

# This Week in The Journal

## Sodium Pump Modulates Locomotor Activity in Mice

Laurence D. Picton, Filipe Nascimento, Matthew J. Broadhead, Keith T. Sillar, and Gareth B. Miles

(see pages 906–921)

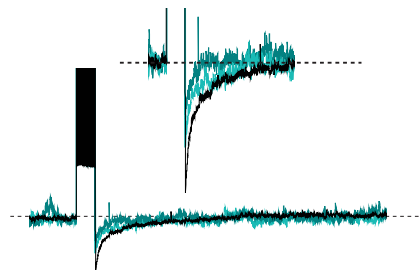
The  $\text{Na}^+/\text{K}^+$  ATPase creates and maintains a hyperpolarized resting membrane potential in neurons by exchanging three intracellular  $\text{Na}^+$  ions for two extracellular  $\text{K}^+$  ions. The rate of pumping depends on the intracellular  $\text{Na}^+$  concentration, and when  $\text{Na}^+$  concentrations increase during strong neural activity, robust pump activity can cause neurons to become hyperpolarized below normal resting membrane potential. This effect has been documented in several types of neurons. In spinal neurons of *Xenopus* tadpoles, for example, activation of the  $\text{Na}^+/\text{K}^+$  pump during swimming produces an ultraslow afterhyperpolarization lasting  $\sim 1$  min. This afterhyperpolarization dampens subsequent activity: swim bouts evoked during the afterhyperpolarization are shorter and weaker than the preceding bout, and this effect is eliminated by the  $\text{Na}^+/\text{K}^+$  ATPase inhibitor ouabain (Zhang and Sillar 2012 *Curr Biol* 22:526).

Picton et al. report that the  $\text{Na}^+/\text{K}^+$  ATPase also regulates burst rate in mouse spinal cord locomotor circuits. The second of two closely spaced locomotor epochs evoked in isolated mouse spinal cords was shorter and weaker than the first. Ouabain prevented reductions in burst frequency and duration, suggesting the reduction depended on  $\text{Na}^+/\text{K}^+$  pump activity. Furthermore, induction of repetitive spiking produced an ultraslow afterhyperpolarization lasting  $>20$  s in many motor neurons; this afterhyperpolarization was also blocked by ouabain. Notably, the input resistance of cells didn't change during the ultraslow afterhyperpolarization, suggesting it was not mediated by opening of ion channels.

Interestingly, dopamine—which decreases the frequency and increases the amplitude of locomotor-related bursting in ventral nerve roots—increased the duration of the ultraslow afterhyperpolarization, suggesting dopamine regulates  $\text{Na}^+/\text{K}^+$  pump activity in these neurons. Consistent with this, ouabain increased the fre-

quency of motor neuron bursts during fictive locomotion in isolated spinal cords treated with dopamine, whereas increasing pump activity with monensin decreased burst frequency. Ouabain had no effect on burst frequency in the absence of dopamine, suggesting the  $\text{Na}^+/\text{K}^+$  pump does not contribute significantly to locomotor activity under baseline conditions.

These results are intriguing because they suggest that neuromodulators influence  $\text{Na}^+/\text{K}^+$  ATPase function in neurons in ways that alter neuronal excitability. Given that  $\text{Na}^+/\text{K}^+$  ATPase-dependent afterhyperpolarization has been found in many neurons, the pump may contribute to activity-dependent regulation of more circuits than previously appreciated.



A burst of spikes in a motor neuron is followed by an ultraslow afterhyperpolarization (black traces), which is reduced dose-dependently by ouabain (green traces). See Picton et al. for details.

## Accumbens nNOS Neurons Promote Drug Seeking

Alexander C.W. Smith, Michael D. Scofield, Jasper A. Heinsbroek, Cassandra D. Gipson, Daniela Neuhofer, et al.

(see pages 742–756)

Addictive drugs modify neural circuits involved in motivation and reward, and these changes contribute to relapse after abstinence. In rodents, cocaine and other addictive drugs downregulate glial glutamate transporters in the nucleus accumbens core (NAcore), resulting in increased spillover of synaptically released glutamate. In addition, several classes of addictive drugs increase the activity of matrix metalloproteinases MMP-2 and MMP-9 in the NAcore, and this leads to transient synaptic potentiation

and increased drug seeking in the presence of drug-associated cues. Importantly, enhancing glutamate uptake or inhibiting MMPs reduces cue-induced reinstatement of cocaine seeking (Mulholland et al. 2016 *Trends Neurosci* 39:472).

Smith et al. have uncovered a pathway linking cocaine-induced glutamate spillover and MMP activation. Rats were trained to press a lever to receive cocaine paired with a cue. Lever pressing was extinguished by withholding cocaine and cues and then reinstated by presenting the cue alone. Consistent with previous results, cue presentation increased glutamate levels in the NAcore and promoted lever pressing. An antagonist of metabotropic glutamate receptor 5 (mGluR5) reduced lever pressing, whereas an mGluR5 agonist increased lever pressing in the absence of conditioned cues.

Because cocaine downregulates mGluR5 in principal neurons of the NAcore, the authors hypothesized that the receptors responsible for relapse were expressed on interneurons that express neuronal nitric oxide synthase (nNOS). Indeed, mGluR5 agonist increased extracellular levels of NO, and an nNOS inhibitor reduced agonist- and cue-evoked lever pressing. Furthermore, selective activation of NAcore nNOS-expressing interneurons caused S-nitrosylation of MMP-2 and increased lever pressing in the absence of conditioned cues. Finally, nNOS inhibition prevented cue-evoked increases in MMP-2 and -9 activity, and killing nNOS-expressing neurons reduced cue-induced lever pressing.

