This Week in The Journal

Fentanyl Primes Neurons for More Pain

Dioneia Araldi, Eugen V. Khomula, Luiz F. Ferrari, and Jon D. Levine

(see pages 2226–2245)

The United States is currently in the grip of an epidemic of misuse of opioids, powerful pain-relieving drugs that cause a range of side effects including addiction and death. A lesser-known side effect of opioids is hyperalgesia, or an exaggerated pain response to a stimulus. Opioid-induced hyperalgesia (OIH) can develop with extended use, and opioids predispose animals and humans to future hyperalgesia, in a phenomenon called priming.

Priming is a form of neuroplasticity at primary sensory afferent neurons that detect painful stimuli in the periphery and synapse onto spinal cord neurons. There are two types of priming: type I, which involves changes in protein translation, and type II, which relies on signaling by a pair of protein kinases. Fentanyl is a potent, fast-acting synthetic opioid drug increasingly contributing to overdose; even a single administration of the drug can cause priming in humans. Araldi et al. set out to understand how the analgesic drug rapidly sensitizes pain.

To determine the mechanisms activated by fentanyl, the researchers treated male rats with intrathecal, intradermal, or systemic fentanyl and used inhibitors of priming at central and peripheral terminals. Thirty minutes after intrathecal treatment, mechanical pain threshold was reduced by approximately one-third, indicative of OIH. To measure fentanyl-induced priming, the authors treated rats with prostaglandin E2 (PGE2), an inflammatory mediator that causes transient mechanical hyperalgesia. The sensitivity was prolonged in rats that had received fentanyl treatment at least 8 h beforehand to initiate priming. Regardless of delivery site, fentanyl led to type II priming at central nociceptor terminals and type I priming at peripheral terminals. When fentanyl was delivered intradermally, priming developed at the injection site. Priming could be blocked by μ-opioid receptor (MOR) antisense oligodeoxynucleotides, confirming that it depended on activation of the MOR.

Ablation of specific types of nociceptors showed that both peptidergic and nonpeptidergic nociceptors were required to establish central priming after intrathecal fentanyl administration. But surprisingly, priming at peripheral terminals arose even when both cell types were absent. Although the cell type involved in this peripheral priming is still unclear, the rapid signaling depended on signaling by calcium released from the endoplasmic reticulum. The findings further demonstrate the drawbacks of fentanyl, but a better understanding of MOR signaling and the mechanisms contributing to priming could lead to better, safer pain treatments.

Derivatives of the opium poppy have been used to ease pain and produce euphoria for millennia. Efforts to produce more potent agonists of endogenous opiate receptors continue. One of the strongest synthetic opiates is fentanyl. Paradoxically, fentanyl and other opiates prime nociceptors to generate exaggerated pain responses to future insults. See Araldi et al. for details. Photo by Kora27, CC BY-SA 4.0, https://commons.wikimedia.org/w/index.php?curid=59048260.

Synaptic Changes in Hyperandrogenized Neuroendocrine System

Tova Berg, Marina A. Silveira, and Suzanne M. Moenter (see pages 2283–2293)

Polycystic ovary syndrome (PCOS) is a leading cause of infertility that affects an estimated 8% of women. PCOS arises from overactivity in the neuroendocrine signaling between the hypothalamus, pituitary, and gonads that controls the reproductive cycle; clinical studies suggest the disruption begins in advance of puberty. Now, Berg et al. have described in detail electrophysiological activity in the circuit from pre-puberty through adulthood in normal male and female mice and those prenatally treated with androgen (PNA), a rodent model of PCOS.

Hypothalamic neurons release gonadotropin-releasing hormone (GnRH) onto pituitary cells that in turn release leutinizing hormone (LH) and follicle-stimulating hormone (FSH) into the bloodstream. In response, the ovaries release steroids that feed back to the hypothalamus, fine-tuning the circuit. In women with PCOS, the cyclic release of GnRH—and thereby other hormones—is disrupted. GnRH neurons receive hypothalamic GABAergic inputs that are excitatory due to GnRH neurons' unusual chloride reversal potential. The researchers made whole-cell voltage-clamp recordings of GABAergic postsynaptic currents (PSCs) from GnRH neurons in brain slices from 1-, 2-, 3-, and 4-week-old and adult mice. Spontaneous GABAergic PSCs were detectable by 1 week in neurons from all mice. Transmission increased between 2 and 3 weeks in females, and by 4 weeks in males. PNA caused a more robust developmental increase in signaling in female mice than in controls, and this persisted through adulthood. In contrast, a boost in male signaling was transient.

