



Cover legend: This image shows dorsal root ganglion sensory neurons of the vesicular glutamate transporter 3 (Vglut3) lineage (red). Neurons are also labeled with antibodies against β III-tubulin (green) and neurofilament heavy chain (blue). Menthol-sensitive Vglut3-lineage neurons are a highly excitable population that fire robust trains of tetrodotoxin-sensitive action potentials and show unique sodium channel inactivation kinetics. For more information, see the article by Griffith et al. (pages 7086–7101).

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Strengthening of the Efferent Olivocochlear System Leads to Synaptic Dysfunction and Tonotopy Disruption of a Central Auditory Nucleus

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The auditory system in many mammals is immature at birth but precisely organized in adults. Spontaneous activity in the inner ear plays a critical role in guiding this maturation process. This is shaped by an efferent pathway that descends from the brainstem and makes transient direct synaptic contacts with inner hair cells. In this work, we used an $\alpha 9$ cholinergic nicotinic receptor knock-in mouse model (of either sex) with enhanced medial efferent activity (*Chrna9L9' T, L9' T*) to further understand the role of the olivocochlear system in the correct establishment of auditory circuits. Wave III of auditory brainstem responses (which represents synchronized activity of synapses within the superior olivary complex) was smaller in *L9' T* mice, suggesting a central dysfunction. The mechanism underlying this functional alteration was analyzed in brain slices containing the medial nucleus of the trapezoid body (MNTB), where neurons are topographically organized along a mediolateral (ML) axis. The topographic organization of MNTB physiological properties observed in wildtype (WT) was abolished in *L9' T* mice. Additionally, electrophysiological recordings in slices indicated MNTB synaptic alterations. *In vivo* multielectrode recordings showed that the overall level of MNTB activity was reduced in the *L9' T*. The present results indicate that the transient cochlear efferent innervation to inner hair cells during the critical period before the onset of hearing is involved in the refinement of topographic maps as well as in setting the properties of synaptic transmission at a central auditory nucleus.

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Learning Induces Transient Upregulation of Brevican in the Auditory Cortex during Consolidation of Long-Term Memories

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It is a daily challenge for our brains to establish new memories via learning while providing stable storage of remote memories. In the adult vertebrate brain, bimodal regulation of the extracellular matrix (ECM) may regulate the delicate balance of learning-dependent plasticity and stable memory formation. Here, we trained adult male mice in a cortex-dependent auditory discrimination task and measured the abundance of ECM proteins brevican (BCN) and tenascin-R over the course of acquisition learning, consolidation, and long-term recall in two learning-relevant brain regions; the auditory cortex and hippocampus. Although early training led to a general downregulation of total ECM proteins, successful retrieval correlated with a region-specific and transient upregulation of BCN levels in the auditory cortex. No other parameter such as arousal or stress could account for the transient and region-specific BCN upregulation. This performance-dependent biphasic regulation of the ECM may assist transient plasticity to facilitate initial learning and subsequently promote the long-term consolidation of memory.

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In Vitro Nociceptor Neuroplasticity Associated with *In Vivo* Opioid-Induced Hyperalgesia

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Opioid-induced hyperalgesia (OIH) is a serious adverse event produced by opioid analgesics. Lack of an *in vitro* model has hindered study of its underlying mechanisms. Recent evidence has implicated a role of nociceptors in OIH. To investigate the cellular and molecular mechanisms of OIH in nociceptors, *in vitro*, subcutaneous administration of an analgesic dose of fentanyl (30 μ g/kg, s.c.) was performed *in vivo* in male rats. Two days later, when fentanyl was administered intradermally (1 μ g, i.d.), in the vicinity of peripheral nociceptor terminals, it produced mechanical hyperalgesia (OIH). Additionally, 2 d after systemic fentanyl, rats had also developed hyperalgesic priming (opioid-primed rats), long-lasting nociceptor neuroplasticity manifested as prolongation of prostaglandin E_2 (PGE₂) hyperalgesia. OIH was reversed, *in vivo*, by intrathecal administration of cordycepin, a protein translation inhibitor that reverses priming. When fentanyl (0.5 nM) was applied to dorsal root ganglion (DRG) neurons, cultured from opioid-primed rats, it induced a μ -opioid receptor (MOR)-dependent increase in $[Ca^{2+}]_i$ in 26% of small-diameter neurons and significantly sensitized (decreased action potential rheobase) weakly IB4⁺ and IB4[−] neurons. This sensitizing effect of fentanyl was reversed in weakly IB4⁺ DRG neurons cultured from opioid-primed rats after *in vivo* treatment with cordycepin, to reverse of OIH. Thus, *in vivo* administration of fentanyl induces nociceptor neuroplasticity, which persists in culture, providing evidence for the role of nociceptor MOR-mediated calcium signaling and peripheral protein translation, in the weakly IB4-binding population of nociceptors, in OIH.