Together with previous work, these results suggest that increased glutamate spillover at NAcore synapses activates mGluR5 on nNOS-expressing interneurons, stimulating NO production. NO S-nitrosylates MMP-2, increasing its activity, which may in turn increase activity of MMP-9. Together, these effects help to elicit transient potentiation of excitatory synapses on medium spiny neurons, thus promoting drug-seeking in the presence of drug-associated cues. Inhibition of nNOS, as well as MMPs and mGluR5 (which appears to contribute to addiction more broadly) might therefore prevent cue-triggered drug seeking, a major cause of relapse in addicts.

This Week in The Journal was written by Teresa Esch, Ph.D.

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**Cover legend:** This image shows an oval squid (*Sepioteuthis lessoniana*) displaying a distinct body pattern at the spawning site offshore in northeastern Taiwan. Body patterning in oval squids is neurally controlled and functions as a conspecific visual signal. Their skin coloration is diverse and can change in a fraction of a second depending on behavioral context. New work reveals a novel mechanism underlying neural control of dynamic body patterning for communication in this species. (Photo taken by Chun-Yen Lin.) For more information, see the article by Liu and Chiao (pages 768–780).

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## Articles

### CELLULAR/MOLECULAR

## Cdk5 Regulation of the GRAB-Mediated Rab8-Rab11 Cascade in Axon Outgrowth

Kotaro Furusawa,<sup>1</sup> Akiko Asada,<sup>1</sup> Pamela Urrutia,<sup>2,3</sup> Christian Gonzalez-Billault,<sup>2,3,4</sup> Mitsunori Fukuda,<sup>5</sup> and Shin-ichi Hisanaga<sup>1</sup>

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Neurons communicate with each other through their axons and dendrites. However, a full characterization of the molecular mechanisms involved in axon and dendrite formation is still incomplete. Neurite outgrowth requires the supply of membrane components for surface expansion. Two membrane sources for axon outgrowth are suggested: Golgi secretory vesicles and endocytic recycling endosomes. In non-neuronal cells, trafficking of secretory vesicles from Golgi is regulated by Rab8, a member of Rab small GTPases, and that of recycling endosomes is by Rab11, another member of Rabs. However, whether these vesicles are coordinately or independently transported in growing axons is unknown. Herein, we find that GRAB, a guanine nucleotide exchange factor for Rab8, is a novel regulator of axon outgrowth. Knockdown of GRAB suppressed axon outgrowth of cultured mouse brain cortical neurons. GRAB mediates the interaction between Rab11A and Rab8A, and this activity is regulated by phosphorylation at Ser169 and Ser180 by Cdk5-p35. The nonphosphorylatable GRAB mutant S169/180A promoted axonal outgrowth to a greater extent than did the phosphomimetic GRAB mutant S169/180D. Phosphorylation of GRAB suppressed its guanine nucleotide exchange factor activity and its ability to recruit Rab8A- to Rab11A-positive endosomes. *In vivo* function of GRAB and its Cdk5-phosphorylation were shown in migration and process formation of developing neurons in embryonic mouse brains. These results indicate that GRAB regulates axonal outgrowth via activation and recruitment of Rab8A- to Rab11A-positive endosomes in a Cdk5-dependent manner.

The Journal of Neuroscience, • 37(4):790–806

### DEVELOPMENT/PLASTICITY/REPAIR

## Contribution of Innate Cortical Mechanisms to the Maturation of Orientation Selectivity in Parvalbumin Interneurons

Dario X. Figueroa Velez, Kyle L. Ellefsen, Ethan R. Hathaway, Mathew C. Carathedathu, and Sunil P. Gandhi

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The maturation of cortical parvalbumin-positive (PV) interneurons depends on the interaction of innate and experience-dependent factors. Dark-rearing experiments suggest that visual experience determines when broad orientation selectivity emerges in visual cortical PV interneurons. Here, using neural transplantation and *in vivo* calcium imaging of mouse visual cortex, we investigated whether innate mechanisms contribute to the maturation of orientation selectivity in PV interneurons. First, we confirmed earlier findings showing that broad orientation selectivity emerges in PV interneurons by 2 weeks after vision onset, ~35 d after these cells are born. Next, we assessed the functional development of transplanted PV (tPV) interneurons. Surprisingly, 25 d after transplantation (DAT) and >2 weeks after vision onset, we found that tPV interneurons have not developed broad orientation selectivity. By 35 DAT, however, broad orientation selectivity emerges in tPV interneurons. Transplantation does not alter orientation selectivity in host interneurons, suggesting that the maturation of tPV interneurons occurs independently from their endogenous counterparts. Together, these results challenge the notion that the onset of vision solely determines when PV interneurons become broadly tuned. Our results reveal that an innate cortical mechanism contributes to the emergence of broad orientation selectivity in PV interneurons.

The Journal of Neuroscience, • 37(4):820–829

## C-Terminal Region Truncation of RELN Disrupts an Interaction with VLDLR, Causing Abnormal Development of the Cerebral Cortex and Hippocampus

Seungshin Ha,<sup>1,3</sup> Prem P. Tripathi,<sup>2</sup> Anca B. Mihalas,<sup>2</sup> Robert F. Hevner,<sup>2,4</sup> and David R. Beier<sup>1,3</sup>

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We discovered a hypomorphic *reelin* (*Reln*) mutant with abnormal cortical lamination and no cerebellar hypoplasia. This mutant, *Reln*<sup>CTRdel</sup>, carries a chemically induced splice-site mutation that truncates the C-terminal region (CTR) domain of RELN protein and displays remarkably distinct phenotypes from *reeler*. The mutant does not have an inverted cortex, but cortical neurons overmigrate and invade the marginal zone, which are characteristics similar to a phenotype seen in the cerebral cortex of *Vldlr*<sup>null</sup> mice. The dentate gyrus shows a novel phenotype: the infrapyramidal blade is absent, while the suprapyramidal blade is present and laminated. Genetic epistasis analysis showed that *Reln*<sup>CTRdel/Apoer2</sup><sup>null</sup> double homozygotes have phenotypes akin to those of *reeler* mutants, while *Reln*<sup>CTRdel</sup>