In females, the frequency of miniature PSCs was higher in PNA-treated females than in controls, indicating increased presynaptic contacts onto GnRH neurons. GnRH neurons from both control and PNA-treated adult females fired in response to acute GABA application, but during development, neurons from PNA mice were significantly less responsive to GABA than controls. And whereas resting membrane potential was unaffected by PNA, at 3 weeks of age, GABA's depolarizing effect was blunted in PNA female mice compared with controls. The chloride reversal potential, however, was not affected by PMA treatment. Together, the results suggest that altered synaptic development underlies the lasting neuroendocrine changes seen in PNA-treated adult mice, perhaps providing clues to the mechanisms behind PCOS.

This Week in The Journal was written by Stephani Sutherland, Ph.D.

JNeurosci
THE JOURNAL OF NEUROSCIENCE
February 28, 2018 • Volume 38 Number 9 • www.jneurosci.org

Cover legend: This image shows cultured hippocampal neurons labeled for dendrites (MAP2, blue), and for the axon initial segment (yellow is an overlay of neurofascin-186, green and β4-spectrin, red). For more information, see the Viewpoint article by Leterrier C. (pages 2135–2145).

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VIEWPOINTS

The Axon Initial Segment: An Updated Viewpoint

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At the base of axons sits a unique compartment called the axon initial segment (AIS). The AIS generates and shapes the action potential before it is propagated along the axon. Neuronal excitability thus depends crucially on the AIS composition and position, and these adapt to developmental and physiological conditions. The AIS also demarcates the boundary between the somatodendritic and axonal compartments. Recent studies have brought insights into the molecular architecture of the AIS and how it regulates protein trafficking. This Viewpoints article summarizes current knowledge about the AIS and highlights future challenges in understanding this key actor of neuronal physiology.
The Journal of Neuroscience, February 28, 2018 • 38(9):2135–2145

Articles

CELLULAR/MOLECULAR

A Unique Homeostatic Signaling Pathway Links Synaptic Inactivity to Postsynaptic mTORC1

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mTORC1-dependent translational control plays a key role in several enduring forms of synaptic plasticity such as long term potentiation (LTP) and mGluR-dependent long term depression. Recent evidence demonstrates an additional role in regulating synaptic homeostasis in response to inactivity, where dendritic mTORC1 serves to modulate presynaptic function via retrograde signaling. Presently, it is unclear whether LTP and homeostatic plasticity use a common route to mTORC1-dependent signaling or whether each engage mTORC1 through distinct pathways. Here, we report a unique signaling pathway that specifically couples homeostatic signaling to postsynaptic mTORC1 after loss of excitatory synaptic input. We find that AMPAR blockade, but not LTP-inducing stimulation, induces phospholipase D (PLD)-dependent synthesis of the lipid second messenger phosphatidic acid (PA) in rat cultured hippocampal neurons of either sex. Pharmacological blockade of PLD1/2 or pharmacogenetic disruption of PA interactions with mTOR eliminates mTORC1 signaling and presynaptic compensation driven by AMPAR blockade, but does not alter mTORC1 activation or functional changes during chemical LTP (cLTP). Overexpression of PLD1, but not PLD2, recapitulates both functional synaptic changes as well as signature cellular adaptations associated with homeostatic plasticity. Finally, transient application of exogenous PA is sufficient to drive rapid presynaptic compensation requiring mTORC1-dependent translation of BDNF in the postsynaptic compartment. These results thus define a unique homeostatic signaling pathway coupling mTORC1 activation to changes in excitatory synaptic drive. Our results further imply that more than one canonical mTORC1 activation pathway may be relevant for the design of novel therapeutic approaches against neurodevelopmental disorders associated with mTORC1 dysregulation.
The Journal of Neuroscience, February 28, 2018 • 38(9):2207–2225

Fentanyl Induces Rapid Onset Hyperalgesic Priming: Type I at Peripheral and Type II at Central Nociceptor Terminals

