

This Week in The Journal

Role of Specific Projections in Extinction and Reinstatement

Colby R. Keistler, Emma Hammarlund, Jacqueline M. Barker, Colin W. Bond, Ralph J. DiLeone, et al.

(see pages 4462–4471)

Relapse is a persistent risk for abstinent drug users, including alcoholics. It is often triggered by exposure to cues or environments associated with drug use. The neural bases of drug addiction and relapse have been elucidated in rodents, which are trained to press a lever to receive a drug, after which lever pressing is extinguished by ceasing drug delivery and then reinstated by presenting drug-associated cues. Such experiments have identified the medial prefrontal cortex (mPFC), basolateral amygdala (BLA), and nucleus accumbens (NAc) as essential for drug-related behaviors. Because these areas have numerous connections with each other and with other brain areas, however, how they interact to influence drug-seeking and extinction has been unclear.

To address this, Keistler et al. developed a technique to kill neurons that project from mPFC to BLA, from mPFC to NAc, or from BLA to NAc in rats. Virus containing floxed diphtheria-toxin receptors was injected into mPFC or BLA, and a retrogradely transported virus containing Cre recombinase was injected into a target area. This caused diphtheria-toxin receptors to be expressed only in neurons that projected to the selected target. Thus, subsequent administration of diphtheria toxin killed only these neurons. The toxin was administered after rats had learned to press a lever to receive alcohol to investigate the effects of specific projections on extinction and reinstatement of alcohol seeking.

Ablating neurons that project from mPFC to NAc had no effect on extinction of lever pressing, but it impaired cue-induced reinstatement. In contrast, ablating neurons that project from mPFC to BLA did not significantly affect extinction

or reinstatement. Finally, killing neurons that project from BLA to NAc did not affect extinction of lever pressing, but it impaired extinction of approach to the alcohol-delivery site, and it impaired cue-induced reinstatement of lever pressing.

These results suggest that both mPFC and BLA regulate cue-induced reinstatement via projections to NAc. This is consistent with the role of the NAc in driving motivated behaviors. More broadly, the work demonstrates the value of combining Cre-dependent expression of diphtheria-toxin receptors and retrogradely transported Cre-expressing viruses to elucidate the functions of specific neural pathways.



The ability to tap in rhythm depends on activity in the medial premotor cortex. See Merchant and Averbeck for details. "Hand drumming" By Hernán Piñera from Marbella - Timbal, CC BY-SA 2.0, <https://commons.wikimedia.org/w/index.php?curid=45183912>.

How the Medial Premotor Cortex Encodes Elapsed Time

Hugo Merchant and Bruno B. Averbeck

(see pages 4452–4564)

Most people can easily tap along with an ongoing beat and continue tapping at the same frequency when external cues stop. This ability—particularly the ability to continue tapping in the absence of cues—depends on neural activity in the medial premotor cortex, which is thought to encode elapsed time between taps. How neurons represent timing information remains unknown, but several computational models have been proposed. These include drift-diffusion models, in which

information accumulates over time until a threshold is reached, at which point an action is initiated. According to these models, differences in response times can occur if either the accumulation rate or the threshold changes.

To determine whether a drift-diffusion model might be used to encode elapsed time in the premotor cortex, Merchant and Averbeck trained monkeys to perform a synchronization-continuation task, in which animals tapped in synchrony with a cue and then continued to tap after the cue stopped. They found that the mean and standard deviation of the time intervals between monkeys' taps, as well as the distribution and other statistical features of the intervals, were consistent with the predictions of a drift-diffusion model.

The authors then recorded neural activity in the medial premotor cortex as monkeys performed the synchronization-continuation task, and used a decoding algorithm to estimate elapsed time between taps using population activity. Estimated elapsed times were generally consistent with actual times; but at the beginning and end of trials, the decoded times were sometimes shifted earlier or later than the actual time, suggesting the time counter did not always reset precisely when a tap occurred. Notably, during the continuation phase of the task (when no external timing cue was present), if neural activity suggested more time had elapsed than actually had, the monkeys tended to tap prematurely, whereas when the decoder lagged actual time, the tap was late.