*Vldlr*<sup>null</sup> mice do not. Given that the receptor double knock-out mice resemble *reeler* mutants, we infer that *Reln*<sup>CTRdel</sup>/*Apoer2*<sup>null</sup> double homozygotes have both receptor pathways disrupted. This suggests that CTR-truncation disrupts an interaction with VLDLR (very low-density lipoprotein receptor), while the APOER2 signaling pathway remains active, which accounts for the hypomorphic phenotype in *Reln*<sup>CTRdel</sup> mice. A RELN-binding assay confirms that CTR truncation significantly decreases RELN binding to VLDLR, but not to APOER2. Together, the *in vitro* and *in vivo* results demonstrate that the CTR domain confers receptor-binding specificity of RELN.

The Journal of Neuroscience, • 37(4):960–971

## Newly Formed Endothelial Cells Regulate Myeloid Cell Activity Following Spinal Cord Injury via Expression of CD200 Ligand

Merav Cohen,<sup>1\*</sup> Hila Ben-Yehuda,<sup>1\*</sup> Ziv Porat,<sup>2</sup> Catarina Raposo,<sup>1</sup> Siamon Gordon,<sup>3</sup> and Michal Schwartz<sup>1</sup>

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The central nervous system (CNS) is endowed with several immune-related mechanisms that contribute to its protection and maintenance in homeostasis and under pathology. Here, we discovered an additional mechanism that controls inflammatory responses within the CNS milieu under injurious conditions, involving CD200 ligand (CD200L) expressed by newly formed endothelial cells. We observed that CD200L is constitutively expressed in the mouse healthy CNS by endothelial cells of the blood–cerebrospinal fluid barrier and of the spinal cord meninges, but not by the endothelium of the blood–spinal cord barrier. Following spinal cord injury (SCI), newly formed endothelial cells, located only at the epicenter of the lesion site, expressed CD200L. Moreover, in the absence of CD200L expression by CNS-resident cells, functional recovery of mice following SCI was impaired. High throughput single-cell flow cytometry image analysis following SCI revealed CD200L-dependent direct interaction between endothelial and local CD200R<sup>+</sup> myeloid cells, including activated microglia and infiltrating monocyte-derived macrophages (mo-MΦ). Absence of CD200L signaling, both *in vitro* and *in vivo*, resulted in a higher inflammatory response of the encountering macrophages, manifested by elevation in mRNA expression of *Tnfα* and *Il1β*, increased intracellular TNFα immunoreactivity, and reduced expression levels of macrophage factors that are associated with resolution of inflammation, Dectin-1, CD206 (mannose receptor), and IL-4R. Collectively, our results highlight the importance of CD200-mediated immune dialogue between endothelial cells and the local resident microglia and infiltrating mo-MΦ within the lesion area, as a mechanism that contributes to regulation of inflammation following acute CNS injury.

The Journal of Neuroscience, • 37(4):972–985

## Cocaine Promotes Coincidence Detection and Lowers Induction Threshold during Hebbian Associative Synaptic Potentiation in Prefrontal Cortex

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Addictive drugs usurp neural plasticity mechanisms that normally serve reward-related learning and memory, primarily by evoking changes in glutamatergic synaptic strength in the mesocorticolimbic dopamine circuitry. Here, we show that repeated cocaine exposure *in vivo* does not alter synaptic strength in the mouse prefrontal cortex during an early period of withdrawal, but instead modifies a Hebbian quantitative synaptic learning rule by broadening the temporal window and lowers the induction threshold for spike-timing-dependent LTP (t-LTP). After repeated, but not single, daily cocaine injections, t-LTP in layer V pyramidal neurons is induced at +30 ms, a normally ineffective timing interval for t-LTP induction in saline-exposed mice. This cocaine-induced, extended-timing t-LTP lasts for ~1 week after terminating cocaine and is accompanied by an increased susceptibility to potentiation by fewer pre–post spike pairs, indicating a reduced t-LTP induction threshold. Basal synaptic strength and the maximal attainable t-LTP magnitude remain unchanged after cocaine exposure. We further show that the cocaine facilitation of t-LTP induction is caused by sensitized D1–cAMP/protein kinase A dopamine signaling in pyramidal neurons, which then pathologically recruits voltage-gated L-type Ca<sup>2+</sup> channels that synergize with GluN2A-containing NMDA receptors to drive t-LTP at extended timing. Our results illustrate a mechanism by which cocaine, acting on a key neuromodulation pathway, modifies the coincidence detection window during Hebbian plasticity to facilitate associative synaptic potentiation in prefrontal excitatory circuits. By modifying rules that govern activity-dependent synaptic plasticity, addictive drugs can derail the experience-driven neural circuit remodeling process important for executive control of reward and addiction.

The Journal of Neuroscience, • 37(4):986–997

## SYSTEMS/CIRCUITS

## Mosaic Organization of Body Pattern Control in the Optic Lobe of Squids

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Cephalopods in nature undergo highly dynamic skin coloration changes that allow rapid camouflage and intraspecies communication. The optic lobe is thought to play a key role in controlling the expansion of the chromatophores that generate these diverse body patterns. However, the functional organization of the optic lobe and neural control of the various body patterns by the optic lobe are largely unknown. We applied electrical stimulation within the optic lobe to investigate the neural basis of body patterning in the oval squid, *Sepioteuthis lessoniana*. Most areas in the optic lobe mediated predominately ipsilateral expansion of chromatophores present on the mantle, but not on the head and arms; furthermore, the expanded areas after electrical stimulation were positively correlated with an increase in stimulating voltage and stimulation

depth. These results suggest a unilaterally dominant and vertically converged organization of the optic lobe. Furthermore, analyzing 14 of the elicited body pattern components and their corresponding stimulation sites revealed that the same components can be elicited by stimulating different parts of the optic lobe and that various subsets of these components can be coactivated by stimulating the same area. These findings suggest that many body pattern components may have multiple motor units in the optic lobe and that these are organized in a mosaic manner. The multiplicity associated with the nature of the neural controls of these components in the cephalopod brain thus reflects the versatility of the individual components during the generation of diverse body patterns.

