the emotional reactivity to social and environmental stimuli, we hypothesized their involvement in the modulation of aggression mediated by MAO A. In comparison with WT male mice, MAO A KO counterparts exhibited increases in 5-HT and NE levels across all brain regions, but no difference in glutamate concentrations and NMDAR binding. Notably, the prefrontal cortex (PFC) of MAO A KO mice exhibited higher expression of NR2A and NR2B, as well as lower levels of glycosylated NR1 subunits. In line with these changes, the current amplitude and decay time of NMDARs in PFC was significantly reduced. Furthermore, the currents of these receptors were hypersensitive to the action of the antagonists of the NMDAR complex (dizocilpine), as well as NR2A (PEAQX) and NR2B (Ro 25-6981) subunits. Notably, systemic administration of these agents selectively countered the enhanced aggression in MAO A KO mice, at doses that did not inherently affect motor activity. Our findings suggest that the role of MAO A in pathological aggression may be mediated by changes in NMDAR subunit composition in the PFC, and point to a critical function of this receptor in the molecular bases of antisocial personality.

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Low-Frequency Stimulation Depresses the Primate Anterior-Cingulate-Cortex and Prevents Spontaneous Recovery of Aversive Memories

Oded Klavir, Rotem Genud-Gabai, and Rony Paz

Department of Neurobiology, Weizmann Institute of Science, Rehovot, Israel 76100

Functional abnormalities in the dorsal-anterior-cingulate-cortex (dACC) underlie anxiety disorders and specifically post-traumatic stress disorder (PTSD). Promising and common behavioral approaches have limited effectiveness and many subjects exhibit spontaneous recovery of fear, as also evident in animal models following extinction training. Here, we use low-frequency stimulation (LFS), a protocol shown to induce long-term depression, with the aim of affecting synaptic plasticity induced by fear acquisition and extinction. We use aversive conditioning of either tone or visual stimuli paired with an aversive air-puff to the eye in a trace-conditioning paradigm. We find that LFS in the nonhuman primate (*Macaca fascicularis*) dACC, when combined with extinction training, was successful in preventing spontaneous recovery of the memory 24–72 h following extinction. We simultaneously record single-units and local-field-potentials across the dACC, and show that LFS gradually depressed evoked responses. Moreover, this decrease in neural excitability predicted the successful reduction of overnight spontaneous recovery on a day-by-day basis. Finally, we show that this effect occurs when using either visual or auditory modality as the conditioned stimulus, and that the reduction was specific to the conditioned modality. Our results suggest that the primate dACC is actively involved in maintaining the original aversive memory, and propose that a combination of LFS with behavioral therapy might significantly improve treatment in severe cases.

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Aversive-Bias and Stage-Selectivity in Neurons of the Primate Amygdala during Acquisition, Extinction, and Overnight Retention

Uri Livneh and Rony Paz

Department of Neurobiology, Weizmann Institute of Science, Rehovot, Israel 76100

Extensive evidence implicates the amygdala as a major station for acquisition, extinction, and consolidation of emotional memories. Most of this work relies on fear-conditioning in rodents and imaging in humans. Few studies have explored coding of value in the primate amygdala, but the circuitry that underlies extinction and overnight retention remains largely unexplored. We developed a learning paradigm for nonhuman primates (*macaca fascicularis*) and recorded the activity of single neurons during the different stages of acquisition, extinction, and overnight consolidation of pleasant and aversive tone-odor associations. We find that many neurons become phase-locked to respiratory cycles in a stage-dependent manner, emphasizing the flexibility of amygdala neurons to represent the current state and change their spontaneous activity accordingly. We suggest that these changes can serve to increase neuronal sensitivity to an upcoming event and facilitate learning mechanisms. We further show formation of aversive-bias during the acquisition of associations and during overnight retention, in the sense that neurons preferentially code for the aversive conditioned stimuli, even if they initially homogeneously represent value of the reinforcer. Our findings show flexible representations in the primate amygdala during the different cycles of learning and memory, and suggest selective potentiation of aversive information.