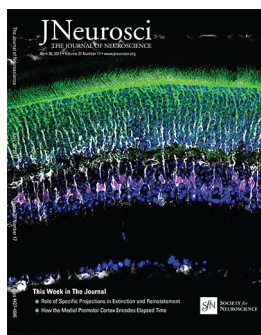
These results are consistent with the drift-diffusion model and suggest that population activity in the medial premotor cortex keeps track of elapsed time between actions in a rhythmic tapping task. With each tap, the internal timing mechanism resets, but resetting of the clock sometimes occurs somewhat before or after the tap occurs. Future work should investigate how the premotor cortex interacts with other components of timing circuitry to represent time across behaviors.

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

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Cover legend: This confocal image shows a retina prepared from a GLT1-EGFP mouse. The widely used astrocyte marker GLT1 (green) is highly expressed by neurons in the outer nuclear layer, while SOX9 (purple) is most prominent on Müller glial cells, as identified by glutamine synthetase (white). Cell nuclei are labeled by DAPI (blue). For more information, see the article by Sun et al. (pages 4493–4507).

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4645 *Correction:* The “Editor Column: Progressions” by Marina R. Picciotto and Teresa Esch, appeared on page 1055 of the February 1, 2017 issue. A correction for this editor column appears on page 4645.

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SOX9 Is an Astrocyte-Specific Nuclear Marker in the Adult Brain Outside the Neurogenic Regions

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Astrocytes have in recent years become the focus of intense experimental interest, yet markers for their definitive identification remain both scarce and imperfect. Astrocytes may be recognized as such by their expression of glial fibrillary acidic protein, glutamine synthetase, glutamate transporter 1 (GLT1), aquaporin-4, aldehyde dehydrogenase 1 family member L1, and other proteins. However, these proteins may all be regulated both developmentally and functionally, restricting their utility. To identify a nuclear marker pathognomonic of astrocytic phenotype, we assessed differential RNA expression by FACS-purified adult astrocytes and, on that basis, evaluated the expression of the transcription factor SOX9 in both mouse and human brain. We found that SOX9 is almost exclusively expressed by astrocytes in the adult brain except for ependymal cells and in the neurogenic regions, where SOX9 is also expressed by neural progenitor cells. Transcriptome comparisons of SOX9+ cells with GLT1+ cells showed that the two populations of cells exhibit largely overlapping gene expression. Expression of SOX9 did not decrease during aging and was instead upregulated by reactive astrocytes in a number of settings, including a murine model of amyotrophic lateral sclerosis (SOD1G93A), middle cerebral artery occlusion, and multiple mini-strokes. We quantified the relative number of astrocytes using the isotropic fractionator technique in combination with SOX9 immunolabeling. The analysis showed that SOX9+ astrocytes constitute ~10–20% of the total cell number in most CNS regions, a smaller fraction of total cell number than previously estimated in the normal adult brain.

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Dynamical Timescale Explains Marginal Stability in Excitability Dynamics

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Action potentials, taking place over milliseconds, are the basis of neural computation. However, the dynamics of excitability over longer, behaviorally relevant timescales remain underexplored. A recent experiment used long-term recordings from single neurons to reveal multiple timescale fluctuations in response to constant stimuli, along with more reliable responses to variable stimuli. Here, we demonstrate that this apparent paradox is resolved if neurons operate in a marginally stable dynamic regime, which we reveal using a novel inference method. Excitability in this regime is characterized by large fluctuations while retaining high sensitivity to external varying stimuli. A new model with a dynamic recovery timescale that interacts with excitability captures this dynamic regime and predicts the neurons' response with high accuracy. The model explains most experimental observations under several stimulus statistics. The compact structure of our model permits further exploration on the network level.