The Journal of Neuroscience, • 37(4):768–780

## Differential Encoding of Time by Prefrontal and Striatal Network Dynamics

Konstantin I. Bakhurin,<sup>1\*</sup> Vishwa Goudar,<sup>2\*</sup> Justin L. Shobe,<sup>2</sup> Leslie D. Claar,<sup>4</sup> Dean V. Buonomano,<sup>2,3,5</sup> and Sotiris C. Masmanidis<sup>2,5,6</sup>

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Telling time is fundamental to many forms of learning and behavior, including the anticipation of rewarding events. Although the neural mechanisms underlying timing remain unknown, computational models have proposed that the brain represents time in the dynamics of neural networks. Consistent with this hypothesis, changing patterns of neural activity dynamically in a number of brain areas—including the striatum and cortex—has been shown to encode elapsed time. To date, however, no studies have explicitly quantified and contrasted how well different areas encode time by recording large numbers of units simultaneously from more than one area. Here, we performed large-scale extracellular recordings in the striatum and orbitofrontal cortex of mice that learned the temporal relationship between a stimulus and a reward and reported their response with anticipatory licking. We used a machine-learning algorithm to quantify how well populations of neurons encoded elapsed time from stimulus onset. Both the striatal and cortical networks encoded time, but the striatal network outperformed the orbitofrontal cortex, a finding replicated both in simultaneously and nonsimultaneously recorded corticostriatal datasets. The striatal network was also more reliable in predicting when the animals would lick up to ~1 s before the actual lick occurred. Our results are consistent with the hypothesis that temporal information is encoded in a widely distributed manner throughout multiple brain areas, but that the striatum may have a privileged role in timing because it has a more accurate “clock” as it integrates information across multiple cortical areas.

The Journal of Neuroscience, • 37(4):854–870

## Sodium Pumps Mediate Activity-Dependent Changes in Mammalian Motor Networks

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Ubiquitously expressed sodium pumps are best known for maintaining the ionic gradients and resting membrane potential required for generating action potentials. However, activity- and state-dependent changes in pump activity can also influence neuronal firing and regulate rhythmic network output. Here we demonstrate that changes in sodium pump activity regulate locomotor networks in the spinal cord of neonatal mice. The sodium pump inhibitor, ouabain, increased the frequency and decreased the amplitude of drug-induced locomotor bursting, effects that were dependent on the presence of the neuromodulator dopamine. Conversely, activating the pump with the sodium ionophore monensin decreased burst frequency. When more “natural” locomotor output was evoked using dorsal-root stimulation, ouabain increased burst frequency and extended locomotor episode duration, whereas monensin slowed and shortened episodes. Decreasing the time between dorsal-root stimulation, and therefore interepisode interval, also shortened and slowed activity, suggesting that pump activity encodes information about past network output and contributes to feedforward control of subsequent locomotor bouts. Using whole-cell patch-clamp recordings from spinal motoneurons and interneurons, we describe a long-duration (~60 s), activity-dependent, TTX- and ouabain-sensitive, hyperpolarization (~5 mV), which is mediated by spike-dependent increases in pump activity. The duration of this dynamic pump potential is enhanced by dopamine. Our results therefore reveal sodium pumps as dynamic regulators of mammalian spinal motor networks that can also be affected by neuromodulatory systems. Given the involvement of sodium pumps in movement disorders, such as amyotrophic lateral sclerosis and rapid-onset dystonia parkinsonism, knowledge of their contribution to motor network regulation also has considerable clinical importance.

The Journal of Neuroscience, • 37(4):906–921

## Noisy Spiking in Visual Area V2 of Amblyopic Monkeys

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Interocular decorrelation of input signals in developing visual cortex can cause impaired binocular vision and amblyopia. Although increased intrinsic noise is thought to be responsible for a range of perceptual deficits in amblyopic humans, the neural basis for the elevated perceptual noise in amblyopic primates is not known. Here, we tested the idea that perceptual noise is linked to the neuronal spiking noise (variability) resulting from developmental alterations in cortical circuitry. To assess spiking noise, we analyzed the contrast-dependent dynamics of spike counts and spiking irregularity by calculating the square of the coefficient of variation in interspike intervals ( $CV^2$ ) and the trial-to-trial fluctuations in spiking, or mean matched Fano factor (m-FF) in visual area V2 of monkeys reared with chronic monocular defocus. In amblyopic neurons, the contrast versus response functions and the spike count dynamics exhibited significant deviations from comparable data for normal monkeys. The  $CV^2$  was pronounced in amblyopic neurons for high-contrast stimuli and the m-FF was abnormally high in amblyopic neurons for low-contrast gratings. The spike count,  $CV^2$ , and m-FF of spontaneous activity were also elevated in amblyopic neurons. These contrast-dependent spiking irregularities were correlated with the level of binocular suppression in these V2 neurons and with the severity of perceptual loss for individual monkeys. Our results suggest that the developmental alterations in normalization mechanisms

resulting from early binocular suppression can explain much of these contrast-dependent spiking abnormalities in V2 neurons and the perceptual performance of our amblyopic monkeys.