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PINK1 Content in Mitochondria is Regulated by ER-Associated Degradation

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Maintaining a pool of functional mitochondria requires degradation of damaged ones within the cell. PINK1 is critical in this quality-control process: loss of mitochondrial membrane potential causes PINK1 to accumulate on the mitochondrial surface, triggering mitophagy. However, little is known about how PINK1 is regulated. Recently, we showed that PINK1 content is kept low in healthy mitochondria by continuous ubiquitination and proteasomal degradation of its mature form via a mechanism inconsistent with the proposed N-end rule process. Using both human female and monkey cell lines, we now demonstrate that once generated within the mitochondria, 52 kDa PINK1 adopts a mitochondrial topology most consistent with it being at the mitochondrial–endoplasmic reticulum (ER) interface. From this particular submitochondrial location, PINK1 interacts with components of the ER-associated degradation pathway, such as the E3 ligases gp78 and HRD1, which cooperate to catalyze PINK1 ubiquitination. The valosin-containing protein and its cofactor, UFD1, then target ubiquitinated PINK1 for proteasomal degradation. Our data show that PINK1 in healthy mitochondria is negatively regulated via an interplay between mitochondria and ER, and shed light on how this mitochondrial protein gains access to the proteasome.

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Tetrodotoxin-Sensitive Sodium Channels Mediate Action Potential Firing and Excitability in Menthol-Sensitive Vglut3-Lineage Sensory Neurons

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Small-diameter vesicular glutamate transporter 3-lineage (Vglut3^{lineage}) dorsal root ganglion (DRG) neurons play an important role in mechanosensation and thermal hypersensitivity; however, little is known about their intrinsic electrical properties. We therefore set out to investigate mechanisms of excitability within this population. Calcium microfluorimetry analysis of male and female mouse DRG neurons demonstrated that the cooling compound menthol selectively activates a subset of Vglut3^{lineage} neurons. Whole-cell recordings showed that small-diameter Vglut3^{lineage} DRG neurons fire menthol-evoked action potentials and exhibited robust, transient receptor potential melastatin 8 (TRPM8)-dependent discharges at room temperature. This heightened excitability was confirmed by current-clamp and action potential phase-plot analyses, which showed menthol-sensitive Vglut3^{lineage} neurons to have more depolarized membrane potentials, lower firing thresholds, and higher evoked firing frequencies compared with menthol-insensitive Vglut3^{lineage} neurons. A biophysical analysis revealed voltage-gated sodium channel (Na_v) currents in menthol-sensitive Vglut3^{lineage} neurons were resistant to entry into slow inactivation compared with menthol-insensitive neurons. Multiplex *in situ* hybridization showed similar distributions of tetrodotoxin (TTX)-sensitive Na_v transcripts between TRPM8-positive and -negative Vglut3^{lineage} neurons; however, Na_v1.8 transcripts, which encode TTX-resistant channels, were more prevalent in TRPM8-negative neurons. Conversely, pharmacological analyses identified distinct functional contributions of Na_v subunits, with Na_v1.1 driving firing in menthol-sensitive neurons, whereas other small-diameter Vglut3^{lineage} neurons rely primarily on TTX-resistant Na_v channels. Additionally, when Na_v1.1 channels were blocked, the remaining Na_v current readily entered into slow inactivation in menthol-sensitive Vglut3^{lineage} neurons. Thus, these data demonstrate that TTX-sensitive Na_vs drive action potential firing in menthol-sensitive sensory neurons and contribute to their heightened excitability.

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TMEM16B Calcium-Activated Chloride Channels Regulate Action Potential Firing in Lateral Septum and Aggression in Male Mice

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The lateral septum (LS) plays an important role in regulating aggression. It is well recognized that LS lesions lead to a dramatic increase in aggressive behaviors. A better understanding of LS neurophysiology and its functional output is therefore important to assess LS involvement in regulating aggression. The LS is a heterogeneous structure that maintains inputs and outputs with multiple brain regions, and is also divided into subregions that innervate one another. Thus, it is challenging to identify the exact cell type and projections for characterization. In this study, we determined the expression pattern of the calcium-activated chloride channel, TMEM16B, in the LS of both male and female mice. We then investigated the physiological contribution of the calcium-activated chloride channel to LS neuronal signaling. By performing whole-cell patch-clamp recording, we showed that TMEM16B alters neurotransmitter release at the hippocampal-LS synapse, and regulates spike frequency and spike frequency adaptation in subpopulations of LS neurons. We further demonstrated that loss of TMEM16B function promotes lengthened displays of aggressive behaviors by

male mice during the resident intruder paradigm. In conclusion, our findings suggest that TMEM16B function contributes to neuronal excitability in subpopulations of LS neurons and the regulation of aggression in male mice.