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Subcortical Neuronal Ensembles: An Analysis of Motor Task Association, Tremor, Oscillations, and Synchrony in Human Patients

Timothy L. Hanson,^{1,2*} Andrew M. Fuller,^{2,3*} Mikhail A. Lebedev,^{1,2} Dennis A. Turner,^{1,5} and Miguel A. L. Nicolelis^{1,2,3,4,6}

¹Department of Neurobiology, ²Center for Neuroengineering, ³Department of Biomedical Engineering, and ⁴Department of Psychology and Neuroscience, Duke University, Durham, North Carolina 27710, ⁵Department of Neurosurgery, Duke University Medical Center, Durham, North Carolina 27710, and

⁶Edmond and Lily Safra International Institute of Neuroscience of Natal, 59066-060 Natal, Brazil

Deep brain stimulation (DBS) has expanded as an effective treatment for motor disorders, providing a valuable opportunity for intraoperative recording of the spiking activity of subcortical neurons. The properties of these neurons and their potential utility in neuroprosthetic applications are not completely understood. During DBS surgeries in 25 human patients with either essential tremor or Parkinson's disease, we acutely recorded the single-unit activity of 274 ventral intermediate/ventral oralis posterior motor thalamus (Vim/Vop) neurons and 123 subthalamic nucleus (STN) neurons. These subcortical neuronal ensembles (up to 23 neurons sampled simultaneously) were recorded while the patients performed a target-tracking motor task using a cursor controlled by a haptic glove. We observed that modulations in firing rate of a substantial number of neurons in both Vim/Vop and STN represented target onset, movement onset/direction, and hand tremor. Neurons in both areas exhibited rhythmic oscillations and pairwise synchrony. Notably, all tremor-associated neurons exhibited synchrony within the ensemble. The data further indicate that oscillatory (likely pathological) neurons and behaviorally tuned neurons are not distinct but rather form overlapping sets. Whereas previous studies have reported a linear relationship between power spectra of neuronal oscillations and hand tremor, we report a nonlinear relationship suggestive of complex encoding schemes. Even in the presence of this pathological activity, linear models were able to extract motor parameters from ensemble discharges. Based on these findings, we propose that chronic multielectrode recordings from Vim/Vop and STN could prove useful for further studying, monitoring, and even treating motor disorders.

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Categorical, Yet Graded – Single-Image Activation Profiles of Human Category-Selective Cortical Regions

Marieke Mur,^{1,3} Douglas A. Ruff,¹ Jerzy Bodurka,² Peter De Weerd,³ Peter A. Bandettini,^{1,2} and Nikolaus Kriegeskorte¹

¹Section on Functional Imaging Methods, Laboratory of Brain and Cognition and ²Functional Magnetic Resonance Imaging Facility, National Institute of Mental Health, National Institutes of Health, Bethesda, Maryland, 20892 and ³Department of Cognitive Neuroscience, Faculty of Psychology and Neuroscience, Maastricht University, 6200 MD Maastricht, The Netherlands

Human inferior temporal cortex contains category-selective visual regions, including the fusiform face area (FFA) and the parahippocampal place area (PPA). These regions are defined by their greater category-average activation to the preferred category (faces and places, respectively) relative to nonpreferred categories. The approach of investigating category-average activation has left unclear to what extent category selectivity holds for individual object images. Here we investigate single-image activation profiles to address (1) whether each image from the preferred category elicits greater activation than any image outside the preferred category (categorical ranking), (2) whether there are activation differences within and outside the preferred category (gradedness), and (3) whether the activation profile falls off continuously across the category boundary or exhibits a discontinuity at the boundary (category step). We used functional magnetic resonance imaging to measure the activation elicited in the FFA and PPA by each of 96 object images from a wide range of categories, including faces and places, but also humans and animals, and natural and manmade objects. Results suggest that responses in FFA and PPA exhibit almost perfect categorical ranking, are graded within and outside the preferred category, and exhibit a category step. The gradedness within the preferred category was more pronounced in FFA; the category step was more pronounced in PPA. These findings support the idea that these regions have category-specific functions, but are also consistent with a distributed object representation emphasizing categories while still distinguishing individual images.

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Behavior-Related Pauses in Simple-Spike Activity of Mouse Purkinje Cells Are Linked to Spike Rate Modulation

Ying Cao (曹莹),^{1*} Selva K. Maran,^{2*} Mukesh Dhamala,³ Dieter Jaeger,² and Detlef H. Heck¹

¹Department of Anatomy and Neurobiology, University of Tennessee Health Science Center, Memphis, Tennessee 38163, ²Department of Biology, Emory University, Atlanta, Georgia 30322, and ³Department of Physics and Astronomy, Neuroscience Institute, Center for Behavioral Neuroscience, Georgia State University, Atlanta, Georgia 30303