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## Nonlinear Y-Like Receptive Fields in the Early Visual Cortex: An Intermediate Stage for Building Cue-Invariant Receptive Fields from Subcortical Y Cells

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Many of the neurons in early visual cortex are selective for the orientation of boundaries defined by first-order cues (luminance) as well as second-order cues (contrast, texture). The neural circuit mechanism underlying this selectivity is still unclear, but some studies have proposed that it emerges from spatial nonlinearities of subcortical Y cells. To understand how inputs from the Y-cell pathway might be pooled to generate cue-invariant receptive fields, we recorded visual responses from single neurons in cat Area 18 using linear multielectrode arrays. We measured responses to drifting and contrast-reversing luminance gratings as well as contrast modulation gratings. We found that a large fraction of these neurons have nonoriented responses to gratings, similar to those of subcortical Y cells: they respond at the second harmonic (F2) to high-spatial frequency contrast-reversing gratings and at the first harmonic (F1) to low-spatial frequency drifting gratings (“Y-cell signature”). For a given neuron, spatial frequency tuning for linear (F1) and nonlinear (F2) responses is quite distinct, similar to orientation-selective cue-invariant neurons. Also, these neurons respond to contrast modulation gratings with selectivity for the carrier (texture) spatial frequency and, in some cases, orientation. Their receptive field properties suggest that they could serve as building blocks for orientation-selective cue-invariant neurons. We propose a circuit model that combines ON- and OFF-center cortical Y-like cells in an unbalanced push–pull manner to generate orientation-selective, cue-invariant receptive fields.

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## Role of Dorsomedial Striatum Neuronal Ensembles in Incubation of Methamphetamine Craving after Voluntary Abstinence

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We recently developed a rat model of incubation of methamphetamine craving after choice-based voluntary abstinence. Here, we studied the role of dorsolateral striatum (DLS) and dorsomedial striatum (DMS) in this incubation. We trained rats to self-administer palatable food pellets (6 d, 6 h/d) and methamphetamine (12 d, 6 h/d). We then assessed relapse to methamphetamine seeking under extinction conditions after 1 and 21 abstinence days. Between tests, the rats underwent voluntary abstinence (using a discrete choice procedure between methamphetamine and food; 20 trials/d) for 19 d. We used *in situ* hybridization to measure the colabeling of the activity marker *Fos* with *Drd1* and *Drd2* in DMS and DLS after the tests. Based on the *in situ* hybridization colabeling results, we tested the causal role of DMS D<sub>1</sub> and D<sub>2</sub> family receptors, and DMS neuronal ensembles in “incubated” methamphetamine seeking, using selective dopamine receptor antagonists (SCH39166 or raclopride) and the Daun02 chemogenetic inactivation procedure, respectively. Methamphetamine seeking was higher after 21 d of voluntary abstinence than after 1 d (incubation of methamphetamine craving). The incubated response was associated with increased *Fos* expression in DMS but not in DLS; *Fos* was colabeled with both *Drd1* and *Drd2*. DMS injections of SCH39166 or raclopride selectively decreased methamphetamine seeking after 21 abstinence days. In *Fos-lacZ* transgenic rats, selective inactivation of relapse test-activated *Fos* neurons in DMS on abstinence day 18 decreased incubated methamphetamine seeking on day 21. Results demonstrate a role of DMS dopamine D<sub>1</sub> and D<sub>2</sub> receptors in the incubation of methamphetamine craving after voluntary abstinence and that DMS neuronal ensembles mediate this incubation.

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### BEHAVIORAL/COGNITIVE

## Accumbens nNOS Interneurons Regulate Cocaine Relapse

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Relapse to drug use can be initiated by drug-associated cues. The intensity of cue-induced relapse is correlated with the induction of transient synaptic potentiation (t-SP) at glutamatergic synapses on medium spiny neurons (MSNs) in the nucleus accumbens core (NAcore) and requires spillover of glutamate from prefrontal cortical afferents. We used a rodent self-administration/reinstatement model of relapse to show that cue-induced t-SP and reinstated cocaine seeking result from

glutamate spillover, initiating a metabotropic glutamate receptor 5 (mGluR5)-dependent increase in nitric oxide (NO) production. Pharmacological stimulation of mGluR5 in NAc core recapitulated cue-induced reinstatement in the absence of drug-associated cues. Using NO-sensitive electrodes, mGluR5 activation by glutamate was shown to stimulate NO production that depended on activation of neuronal nitric oxide synthase (nNOS). nNOS is expressed in ~1% of NAc core neurons. Using a transgene strategy to express and stimulate designer receptors that mimicked mGluR5 signaling through Gq in nNOS interneurons, we recapitulated cue-induced reinstatement in the absence of cues. Conversely, using a transgenic caspase strategy, the intensity of cue-induced reinstatement was correlated with the extent of selective elimination of nNOS interneurons. The induction of t-SP during cued reinstatement depends on activating matrix metalloproteinases (MMPs) and selective chemogenetic stimulation of nNOS interneurons recapitulated MMP activation and t-SP induction (increase in AMPA currents in MSNs). These data demonstrate critical involvement of a sparse population of nNOS-expressing interneurons in cue-induced cocaine seeking, revealing a bottleneck in brain processing of drug-associated cues where therapeutic interventions could be effective in treating drug addiction.