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DEVELOPMENT/PLASTICITY/REPAIR

MAP7 Prevents Axonal Branch Retraction by Creating a Stable Microtubule Boundary to Rescue Polymerization

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Complex neural circuits are built from axonal branches that allow each neuron to connect with multiple targets. During development, maturation of nascent branches depends on stabilization of newly assembled or transported microtubules, which are thought to be regulated by microtubule-associated proteins (MAPs). However, because many known MAPs inhibit branch formation, it is not clear which MAP is responsible for regulating microtubule stability during branch development. Here, we show that MAP7, a less-well understood MAP that is localized to branch junctions, provides a key molecular mechanism to regulate microtubule stability during branch formation. In developing rodent sensory neurons of mixed sex, MAP7 is required for branch maturation mainly by preventing branch retraction. This function is mediated by the ability of MAP7 to control microtubule stability, as microtubules are more stable at branch junctions where MAP7 is localized. Consistently, nascent branches depleted of MAP7 have decreased stable microtubules but increased dynamic microtubules. Moreover, MAP7 binds to the acetylated and stable region of individual microtubules and avoids the dynamic plus end, thereby creating a boundary that prevents microtubule depolymerization and rescues microtubule polymerization. This unique binding property, which is not observed for other MAPs, can prevent branch retraction caused by laser-induced severing or nocodazole-induced microtubule depolymerization. Together, our study identifies a novel molecular mechanism mediated by MAP7 to regulate microtubule stability and strengthen branches at different stages of axonal branch morphogenesis.

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SYSTEMS/CIRCUITS

Ca²⁺-Activated K⁺ Channels Reduce Network Excitability, Improving Adaptability and Energetics for Transmitting and Perceiving Sensory Information

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Ca²⁺-activated K⁺ channels (BK and SK) are ubiquitous in synaptic circuits, but their role in network adaptation and sensory perception remains largely unknown. Using electrophysiological and behavioral assays and biophysical modeling, we discover how visual information transfer in mutants lacking the BK channel (*dSlo*[−]), SK channel (*dSK*[−]), or both (*dSK*[−]; *dSlo*[−]) is shaped in the female fruit fly (*Drosophila melanogaster*) R1–R6 photoreceptor-LMC circuits (R-LMC-R system) through synaptic feedforward-feedback interactions and reduced R1–R6 *Shaker* and *Shab* K⁺ conductances. This homeostatic compensation is specific for each mutant, leading to distinctive adaptive dynamics. We show how these dynamics inescapably increase the energy cost of information and promote the mutants' distorted motion perception, determining the true price and limits of chronic homeostatic compensation in an *in vivo* genetic animal model. These results reveal why Ca²⁺-activated K⁺ channels reduce network excitability (energetics), improving neural adaptability for transmitting and perceiving sensory information.

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Development of Human Emotion Circuits Investigated Using a Big-Data Analytic Approach: Stability, Reliability, and Robustness

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Emotion perception is fundamental to affective and cognitive development and is thought to involve distributed brain circuits. Efforts to chart neurodevelopmental changes in emotion have been severely hampered by narrowly focused approaches centered on activation of individual brain regions and small sample sizes. Here we investigate the maturation of human functional brain circuits associated with identification of fearful, angry, sad, happy, and neutral faces using a large sample of 759 children, adolescents, and adults (ages 8–23; female/male = 419/340). Network analysis of emotion-related brain circuits revealed three functional modules, encompassing lateral frontoparietal, medial prefrontal-posterior cingulate, and subcortical-posterior insular cortices, with hubs in medial prefrontal, but not posterior cingulate, cortex. This overall network architecture was stable by age 8, and it anchored maturation of circuits important for salience detection and cognitive control, as well as dissociable circuit patterns across distinct emotion categories. Our findings point to similarities and differences in functional circuits associated with identification of fearful, angry, sad, happy, and neutral faces, and reveal aspects of brain circuit organization underlying emotion perception that are stable over development as well as features that change with age. Reliability analyses demonstrated the robustness of our findings and highlighted the importance of large samples for probing functional brain circuit development. Our study emphasizes a need to focus beyond amygdala circuits and provides a robust neurodevelopmental template for investigating emotion perception and identification in psychopathology.