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Early Golgi Abnormalities and Neurodegeneration upon Loss of Presynaptic Proteins Munc18-1, Syntaxin-1, or SNAP-25

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The loss of presynaptic proteins Munc18-1, syntaxin-1, or SNAP-25 is known to produce cell death, but the underlying features have not been compared experimentally. Here, we investigated these features in cultured mouse CNS and DRG neurons. Side-by-side comparisons confirmed massive cell death, before synaptogenesis, within 1–4 DIV upon loss of t-SNAREs (syntaxin-1, SNAP-25) or Munc18-1, but not v-SNAREs (synaptobrevins/VAMP1/2/3 using tetanus neurotoxin (TeNT), also in TI-VAMP/VAMP7 knock-out (KO) neurons). A condensed *cis*-Golgi was the first abnormality observed upon Munc18-1 or SNAP-25 loss within 3 DIV. This phenotype was distinct from the Golgi fragmentation observed in apoptosis. Cell death was too rapid after syntaxin-1 loss to study Golgi abnormalities. Syntaxin-1 and Munc18-1 depend on each other for normal cellular levels. We observed that endogenous syntaxin-1 accumulates at the Golgi of Munc18-1 KO neurons. However, expression of a non-neuronal Munc18 isoform that does not bind syntaxin-1, Munc18-3, in Munc18-1 KO neurons prevented cell death and restored normal *cis*-Golgi morphology, but not synaptic transmission or syntaxin-1 targeting. Finally, we observed that DRG neurons are the only Munc18-1 KO neurons that do not degenerate *in vivo* or *in vitro*. In these neurons, *cis*-Golgi abnormalities were less severe, with no changes in Golgi shape. Together, these data demonstrate that cell death upon Munc18-1, syntaxin-1, or SNAP-25 loss occurs via a degenerative pathway unrelated to the known synapse function of these proteins and involving early *cis*-Golgi abnormalities, distinct from apoptosis.

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Synaptotagmin2 (Syt2) Drives Fast Release Redundantly with Syt1 at the Output Synapses of Parvalbumin-Expressing Inhibitory Neurons

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Parvalbumin-expressing inhibitory neurons in the mammalian CNS are specialized for fast transmitter release at their output synapses. However, the Ca^{2+} sensor(s) used by identified inhibitory synapses, including the output synapses of parvalbumin-expressing inhibitory neurons, have only recently started to be addressed. Here, we investigated the roles of Syt1 and Syt2 at two types of fast-releasing inhibitory connections in the mammalian CNS: the medial nucleus of the trapezoid body to lateral superior olive glycinergic synapse, and the basket/stellate cell-Purkinje GABAergic synapse in the cerebellum. We used conditional and conventional knock-out (KO) mouse lines, with viral expression of Cre-recombinase and a light-activated ion channel for optical stimulation of the transduced fibers, to produce Syt1-Syt2 double KO synapses *in vivo*. Surprisingly, we found that KO of Syt2 alone had only minor effects on evoked transmitter release, despite the clear presence of the protein in inhibitory nerve terminals revealed by immunohistochemistry. We show that Syt1 is weakly coexpressed at these inhibitory synapses and must be genetically inactivated together with Syt2 to achieve a significant reduction and desynchronization of fast release. Thus, our work identifies the functionally relevant Ca^{2+} sensor(s) at fast-releasing inhibitory synapses and shows that two major Syt isoforms can cooperate to mediate release at a given synaptic connection.

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A Presynaptic Group III mGluR Recruits $\text{G}\beta\gamma$ /SNARE Interactions to Inhibit Synaptic Transmission by Cone Photoreceptors in the Vertebrate Retina