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## Loss of Plasticity in the D2-Accumbens Pallidal Pathway Promotes Cocaine Seeking

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Distinct populations of D1- and D2-dopamine receptor-expressing medium spiny neurons (D1-/D2-MSNs) comprise the nucleus accumbens, and activity in D1-MSNs promotes, whereas activity in D2-MSNs inhibits, motivated behaviors. We used chemogenetics to extend D1-/D2-MSN cell specific regulation to cue-reinstated cocaine seeking in a mouse model of self-administration and relapse, and found that either increasing activity in D1-MSNs or decreasing activity in D2-MSNs augmented cue-induced reinstatement. Both D1- and D2-MSNs provide substantial GABAergic innervation to the ventral pallidum, and chemogenetic inhibition of ventral pallidal neurons blocked the augmented reinstatement elicited by chemogenetic regulation of either D1- or D2-MSNs. Because D1- and D2-MSNs innervate overlapping populations of ventral pallidal neurons, we next used optogenetics to examine whether changes in synaptic plasticity in D1- versus D2-MSN GABAergic synapses in the ventral pallidum could explain the differential regulation of VP activity. In mice trained to self-administer cocaine, GABAergic LTD was abolished in D2-, but not in D1-MSN synapses. A  $\mu$  opioid receptor antagonist restored GABA currents in D2-, but not D1-MSN synapses of cocaine-trained mice, indicating that increased enkephalin tone on presynaptic  $\mu$  opioid receptors was responsible for occluding the LTD. These results identify a behavioral function for D1-MSN innervation of the ventral pallidum, and suggest that losing LTD<sub>GABA</sub> in D2-MSN, but not D1-MSN input to ventral pallidum may promote cue-induced reinstatement of cocaine-seeking.

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## Sure I'm Sure: Prefrontal Oscillations Support Metacognitive Monitoring of Decision Making

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Successful decision making critically involves metacognitive processes such as monitoring and control of our decision process. Metacognition enables agents to modify ongoing behavior adaptively and determine what to do next in situations in which external feedback is not (immediately) available. Despite the importance of metacognition for many aspects of life, little is known about how our metacognitive system operates or about what kind of information is used for metacognitive (second-order) judgments. In particular, it remains an open question whether metacognitive judgments are based on the same information as first-order decisions. Here, we investigated the relationship between metacognitive performance and first-order task performance by recording EEG signals while participants were asked to make a “diagnosis” after seeing a sample of fictitious patient data (a complex pattern of colored moving dots of different sizes). To assess metacognitive performance, participants provided an estimate about the quality of their diagnosis on each trial. Results demonstrate that the information that contributes to first-order decisions differs from the information that supports metacognitive judgments. Further, time–frequency analyses of EEG signals reveal that metacognitive performance is associated specifically with prefrontal theta-band activity. Together, our findings are consistent with a hierarchical model of metacognition and suggest a crucial role for prefrontal oscillations in metacognitive performance.

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## Spontaneous Neural Oscillations Bias Perception by Modulating Baseline Excitability

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The brain exhibits organized fluctuations of neural activity, even in the absence of tasks or sensory input. A prominent type of such spontaneous activity is the alpha rhythm, which influences perception and interacts with other ongoing neural activity. It is currently hypothesized that states of decreased prestimulus  $\alpha$  oscillations indicate enhanced neural excitability, resulting in improved perceptual acuity. Nevertheless, it remains debated how changes in excitability manifest at the behavioral level in perceptual tasks. We addressed this issue by comparing two alternative models describing the effect of spontaneous  $\alpha$  power on signal detection. The first model assumes that decreased  $\alpha$  power increases baseline excitability, amplifying the response to both signal and noise, predicting a liberal detection criterion with no effect on sensitivity.

The second model predicts that decreased  $\alpha$  power increases the trial-by-trial precision of the sensory response, resulting in improved sensitivity. We tested these models in two EEG experiments in humans where we analyzed the effects of prestimulus  $\alpha$  power on visual detection and discrimination using a signal detection framework. Both experiments provide strong evidence that decreased  $\alpha$  power reflects a more liberal detection criterion, rather than improved sensitivity, consistent with the baseline model. In other words, when the task requires detecting stimulus presence versus absence, reduced  $\alpha$  oscillations make observers more likely to report the stimulus regardless of actual stimulus presence. Contrary to previous interpretations, these results suggest that states of decreased  $\alpha$  oscillations increase the global baseline excitability of sensory systems without affecting perceptual acuity.

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## Cortical Correlates of the Auditory Frequency-Following and Onset Responses: EEG and fMRI Evidence

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The frequency-following response (FFR) is a measure of the brain's periodic sound encoding. It is of increasing importance for studying the human auditory nervous system due to numerous associations with auditory cognition and dysfunction. Although the FFR is widely interpreted as originating from brainstem nuclei, a recent study using MEG suggested that there is also a right-lateralized contribution from the auditory cortex at the fundamental frequency (Coffey et al., 2016b). Our objectives in the present work were to validate and better localize this result using a completely different neuroimaging modality and to document the relationships between the FFR, the onset response, and cortical activity. Using a combination of EEG, fMRI, and diffusion-weighted imaging, we show that activity in the right auditory cortex is related to individual differences in FFR–fundamental frequency ( $f_0$ ) strength, a finding that was replicated with two independent stimulus sets, with and without acoustic energy at the fundamental frequency. We demonstrate a dissociation between this FFR– $f_0$ -sensitive response in the right and an area in left auditory cortex that is sensitive to individual differences in the timing of initial response to sound onset. Relationships to timing and their lateralization are supported by parallels in the microstructure of the underlying white matter, implicating a mechanism involving neural conduction efficiency. These data confirm that the FFR has a cortical contribution and suggest ways in which auditory neuroscience may be advanced by connecting early sound representation to measures of higher-level sound processing and cognitive function.