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Stimulation of the Posterior Cingulate Cortex Impairs Episodic Memory Encoding

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Neuroimaging experiments implicate the posterior cingulate cortex (PCC) in episodic memory processing, making it a potential target for responsive neuromodulation strategies outside of the hippocampal network. However, causal evidence for the role that PCC plays in memory encoding is lacking. In human female and male participants ($N = 17$) undergoing seizure mapping, we investigated functional properties of the PCC using deep brain stimulation (DBS) and stereotactic electroencephalography. We used a verbal free recall paradigm in which the PCC was stimulated during presentation of half of the study lists, whereas no stimulation was applied during presentation of the remaining lists. We investigated whether stimulation affected memory and modulated hippocampal activity. Results revealed four main findings. First, stimulation during episodic memory encoding impaired subsequent free recall, predominantly for items presented early in the study lists. Second, PCC stimulation increased hippocampal gamma-band power. Third, stimulation-induced hippocampal gamma power predicted the magnitude of memory impairment. Fourth, functional connectivity between the hippocampus and PCC predicted the strength of the stimulation effect on memory. Our findings offer causal evidence implicating the PCC in episodic memory encoding. Importantly, the results indicate that stimulation targeted outside of the temporal lobe can modulate hippocampal activity and impact behavior. Furthermore, measures of connectivity between brain regions within a functional network can be informative in predicting behavioral effects of stimulation. Our findings have significant implications for developing therapies to treat memory disorders and cognitive impairment using DBS.

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Two Spatially Distinct Posterior Alpha Sources Fulfill Different Functional Roles in Attention

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Directing attention helps to extract relevant information and suppress distracters. Alpha brain oscillations (8–12 Hz) are crucial for this process, with power decreases facilitating processing of important information and power increases inhibiting brain regions processing irrelevant information. Evidence for this phenomenon arises from visual attention studies (Worden et al., 2000); however, the effect also exists in other modalities, including the somatosensory system (Haegens et al., 2011) and intersensory attention tasks (Foxe and Snyder, 2011). We investigated in human participants (10 females, 10 males) the role of alpha oscillations in focused (0/100%) versus divided (40/60%) attention, both across modalities (visual/somatosensory; Experiment 1) and within the same modality (visual domain: across hemifields; Experiment 2) while recording EEG over 128 scalp electrodes. In Experiment 1, participants divided their attention between visual and somatosensory modality to determine the temporal/spatial frequency of a target stimulus (vibrotactile stimulus/Gabor grating). In Experiment 2, participants divided attention between two visual hemifields to identify the orientation of a Gabor grating. In both experiments, prestimulus alpha power in visual areas decreased linearly with increasing attention to visual stimuli. In contrast, prestimulus alpha power in parietal areas was lower when attention was divided between modalities/hemifields compared with focused attention. These results suggest there are two alpha sources, one of which reflects the “visual spotlight of attention” and the other reflects attentional effort. To our knowledge, this is the first study to show that attention recruits two spatially distinct alpha sources in occipital and parietal brain regions, acting simultaneously but serving different functions in attention.

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Diverse Mechanisms Lead to Common Dysfunction of Striatal Cholinergic Interneurons in Distinct Genetic Mouse Models of Dystonia

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Clinical and experimental data indicate striatal cholinergic dysfunction in dystonia, a movement disorder typically resulting in twisted postures via abnormal muscle contraction. Three forms of isolated human dystonia result from mutations in the *TOR1A* (DYT1), *THAP1* (DYT6), and *GNAL* (DYT25) genes. Experimental models carrying these mutations facilitate identification of possible shared cellular mechanisms. Recently, we reported elevated extracellular striatal acetylcholine by *in vivo* microdialysis and paradoxical excitation of cholinergic interneurons (ChIs) by dopamine D2 receptor (D2R) agonism using *ex vivo* slice electrophysiology in *Dyt1*^{ΔGAG/+} mice. The paradoxical excitation was caused by overactive muscarinic receptors (mAChRs), leading to a switch in D2R coupling from canonical G_{i/o} to noncanonical β-arrestin signaling. We sought to determine whether these mechanisms in *Dyt1*^{ΔGAG/+} mice are shared with *Thap1*^{C54Y/+} knock-in and *Gnal*^{+/-} knock-out dystonia models and to determine the impact of sex. We found *Thap1*^{C54Y/+} mice of both sexes have elevated extracellular striatal acetylcholine and D2R-induced paradoxical ChI excitation, which was reversed by mAChR inhibition. Elevated extracellular acetylcholine was absent in male and female *Gnal*^{+/-} mice, but the paradoxical D2R-mediated ChI excitation was retained and only reversed by inhibition of adenosine A2ARs. The G_{i/o}-preferring D2R agonist failed to increase ChI excitability, suggesting a possible switch in coupling of D2Rs to β-arrestin, as seen previously in a DYT1 model. These data show that, whereas elevated extracellular acetylcholine levels are not always detected across these genetic models of human dystonia, the D2R-mediated paradoxical excitation of ChIs is shared and is caused by altered function of distinct G-protein-coupled receptors. The Journal of Neuroscience, September 4, 2019 • 39(36):7195–7205