Purkinje cells (PCs) in the mammalian cerebellum express high-frequency spontaneous activity with average spike rates between 30 and 200 Hz. Cerebellar nuclear (CN) neurons receive converging input from many PCs, resulting in a continuous barrage of inhibitory inputs. It has been hypothesized that pauses in PC activity trigger increases in CN spiking activity. A prediction derived from this hypothesis is that pauses in PC simple-spike activity represent relevant behavioral or sensory events. Here, we asked whether pauses in the simple-spike activity of PCs related to either fluid licking or respiration, play a special role in representing information about behavior. Both behaviors are widely represented in cerebellar PC simple-spike activity. We recorded PC activity in the vermis and lobus simplex of head-fixed mice while monitoring licking and respiratory behavior. Using cross-correlation and Granger causality analysis, we examined whether short interspike intervals (ISIs) had a different temporal relationship to behavior than long ISIs or pauses. Behavior-related simple-spike pauses occurred during low-rate simple-spike activity in both licking- and breathing-related PCs. Granger causality analysis revealed causal relationships between simple-spike pauses and behavior. However, the same results were obtained from an analysis of surrogate spike trains with gamma ISI distributions constructed to match rate modulations of behavior-related Purkinje cells. Our results therefore suggest that the occurrence of pauses in simple-spike activity does not represent additional information about behavioral or sensory events that goes beyond the simple-spike rate modulations.

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Gene Network Effects on Brain Microstructure and Intellectual Performance Identified in 472 Twins

Ming-Chang Chiang,^{1,2} Marina Barysheva,² Katie L. McMahon,³ Greig I. de Zubicaray,⁴ Kori Johnson,³ Grant W. Montgomery,⁵ Nicholas G. Martin,⁵ Arthur W. Toga,² Margaret J. Wright,⁵ Paul Shapshak,⁶ and Paul M. Thompson²

¹Department of Biomedical Engineering, National Yang-Ming University, Taipei, 112, Taiwan, ²Laboratory of Neuro Imaging, Department of Neurology, University of California, Los Angeles School of Medicine, Los Angeles, California 90095-7334, ³Centre for Advanced Imaging and ⁴School of Psychology, University of Queensland, Brisbane, St. Lucia, Queensland 407, Australia, ⁵Queensland Institute of Medical Research, Brisbane, Queensland 4029, Australia, and ⁶Division of Infectious Disease and International Medicine, Department of Medicine and Department of Psychiatry and Behavioral Medicine, University of South Florida Morsani College of Medicine, Tampa General Hospital, Tampa, Florida 33606

A major challenge in neuroscience is finding which genes affect brain integrity, connectivity, and intellectual function. Discovering influential genes holds vast promise for neuroscience, but typical genome-wide searches assess approximately one million genetic variants one-by-one, leading to intractable false positive rates, even with vast samples of subjects. Even more intractable is the question of which genes interact and how they work together to affect brain connectivity. Here, we report a novel approach that discovers which genes contribute to brain wiring and fiber integrity at all pairs of points in a brain scan. We studied genetic correlations between thousands of points in human brain images from 472 twins and their nontwin siblings (mean age: 23.7 ± 2.1 SD years; 193 male/279 female). We combined clustering with genome-wide scanning to find brain systems with common genetic determination. We then filtered the image in a new way to boost power to find causal genes. Using network analysis, we found a network of genes that affect brain wiring in healthy young adults. Our new strategy makes it computationally more tractable to discover genes that affect brain

integrity. The gene network showed small-world and scale-free topologies, suggesting efficiency in genetic interactions and resilience to network disruption. Genetic variants at hubs of the network influence intellectual performance by modulating associations between performance intelligence quotient and the integrity of major white matter tracts, such as the callosal genu and splenium, cingulum, optic radiations, and the superior longitudinal fasciculus.

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NEUROBIOLOGY OF DISEASE

Peripherin Is a Subunit of Peripheral Nerve Neurofilaments: Implications for Differential Vulnerability of CNS and Peripheral Nervous System Axons

Aidong Yuan,^{1,2} Takahiro Sasaki,¹ Asok Kumar,^{1,2} Corrinne M. Peterhoff,¹ Mala V. Rao,^{1,2} Ronald K. Liem,⁴ Jean-Pierre Julien,⁵ and Ralph A. Nixon^{1,2,3}

¹Center for Dementia Research, Nathan Kline Institute, Orangeburg, New York 10962, Departments of ²Psychiatry and ³Cell Biology, New York University School of Medicine, New York, New York 10016, ⁴Department of Pathology, College of Physicians and Surgeons, Columbia University, New York, New York 10032, and ⁵Centre de Recherche du Centre Hospitalier de l'Université Laval, Département d'Anatomie et Physiologie de l'Université Laval, Québec G1V 4G2, Canada