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## Dynamic Reconfiguration of Visuomotor-Related Functional Connectivity Networks

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Cognitive functions arise from the coordination of large-scale brain networks. However, the principles governing interareal functional connectivity dynamics (FCD) remain elusive. Here, we tested the hypothesis that human executive functions arise from the dynamic interplay of multiple networks. To do so, we investigated FCD mediating a key executing function, known as arbitrary visuomotor mapping, using brain connectivity analyses of high-gamma activity recorded using MEG and intracranial EEG. Visuomotor mapping was found to arise from the dynamic interplay of three partly overlapping cortico-cortical and cortico-subcortical functional connectivity (FC) networks. First, visual and parietal regions coordinated with sensorimotor and premotor areas. Second, the dorsal frontoparietal circuit together with the sensorimotor and associative frontostriatal networks took the lead. Finally, cortico-cortical interhemispheric coordination among bilateral sensorimotor regions coupled with the left frontoparietal network and visual areas. We suggest that these networks reflect the processing of visual information, the emergence of visuomotor plans, and the processing of somatosensory reafference or action's outcomes, respectively. We thus demonstrated that visuomotor integration resides in the dynamic reconfiguration of multiple cortico-cortical and cortico-subcortical FC networks. More generally, we showed that visuomotor-related FC is nonstationary and displays switching dynamics and areal flexibility over timescales relevant for task performance. In addition, visuomotor-related FC is characterized by sparse connectivity with density <10%. To conclude, our results elucidate the relation between dynamic network reconfiguration and executive functions over short timescales and provide a candidate entry point toward a better understanding of cognitive architectures.

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## Role of TAAR1 within the Subregions of the Mesocorticolimbic Dopaminergic System in Cocaine-Seeking Behavior

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A novel G-protein coupled receptor, trace amine-associated receptor 1 (TAAR1), has been shown to be a promising target to prevent stimulant relapse. Our recent studies showed that systemic administration of TAAR1 agonists decreased abuse-related behaviors of cocaine. However, the role of TAAR1 in specific subregions of the reward

system in drug addiction is unknown. Here, using a local pharmacological activation method, we assessed the role of TAAR1 within the subregions of the mesocorticolimbic system: that is, the VTA, the prelimbic cortex (PrL), and infralimbic cortex of medial prefrontal cortex, the core and shell of NAc, BLA, and CeA, on cue- and drug-induced cocaine-seeking in the rat cocaine reinstatement model. We first showed that TAAR1 mRNA was expressed throughout these brain regions. Rats underwent cocaine self-administration, followed by extinction training. R05166017 (1.5 or 5.0  $\mu$ g/side) or vehicle was microinjected into each brain region immediately before cue- and drug-induced reinstatement of cocaine-seeking. The results showed that microinjection of R05166017 into the VTA and PrL decreased both cue- and drug priming-induced cocaine-seeking. Microinjection of R05166017 into the NAc core and shell inhibited cue- and drug-induced cocaine-seeking, respectively. Locomotor activity or food reinforced operant responding was unaffected by microinjection of R05166017 into these brain regions. Cocaine-seeking behaviors were not affected by R05166017 when microinjected into the substantia nigra, infralimbic cortex, BLA, and CeA. Together, these results indicate that TAAR1 in different subregions of the mesocorticolimbic system distinctly contributes to cue- and drug-induced reinstatement of cocaine-seeking behavior.

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## The Caudate Nucleus Mediates Learning of Stimulus–Control State Associations

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A longstanding dichotomy in cognitive psychology and neuroscience pits controlled, top-down driven behavior against associative, bottom-up driven behavior, where cognitive control processes allow us to override well-learned stimulus–response (S–R) associations. By contrast, some previous studies have raised the intriguing possibility of an integration between associative and controlled processing in the form of stimulus–control state (S–C) associations, the learned linkage of specific stimuli to particular control states, such as high attentional selectivity. The neural machinery mediating S–C learning remains poorly understood, however. Here, we combined human functional magnetic resonance imaging (fMRI) with a previously developed Stroop protocol that allowed us to dissociate reductions in Stroop interference based on S–R learning from those based on S–C learning. We modeled subjects' acquisition of S–C and S–R associations using an associative learning model and then used trial-by-trial S–C and S–R prediction error (PE) estimates in model-based behavioral and fMRI analyses. We found that PE estimates derived from S–C and S–R associations accounted for the reductions in behavioral Stroop interference effects in the S–C and S–R learning conditions, respectively. Moreover, model-based fMRI analyses identified the caudate nucleus as the key structure involved in selectively updating stimulus–control state associations. Complementary analyses also revealed a greater reliance on parietal cortex when using the learned S–R versus S–C associations to minimize Stroop interference. These results support the emerging view that generalizable control states can become associated with specific bottom-up cues, and they place the caudate nucleus of the dorsal striatum at the center of the neural stimulus–control learning machinery.

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## NEUROBIOLOGY OF DISEASE

## TNF- $\alpha$ Differentially Regulates Synaptic Plasticity in the Hippocampus and Spinal Cord by Microglia-Dependent Mechanisms after Peripheral Nerve Injury

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Clinical studies show that chronic pain is accompanied by memory deficits and reduction in hippocampal volume. Experimental studies show that spared nerve injury (SNI) of the sciatic nerve induces long-term potentiation (LTP) at C-fiber synapses in spinal dorsal horn, but impairs LTP in the hippocampus. The opposite changes may contribute to neuropathic pain and memory deficits, respectively. However, the cellular and molecular mechanisms underlying the functional synaptic changes are unclear. Here, we show that the dendrite lengths and spine densities are reduced significantly in hippocampal CA1 pyramidal neurons, but increased in spinal neurokinin-1-positive neurons in mice after SNI, indicating that the excitatory synaptic connectivity is reduced in hippocampus but enhanced in spinal dorsal horn in this neuropathic pain model. Mechanistically, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) is upregulated in bilateral hippocampus and in ipsilateral spinal dorsal horn, whereas brain-derived neurotrophic factor (BDNF) is decreased in the hippocampus but increased in the ipsilateral spinal dorsal horn after SNI. Importantly, the SNI-induced opposite changes in synaptic connectivity and BDNF expression are prevented by genetic deletion of TNF receptor 1 *in vivo* and are mimicked by TNF- $\alpha$  in cultured slices. Furthermore, SNI activated microglia in both spinal dorsal horn and hippocampus; pharmacological inhibition or genetic ablation of microglia prevented the region-dependent synaptic changes, neuropathic pain, and memory deficits induced by SNI. The data suggest that neuropathic pain involves different structural synaptic alterations in spinal and hippocampal neurons that are mediated by overproduction of TNF- $\alpha$  and microglial activation and may underlie chronic pain and memory deficits.