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G-protein $\beta\gamma$ subunits ($\text{G}\beta\gamma$) interact with presynaptic proteins and regulate neurotransmitter release downstream of Ca^{2+} influx. To accomplish their roles in sensory signaling, photoreceptor synapses use specialized presynaptic proteins that support neurotransmission at active zone structures known as ribbons. While several G-protein coupled receptors (GPCRs) influence synaptic transmission at ribbon synapses of cones and other retinal neurons, it is unknown whether $\text{G}\beta\gamma$ contributes to these effects. We tested whether activation of one particular GPCR, a metabotropic glutamate receptor (mGluR), can reduce cone synaptic transmission via $\text{G}\beta\gamma$ in tiger salamander retinas. In recordings from horizontal cells, we found that an mGluR agonist (L-AP4) reduced cone-driven light responses and mEPSC frequency. In paired recordings of cones and horizontal cells, L-AP4 slightly reduced cone I_{Ca} (~10%) and caused a larger reduction in cone-driven EPSCs (~30%). Proximity ligation assay revealed direct interactions between SNAP-25 and $\text{G}\beta\gamma$ subunits in retinal synaptic layers. Pretreatment with the SNAP-25 cleaving protease BoNT/A inhibited L-AP4 effects on synaptic transmission, as did introduction of a peptide derived from the SNAP-25 C terminus. Introducing $\text{G}\beta\gamma$ subunits directly into cones reduced EPSC amplitude. This effect was inhibited by BoNT/A, supporting a role for $\text{G}\beta\gamma$ /SNAP-25 interactions. However, the mGluR-dependent reduction in I_{Ca} was not mimicked by $\text{G}\beta\gamma$, indicating that this effect was independent of $\text{G}\beta\gamma$. The finding that synaptic transmission at cone ribbon synapses is regulated by $\text{G}\beta\gamma$ /SNAP-25 interactions indicates that these mechanisms are shared by conventional and ribbon-type synapses. $\text{G}\beta\gamma$ liberated from other photoreceptor GPCRs is also likely to regulate synaptic transmission.

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DEVELOPMENT/PLASTICITY/REPAIR

K^{+} Channel Kv3.4 Is Essential for Axon Growth by Limiting the Influx of Ca^{2+} into Growth Cones

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Membrane excitability in the axonal growth cones of embryonic neurons influences axon growth. Voltage-gated K^{+} (Kv) channels are key factors in controlling membrane excitability, but whether they regulate axon growth remains unclear. Here, we report that Kv3.4 is expressed in the axonal growth cones of embryonic spinal commissural neurons, motoneurons, dorsal root ganglion neurons, retinal ganglion cells, and callosal projection neurons during axon growth. Our *in vitro* (cultured dorsal spinal neurons of chick embryos) and *in vivo* (developing chick spinal commissural axons and rat callosal axons) findings demonstrate that knockdown of Kv3.4 by a specific shRNA impedes axon initiation, elongation, pathfinding, and fasciculation. In cultured dorsal spinal neurons, blockade of Kv3.4 by blood depressing substance II suppresses axon growth via an increase in the amplitude and frequency of Ca^{2+} influx through T-type and L-type Ca^{2+} channels. Electrophysiological results show that Kv3.4, the major Kv channel in the axonal growth cones of embryonic dorsal spinal neurons, is activated at more hyperpolarized potentials and inactivated more slowly than it is in postnatal and adult neurons. The opening of Kv3.4 channels effectively reduces growth cone membrane excitability, thereby limiting excessive Ca^{2+} influx at subthreshold potentials or during Ca^{2+} -dependent action potentials. Furthermore, excessive Ca^{2+} influx induced by an optogenetic approach also inhibits axon growth. Our findings suggest that Kv3.4 reduces growth cone membrane excitability and maintains $[\text{Ca}^{2+}]_{\text{i}}$ at an optimal concentration for normal axon growth.

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Deafferented Adult Rod Bipolar Cells Create New Synapses with Photoreceptors to Restore Vision

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Upon degeneration of photoreceptors in the adult retina, interneurons, including bipolar cells, exhibit a plastic response leading to their aberrant rewiring. Photoreceptor reintroduction has been suggested as a potential approach to sight restoration, but the ability of deafferented bipolar cells to establish functional synapses with photoreceptors is poorly understood. Here we use photocoagulation to selectively destroy photoreceptors in adult rabbits while preserving the inner retina. We find that rods and cones shift into the ablation zone over several weeks, reducing the blind spot at scotopic and photopic luminances. During recovery, rod and cone bipolar cells exhibit markedly different responses to deafferentation. Rod bipolar cells extend their dendrites to form new synapses with healthy photoreceptors outside the lesion, thereby restoring visual function in the deafferented retina. Secretagogen-positive cone bipolar cells did not exhibit such obvious dendritic restructuring. These findings are encouraging to the idea of photoreceptor reintroduction for vision restoration in patients blinded by retinal degeneration. At the same time, they draw attention to the postsynaptic side of photoreceptor reintroduction; various bipolar cell types, representing different visual pathways, vary in their response to the photoreceptor loss and in their consequent dendritic restructuring.