Peripherin, a neuronal intermediate filament protein implicated in neurodegenerative disease, coexists with the neurofilament triplet proteins [neurofilament light (NFL), medium (NFM), and heavy (NFH) chain] but has an unknown function. The earlier peak expression of peripherin than the triplet during brain development and its ability to form homopolymers, unlike the triplet, which are obligate heteropolymers, have supported a widely held view that peripherin and neurofilament triplets form separate filament systems. However, here, we demonstrate that, despite a postnatal decline in expression, peripherin is as abundant as the triplet in the adult PNS and exists in a relatively fixed stoichiometry with these subunits. Peripherin exhibits a distribution pattern identical to those of triplet proteins in sciatic axons and colocalizes with NFL on single neurofilaments by immunogold electron microscopy. Peripherin also coassembles into a single network of filaments containing NFL, NFM, and NFH with and without α -internexin in quadruple- or quintuple-transfected SW13vim(–) cells. Genetically deleting NFL in mice dramatically reduces peripherin content in sciatic axons. Moreover, peripherin mutations has been shown to disrupt the neurofilament network in transfected SW13vim(–) cells. These data show that peripherin and the neurofilament proteins are functionally interdependent. The results strongly support the view that, rather than forming an independent structure, peripherin is a subunit of neurofilaments in the adult PNS. Our findings provide a basis for its close relationship with neurofilaments in PNS diseases associated with neurofilament accumulation.

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Novel Allosteric Agonists of M₁ Muscarinic Acetylcholine Receptors Induce Brain Region-Specific Responses That Correspond with Behavioral Effects in Animal Models

Gregory J. Digby,^{1,2} Meredith J. Noetzel,^{1,2} Michael Bubser,^{1,2} Thomas J. Utley,^{1,2} Adam G. Walker,^{1,2} Nellie E. Byun,^{1,2} Evan P. Lebois,¹ Zixiu Xiang,^{1,2} Douglas J. Sheffler,^{1,2} Hyekyung P. Cho,^{1,2,3} Albert A. Davis,¹ Natali E. Nemirovsky,^{5,6} Sarah E. Mennenga,^{5,6} Bryan W. Camp,^{5,6} Heather A. Bimonte-Nelson,^{5,6} Jacob Bode,⁷ Kimberly Italiano,⁷ Ryan Morrison,^{2,3} J. Scott Daniels,^{1,2,3} Colleen M. Niswender,^{1,2,3} M. Foster Olive,^{5,6} Craig W. Lindsley,^{1,2,3,4} Carrie K. Jones,^{1,2,3} and P. Jeffrey Conn^{1,2,3}

¹Department of Pharmacology and ²Vanderbilt Center for Neuroscience Drug Discovery, Vanderbilt University Medical Center, Nashville, Tennessee 37232, ³Vanderbilt Specialized Chemistry Center for Probe Development (MLPCN), Nashville, Tennessee 37232, ⁴Department of Chemistry, Vanderbilt University, Nashville, Tennessee 37232, ⁵Department of Psychology, Arizona State University, Tempe, Arizona 85287, ⁶Arizona Alzheimer's Consortium, Tempe, Arizona 85287, and ⁷Millipore Corporation, Billerica, Massachusetts 01821

M₁ muscarinic acetylcholine receptors (mAChRs) represent a viable target for treatment of multiple disorders of the central nervous system (CNS) including Alzheimer's disease and schizophrenia. The recent discovery of highly selective allosteric agonists of M₁ receptors has provided a major breakthrough in developing a viable approach for the discovery of novel therapeutic agents that target these receptors. Here we describe the characterization of two novel M₁ allosteric agonists, VU0357017 and VU0364572, that display profound differences in their efficacy in activating M₁ coupling to different signaling pathways including Ca²⁺ and β -arrestin responses. Interestingly, the ability of these agents to differentially activate coupling of M₁ to specific signaling pathways leads to selective actions on some but not all M₁-mediated responses in brain circuits. These novel M₁ allosteric agonists induced robust electrophysiological effects in rat hippocampal slices, but showed lower efficacy in striatum and no measureable effects on M₁-mediated responses in medial prefrontal cortical pyramidal cells in mice. Consistent with these actions, both M₁ agonists enhanced acquisition of hippocampal-dependent cognitive function but did not reverse amphetamine-induced hyperlocomotion in rats. Together, these data reveal that M₁ allosteric agonists can differentially regulate coupling of M₁ to different signaling pathways, and this can dramatically alter the actions of these compounds on specific brain circuits important for learning and memory and psychosis.