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# DNA-PKcs, ATM, and ATR Interplay Maintains Genome Integrity during Neurogenesis

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The DNA damage response (DDR) orchestrates a network of cellular processes that integrates cell-cycle control and DNA repair or apoptosis, which serves to maintain genome stability. DNA-PKcs (the catalytic subunit of the DNA-dependent kinase, encoded by *PRKDC*), ATM (ataxia telangiectasia, mutated), and ATR (ATM and Rad3-related) are related PI3K-like protein kinases and central regulators of the DDR. Defects in these kinases have been linked to neurodegenerative or neurodevelopmental syndromes. In all cases, the key neuroprotective function of these kinases is uncertain. It also remains unclear how interactions between the three DNA damage-responsive kinases coordinate genome stability, particularly in a physiological context. Here, we used a genetic approach to identify the neural function of DNA-PKcs and the interplay between ATM and ATR during neurogenesis. We found that DNA-PKcs loss in the mouse sensitized neuronal progenitors to apoptosis after ionizing radiation because of excessive DNA damage. DNA-PKcs was also required to prevent endogenous DNA damage accumulation throughout the adult brain. In contrast, ATR coordinated the DDR during neurogenesis to direct apoptosis in cycling neural progenitors, whereas ATM regulated apoptosis in both proliferative and noncycling cells. We also found that ATR controls a DNA damage-induced G<sub>2</sub>/M checkpoint in cortical progenitors, independent of ATM and DNA-PKcs. These nonoverlapping roles were further confirmed via sustained murine embryonic or cortical development after all three kinases were simultaneously inactivated. Thus, our results illustrate how DNA-PKcs, ATM, and ATR have unique and essential roles during the DDR, collectively ensuring comprehensive genome maintenance in the nervous system.

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# Innate Immunity Stimulation via Toll-Like Receptor 9 Ameliorates Vascular Amyloid Pathology in Tg-SwDI Mice with Associated Cognitive Benefits

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Alzheimer's disease (AD) is characterized by the presence of parenchymal amyloid- $\beta$  ( $A\beta$ ) plaques, cerebral amyloid angiopathy (CAA) and neurofibrillary tangles. Currently there are no effective treatments for AD. Immunotherapeutic approaches under development are hampered by complications related to ineffectual clearance of CAA. Genome-wide association studies have demonstrated the importance of microglia in AD pathogenesis. Microglia are the primary innate immune cells of the brain. Depending on their activation state and environment, microglia can be beneficial or detrimental. In our prior work, we showed that stimulation of innate immunity with Toll-like receptor 9 agonist, class B CpG (cytosine-phosphate-guanine) oligodeoxynucleotides (ODNs), can reduce amyloid and tau pathologies without causing toxicity in Tg2576 and 3xTg-AD mouse models. However, these transgenic mice have relatively little CAA. In the current study, we evaluated the therapeutic profile of CpG ODN in a triple transgenic mouse model, Tg-SwDI, with abundant vascular amyloid, in association with low levels of parenchymal amyloid deposits. Peripheral administration of CpG ODN, both before and after the development of CAA, negated short-term memory deficits, as assessed by object-recognition tests, and was effective at improving spatial and working memory evaluated using a radial arm maze. These findings were associated with significant reductions of CAA pathology lacking adverse effects. Together, our extensive evidence suggests that this innovative immunomodulation may be a safe approach to ameliorate all hallmarks of AD pathology, supporting the potential clinical applicability of CpG ODN.

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# Opposing Effects of Valproic Acid Treatment Mediated by Histone Deacetylase Inhibitor Activity in Four Transgenic *X. laevis* Models of Retinitis Pigmentosa

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Retinitis pigmentosa (RP) is an inherited retinal degeneration (RD) that leads to blindness for which no treatment is available. RP is frequently caused by mutations in *Rhodopsin*; in some animal models, RD is exacerbated by light. Valproic acid (VPA) is a proposed treatment for RP and other neurodegenerative disorders, with a phase II trial for RP under way. However, the therapeutic mechanism is unclear, with minimal research supporting its use in RP. We investigated the effects of VPA on *Xenopus laevis* models of RP expressing human P23H, T17M, T4K, and Q344ter rhodopsins, which are associated with RP in humans. VPA ameliorated RD associated with P23H rhodopsin and promoted clearing of mutant rhodopsin from photoreceptors. The effect was equal to that of dark rearing, with no additive effect observed. Rescue of visual function was confirmed by electroretinography. In contrast, VPA exacerbated RD caused by T17M rhodopsin in light, but had no effect in darkness. Effects in T4K and Q344ter rhodopsin models were also negative. These effects of VPA were paralleled by treatment with three additional histone deacetylase (HDAC) inhibitors, but not other antipsychotics, chemical chaperones, or VPA structural analogues. In WT retinas, VPA treatment increased histone H3 acetylation. In addition, electron microscopy showed increased autophagosomes in rod inner segments with HDAC inhibitor (HDACi) treatment, potentially linking the therapeutic effects in P23H rhodopsin animals

and negative effects in other models with autophagy. Our results suggest that the success or failure of VPA treatment is dependent on genotype and that HDACi treatment is contraindicated for some RP cases.

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