Indirect Medium Spiny Neurons in the Dorsomedial Striatum Regulate Ethanol-Containing Conditioned Reward Seeking

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Adenosine 2A receptor (A_{2A}R)-containing indirect medium spiny neurons (iMSNs) in the dorsomedial striatum (DMS) contribute to reward-seeking behaviors. However, those roles for ethanol-seeking behaviors remain unknown. To investigate ethanol-seeking behaviors, we used an ethanol-containing reward (10% ethanol and 10% sucrose solution; 10E10S). Upon conditioning with 10E10S, mice that initially only preferred 10% sucrose, not 10E10S, showed a stronger preference for 10E10S. Then, we investigated whether the manipulation of the DMS–external globus pallidus (GPe) iMSNs circuit alters the ethanol-containing reward (10E10S) seeking behaviors using the combination of pharmacologic and optogenetic approaches. DMS A_{2A}R activation dampened operant conditioning-induced ethanol-containing reward, whereas A_{2A}R antagonist abolished the effects of the A_{2A}R agonist and restored ethanol-containing reward-seeking. Moreover, pre-ethanol exposure potentiated the A_{2A}R-dependent reward-seeking. Interestingly, mice exhibiting ethanol-containing reward-seeking showed the reduction of the DMS iMSNs activity, suggesting that disinhibiting iMSNs decreases reward-seeking behaviors. In addition, we found that A_{2A}R activation reversed iMSNs neural activity in the DMS. Similarly, optogenetic stimulation of the DMS-GPe iMSNs reduced ethanol-containing reward-seeking, whereas optogenetic inhibition of the DMS-GPe iMSNs reversed this change. Together, our study demonstrates that DMS A_{2A}R and iMSNs regulate ethanol-containing reward-seeking behaviors. The Journal of Neuroscience, September 4, 2019 • 39(36):7206–7217

Neuroinflammation and Functional Connectivity in Alzheimer's Disease: Interactive Influences on Cognitive Performance

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Neuroinflammation is a key part of the etio-pathogenesis of Alzheimer's disease (AD). We tested the relationship between neuroinflammation and the disruption of functional connectivity in large-scale networks, and their joint influence on cognitive impairment. We combined [¹¹C]PK11195 positron emission tomography (PET) and resting-state functional magnetic resonance imaging (rs-fMRI) in 28 patients (12 females/16 males) with clinical diagnosis of probable AD or mild cognitive impairment with positive PET biomarker for amyloid, and 14 age-, sex-, and education-matched healthy controls (8 females/6 males). Source-based “inflammometry” was used to extract principal components of [¹¹C]PK11195 PET signal variance across all participants. rs-fMRI data were preprocessed via independent component analyses to classify neuronal and non-neuronal signals. Multiple linear regression models identified sources of signal covariance between neuroinflammation and brain connectivity profiles, in relation to the diagnostic group (patients, controls) and cognitive status.

Patients showed significantly higher [^{11}C]PK11195 binding relative to controls, in a distributed spatial pattern including the hippocampus, frontal, and inferior temporal cortex. Patients with enhanced loading on this [^{11}C]PK11195 binding distribution displayed diffuse abnormal functional connectivity. The expression of a stronger association between such abnormal connectivity and higher levels of neuroinflammation correlated with worse cognitive deficits.

Our study suggests that neuroinflammation relates to the pathophysiological changes in network function that underlie cognitive deficits in Alzheimer's disease. Neuroinflammation, and its association with functionally-relevant reorganization of brain networks, is proposed as a target for emerging immunotherapeutic strategies aimed at preventing or slowing the emergence of dementia.

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