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SYSTEMS/CIRCUITS

Driving Human Motor Cortical Oscillations Leads to Behaviorally Relevant Changes in Local GABA_A Inhibition: A tACS-TMS Study

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Beta and gamma oscillations are the dominant oscillatory activity in the human motor cortex (M1). However, their physiological basis and precise functional significance remain poorly understood. Here, we used transcranial magnetic stimulation (TMS) to examine the physiological basis and behavioral relevance of driving beta and gamma oscillatory activity in the human M1 using transcranial alternating current stimulation (tACS). tACS was applied using a sham-controlled crossover design at individualized intensity for 20 min and TMS was performed at rest (before, during, and after tACS) and during movement preparation (before and after tACS). We demonstrated that driving gamma frequency oscillations using tACS led to a significant, duration-dependent decrease in local resting-state GABA_A inhibition, as quantified by short interval intracortical inhibition. The magnitude of this effect was positively correlated with the magnitude of GABA_A decrease during movement preparation, when gamma activity in motor circuitry is known to increase. In addition, gamma tACS-induced change in GABA_A inhibition was closely related to performance in a motor learning task such that subjects who demonstrated a greater increase in GABA_A inhibition also showed faster short-term learning. The findings presented here contribute to our understanding of the neurophysiological basis of motor rhythms and suggest that tACS may have similar physiological effects to endogenously driven local oscillatory activity. Moreover, the ability to modulate local interneuronal circuits by tACS in a behaviorally relevant manner provides a basis for tACS as a putative therapeutic intervention.

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Blood Pressure Regulation by the Rostral Ventrolateral Medulla in Conscious Rats: Effects of Hypoxia, Hypercapnia, Baroreceptor Denervation, and Anesthesia

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Current understanding of the contribution of C1 neurons to blood pressure (BP) regulation derives predominantly from experiments performed in anesthetized animals or reduced *ex vivo* preparations. Here, we use ArchT loss-of-function optogenetics to explore BP regulation by C1 neurons in intact, unanesthetized rats. Using a lentivirus that expresses ArchT under the Phox2b-activated promoter PRSx8 (PRSx8-ArchT), ~65% of transduced neurons were C1 (balance retrotrapezoid nucleus, RTN). Other rats received CaMKII-ArchT3.0 AAV2 (CaMKII-ArchT), which transduced C1 neurons and larger numbers of unidentified glutamatergic and GABAergic cells. Under anesthesia, ArchT photoactivation reduced sympathetic nerve activity and BP and silenced/strongly inhibited most (7/12) putative C1 neurons. In unanesthetized PRSx8-ArchT-treated rats breathing room air, bilateral ArchT photoactivation caused a very small BP reduction that was only slightly larger under hypercapnia (6% FiCO₂), but was greatly enhanced during hypoxia (10 and 12% FiO₂), after sino-aortic denervation, or during isoflurane anesthesia. The degree of hypotension correlated with percentage of ArchT-transduced C1 neurons. ArchT photoactivation produced similar BP changes in CaMKII-ArchT-treated rats. Photoactivation in PRSx8-ArchT rats reduced breathing frequency (*F_R*), whereas *F_R* increased in CaMKII-ArchT rats. We conclude that the BP drop elicited by ArchT activation resulted from C1 neuron inhibition and was unrelated to breathing changes. C1 neurons have low activity under normoxia, but their activation is important to BP stability.

during hypoxia or anesthesia and contributes greatly to the hypertension caused by baroreceptor deafferentation. Finally, C1 neurons are marginally activated by hypercapnia and the large breathing stimulation caused by this stimulus has very little impact on resting BP.
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BEHAVIORAL/COGNITIVE

Regulation of Alcohol Extinction and Cue-Induced Reinstatement by Specific Projections among Medial Prefrontal Cortex, Nucleus Accumbens, and Basolateral Amygdala