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NKCC1 Upregulation Disrupts Chloride Homeostasis in the Hypothalamus and Increases Neuronal Activity–Sympathetic Drive in Hypertension

Zeng-You Ye (叶增友),^{1,2} De-Pei Li (李德培),^{1,3} Hee Sun Byun (변희선),^{1,2} Li Li (李莉),^{1,2} and Hui-Lin Pan (潘惠麟)^{1,2,4}

¹Center for Neuroscience and Pain Research, ²Department of Anesthesiology and Perioperative Medicine, and ³Department of Critical Care, The University of Texas MD Anderson Cancer Center, Houston, Texas 77030, and ⁴Graduate Programs in Neuroscience and Experimental Therapeutics, The University of Texas Graduate School of Biomedical Sciences, Houston, Texas 77225

Hypertension is a major risk factor for coronary artery disease, stroke, and kidney failure. However, the etiology of hypertension in most patients is poorly understood. Increased sympathetic drive emanating from the hypothalamic paraventricular nucleus (PVN) plays a major role in the development of hypertension. $\text{Na}^+ - \text{K}^+ - 2\text{Cl}^-$ cotransporter-1 (NKCC1) in the brain is critically involved in maintaining chloride homeostasis and in neuronal responses mediated by GABA_A receptors. Here we present novel evidence that the GABA reversal potential (E_{GABA}) of PVN presympathetic neurons undergoes a depolarizing shift that diminishes GABA inhibition in spontaneously hypertensive rats (SHRs). Inhibition of NKCC1, but not KCC2, normalizes E_{GABA} and restores GABA inhibition of PVN neurons in SHRs. The mRNA and protein levels of NKCC1, but not KCC2, in the PVN are significantly increased in SHRs, and the NKCC1 proteins on the plasma membrane are highly glycosylated. Inhibiting NKCC1 *N*-glycosylation restores E_{GABA} and GABA_{A} ergic inhibition of PVN presympathetic neurons in SHRs. Furthermore, NKCC1 inhibition significantly reduces the sympathetic vasomotor tone and augments the sympathoinhibitory responses to GABA_A receptor activation in the PVN in SHRs. These findings suggest that increased NKCC1 activity and glycosylation disrupt chloride homeostasis and impair synaptic inhibition in the PVN to augment the sympathetic drive in hypertension. This information greatly improves our understanding of the pathogenesis of hypertension and helps to design better treatment strategies for neurogenic hypertension.

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Survival Motor Neuron Protein in Motor Neurons Determines Synaptic Integrity in Spinal Muscular Atrophy

Tara L. Martinez,^{1,3*} Lingling Kong,^{1*} Xueyong Wang,⁴ Melissa A. Osborne,⁵ Melissa E. Crowder,¹ James P. Van Meerbeke,¹ Xixi Xu,¹ Crystal Davis,⁵ Joe Wooley,¹ David J. Goldhamer,⁶ Cathleen M. Lutz,⁵ Mark M. Rich,⁴ and Charlotte J. Sumner^{1,2}

Departments of ¹Neurology and ²Neuroscience, Johns Hopkins University, Baltimore, Maryland 21205, ³W. Harry Feinstone Department of Molecular Microbiology and Immunology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland 21205, ⁴Departments of Neurology, Neuroscience, Cell Biology and Physiology, Wright State University, Dayton, Ohio 45435, ⁵The Jackson Laboratory, Bar Harbor, Maine 04609, and ⁶Center for Regenerative Biology, Department of Molecular and Cell Biology, University of Connecticut, Storrs, Connecticut 06269

The inherited motor neuron disease spinal muscular atrophy (SMA) is caused by deficient expression of survival motor neuron (SMN) protein and results in severe muscle weakness. In SMA mice, synaptic dysfunction of both neuromuscular junctions (NMJs) and central sensorimotor synapses precedes motor neuron cell death. To address whether this synaptic dysfunction is due to SMN deficiency in motor neurons, muscle, or both, we generated three lines of conditional SMA mice with tissue-specific increases in SMN expression. All three lines of mice showed increased survival, weights, and improved motor behavior. While increased SMN expression in motor neurons prevented synaptic dysfunction at the NMJ and restored motor neuron somal synapses, increased SMN expression in muscle did not affect synaptic function although it did improve myofiber size. Together these data indicate that both peripheral and central synaptic integrity are dependent on motor neurons in SMA, but SMN may have variable roles in the maintenance of these different synapses. At the NMJ, it functions at the presynaptic terminal in a cell-autonomous fashion, but may be necessary for retrograde trophic signaling to presynaptic inputs onto motor neurons. Importantly, SMN also appears to function in muscle growth and/or maintenance independent of motor neurons. Our data suggest that SMN plays distinct roles in muscle, NMJs, and motor neuron somal synapses and that restored function of SMN at all three sites will be necessary for full recovery of muscle power.

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