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The ability to inhibit drinking is a significant challenge for recovering alcoholics, especially in the presence of alcohol-associated cues. Previous studies have demonstrated that the regulation of cue-guided alcohol seeking is mediated by the basolateral amygdala (BLA), nucleus accumbens (NAc), and medial prefrontal cortex (mPFC). However, given the high interconnectivity between these structures, it is unclear how mPFC projections to each subcortical structure, as well as projections between BLA and NAc, mediate alcohol-seeking behaviors. Here, we evaluate how cortico-striatal, cortico-amygdalar, and amygdalo-striatal projections control extinction and relapse in a rat model of alcohol seeking. Specifically, we used a combinatorial viral technique to express diphtheria toxin receptors in specific neuron populations based on their projection targets. We then used this strategy to create directionally selective ablations of three distinct pathways after acquisition of ethanol self-administration but before extinction and reinstatement. We demonstrate that ablation of mPFC neurons projecting to NAc, but not BLA, blocks cue-induced reinstatement of alcohol seeking and neither pathway is necessary for extinction of responding. Further, we show that ablating BLA neurons that project to NAc disrupts extinction of alcohol approach behaviors and attenuates reinstatement. Together, these data provide evidence that the mPFC→NAc pathway is necessary for cue-induced reinstatement of alcohol seeking, expand our understanding of how the BLA→NAc pathway regulates alcohol behavior, and introduce a new methodology for the manipulation of target-specific neural projections.
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Cued Memory Retrieval Exhibits Reinstatement of High Gamma Power on a Faster Timescale in the Left Temporal Lobe and Prefrontal Cortex

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Converging evidence suggests that reinstatement of neural activity underlies our ability to successfully retrieve memories. However, the temporal dynamics of reinstatement in the human cortex remain poorly understood. One possibility is that neural activity during memory retrieval, like replay of spiking neurons in the hippocampus, occurs at a faster timescale than during encoding. We tested this hypothesis in 34 participants who performed a verbal episodic memory task while we recorded high gamma (62–100 Hz) activity from subdural electrodes implanted for seizure monitoring. We show that reinstatement of distributed patterns of high gamma activity occurs faster than during encoding. Using a time-warping algorithm, we quantify the timescale of the reinstatement and identify brain regions that show significant timescale differences between encoding and retrieval. Our data suggest that temporally compressed reinstatement of cortical activity is a feature of cued memory retrieval.
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BK Channels Mediate Synaptic Plasticity Underlying Habituation in Rats

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Habituation is a basic form of implicit learning and represents a sensory filter that is disrupted in autism, schizophrenia, and several other mental disorders. Despite extensive research in the past decades on habituation of startle and other escape responses, the underlying neural mechanisms are still not fully understood. There is evidence from previous studies indicating that BK channels might play a critical role in habituation. We here used a wide array of approaches to test this hypothesis. We show that BK channel activation and subsequent phosphorylation of these channels are essential for synaptic depression presumably underlying startle habituation in rats, using patch-clamp recordings and voltage-sensitive dye imaging in slices. Furthermore, positive modulation of BK channels *in vivo* can enhance short-term habituation. Although results using different approaches do not always perfectly align, together they provide convincing evidence for a crucial role of BK channel phosphorylation in synaptic depression underlying short-term habituation of startle. We also show that this mechanism can be targeted to enhance short-term habituation and therefore to potentially ameliorate sensory filtering deficits associated with psychiatric disorders.
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The Computational and Neural Basis of Rhythmic Timing in Medial Premotor Cortex

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The neural underpinnings of rhythmic behavior, including music and dance, have been studied using the synchronization-continuation task (SCT), where subjects initially tap in synchrony with an isochronous metronome and then keep tapping at a similar rate via an internal beat mechanism. Here, we provide behavioral and neural evidence that supports a resetting drift-diffusion model (DDM) during SCT. Behaviorally, we show the model replicates the linear relation between the mean and standard-deviation of the intervals produced by monkeys in SCT. We then show that neural populations in the medial premotor cortex (MPC) contain an accurate trial-by-trial representation of elapsed-time between taps. Interestingly, the autocorrelation structure of the elapsed-time representation is consistent with a DDM. These results indicate that MPC has an orderly representation of time with features characteristic of concatenated DDMs and that this population signal can be used to orchestrate the rhythmic structure of the internally timed elements of SCT.

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NEUROBIOLOGY OF DISEASE

Electrocorticographic Dynamics as a Novel Biomarker in Five Models of Epileptogenesis

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Postinjury epilepsy (PIE) is a devastating sequela of various brain insults. While recent studies offer novel insights into the mechanisms underlying epileptogenesis and discover potential preventive treatments, the lack of PIE biomarkers hinders the clinical implementation of such treatments. Here we explored the biomarker potential of different electrographic features in five models of PIE. Electrocorticographic or intrahippocampal recordings of epileptogenesis (from the insult to the first spontaneous seizure) from two laboratories were analyzed in three mouse and two rat PIE models. Time, frequency, and fractal and nonlinear properties of the signals were examined, in addition to the daily rate of epileptiform spikes, the relative power of five frequency bands (theta, alpha, beta, low gamma, and high gamma) and the dynamics of these features over time. During the latent pre-seizure period, epileptiform spikes were more frequent in epileptic compared with nonepileptic rodents; however, this feature showed limited predictive power due to high inter- and intra-animal variability. While nondynamic rhythmic representation failed to predict epilepsy, the dynamics of the theta band were found to predict PIE with a sensitivity and specificity of >90%. Moreover, theta dynamics were found to be inversely correlated with the latency period (and thus predict the onset of seizures) and with the power change of the high-gamma rhythm. In addition, changes in theta band power during epileptogenesis were associated with altered locomotor activity and distorted circadian rhythm. These results suggest that changes in theta band during the epileptogenic period may serve as a diagnostic biomarker for epileptogenesis, able to predict the future onset of spontaneous seizures.

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Deficiency in Neuronal TGF- β Signaling Leads to Nigrostriatal Degeneration and Activation of TGF- β Signaling Protects against MPTP Neurotoxicity in Mice

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Transforming growth factor- β (TGF- β) plays an important role in the development and maintenance of embryonic dopaminergic (DA) neurons in the midbrain. To study the function of TGF- β signaling in the adult nigrostriatal system, we generated transgenic mice with reduced TGF- β signaling in mature neurons. These mice display age-related motor deficits and degeneration of the nigrostriatal system. Increasing TGF- β signaling in the substantia nigra through adeno-associated virus expressing a constitutively active type I receptor significantly reduces 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced dopaminergic neurodegeneration and motor deficits. These results suggest that TGF- β signaling is critical for adult DA neuron survival and that modulating this signaling pathway has therapeutic potential in Parkinson disease.

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Alcohol Dependence Disrupts Amygdalar L-Type Voltage-Gated Calcium Channel Mechanisms

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L-type voltage-gated calcium channels (LTCCs) are implicated in several psychiatric disorders that are comorbid with alcoholism and involve amygdala dysfunction. Within the amygdala, the central nucleus (CeA) is critical in acute alcohol's reinforcing actions, and its dysregulation in human alcoholics drives their negative emotional state and motivation to drink. Here we investigated the specific role of CeA LTCCs in the effects of acute alcohol at the molecular, cellular physiology, and behavioral levels, and their potential neuroadaptation in alcohol-dependent rats. Alcohol increases CeA activity (neuronal firing rates and GABA release) in naive rats by engaging LTCCs, and intra-CeA LTCC blockade reduces alcohol intake in nondependent rats. Alcohol dependence reduces CeA LTCC membrane abundance and disrupts this LTCC-based mechanism; instead, corticotropin-releasing factor type 1 receptors (CRF₁s) mediate alcohol's effects on CeA activity and drive the escalated alcohol intake of alcohol-dependent rats. Collectively, our data indicate that alcohol dependence functionally alters the molecular mechanisms underlying the CeA's response to alcohol (from LTCC- to CRF₁-driven). This mechanistic switch contributes to and reflects the prominent role of the CeA in the negative emotional state that drives excessive drinking.

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