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Systemic fentanyl induces hyperalgesic priming, long-lasting neuroplasticity in nociceptor function characterized by prolongation of inflammatory mediator hyperalgesia. To evaluate priming at both nociceptor terminals, we studied, in male Sprague Dawley rats, the effect of local administration of agents that reverse type I (protein translation) or type II [combination of Src and mitogen-activated protein kinase (MAPK)] priming. At the central terminal, priming induced by systemic, intradermal, or intrathecal fentanyl was reversed by the combination of Src and MAPK inhibitors, but at the peripheral terminal, it was reversed by the protein translation inhibitor. Mu-opioid receptor (MOR) antisense prevented fentanyl hyperalgesia and priming. To determine whether type I and II priming occur in the same population of neurons, we used isolectin B4 –saporin or [Sar^9, $Met(O_2)^{11}$]-substance P–saporin to deplete nonpeptidergic or peptidergic nociceptors, respectively. Following intrathecal fentanyl, central terminal priming was prevented by both saporins, whereas that in peripheral terminal was not attenuated even by their combination. However, after intradermal fentanyl, priming in the peripheral terminal requires both peptidergic and nonpeptidergic nociceptors, whereas that in the central terminal is dependent only on peptidergic nociceptors. Pretreatment with dantrolene at either terminal prevented fentanyl-induced priming in both terminals, suggesting communication between central and peripheral terminals mediated by intracellular Ca^{2+} signaling. *In vitro* application of fentanyl increased cytoplasmic Ca^{2+} concentration in dorsal root ganglion neurons, which was prevented by pretreatment with dantrolene and naloxone. Therefore, acting at MOR in the nociceptor, fentanyl induces hyperalgesia and priming rapidly at both the central (type II) and peripheral (type I) terminal and this is mediated by Ca^{2+} signaling.
The Journal of Neuroscience, February 28, 2018 • 38(9):2226 –2245

DEVELOPMENT/PLASTICITY/REPAIR

Notch Suppression Collaborates with Ascl1 and Lin28 to Unleash a Regenerative Response in Fish Retina, But Not in Mice

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Müller glial (MG) cells in the zebrafish retina respond to injury by acquiring retinal stem-cell characteristics. Thousands of gene expression changes are associated with this event. Key among these changes is the induction of Ascl1a and Lin28a, two reprogramming factors whose expression is necessary for retina regeneration. Whether these factors are sufficient to drive MG proliferation and subsequent neuronal-fate specification remains unknown. To test this, we conditionally expressed Ascl1a and Lin28a in the uninjured retina of male and female fish. We found that together, their forced expression only stimulates sparse MG proliferation. However, in combination with Notch signaling inhibition, widespread MG proliferation and neuron regeneration ensued. Remarkably, Ascl1 and Lin28a expression in the retina of male and female mice also stimulated sparse MG proliferation, although this was not enhanced when combined with inhibitors of Notch signaling. Lineage tracing in both fish and mice suggested that the proliferating MG generated multipotent progenitors; however, this process was much more efficient in fish than mice. Overall, our studies suggest that the overexpression of Ascl1a and Lin28a in zebrafish, in combination with inhibition of Notch signaling, can phenocopy the effects of retinal injury in Müller glia. Interestingly, Ascl1 and Lin28a seem to have similar effects in fish and mice, whereas Notch signaling may differ. Understanding the different consequences of Notch signaling inhibition in fish and mice, may suggest additional strategies for enhancing retina regeneration in mammals.

The Journal of Neuroscience, February 28, 2018 • 38(9):2246 –2261

Age-Dependent Decline in Fate Switch from NG2 Cells to Astrocytes After Olig2 Deletion

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NG2 cells are a resident glial progenitor cell population that is uniformly distributed throughout the developing and mature mammalian CNS. Those in the postnatal CNS generate exclusively myelinating and non-myelinating oligodendrocytes and are thus equated with oligodendrocyte precursor cells. Prenatally, NG2 cells in the ventral gray matter of the forebrain generate protoplasmic astrocytes as well as oligodendrocytes. The fate conversion from NG2 cells into protoplasmic astrocytes is dependent on downregulation of the key oligodendrocyte transcription factor Olig2. We showed previously that constitutive deletion of Olig2 in NG2 cells converts NG2 cells in the neocortex into protoplasmic astrocytes at the expense of oligodendrocytes. In this study, we show that postnatal deletion of Olig2 caused NG2 cells in the neocortex but not in other gray matter regions to become protoplasmic astrocytes. However, NG2 cells in the neocortex became more resistant to astrocyte fate switch over the first 3 postnatal weeks. Fewer NG2 cells differentiated into astrocytes and did so with longer latency after Olig2 deletion at postnatal day 18 (P18) compared with deletion at P2. The high-mobility group transcription factor Sox10 was not downregulated for at least 1 month after Olig2 deletion at P18 despite an early transient upregulation of the astrocyte transcription factor NFIA. Furthermore, inhibiting cell proliferation in slice culture reduced astrocyte differentiation from Olig2-deleted perinatal NG2 cells, suggesting that cell division might facilitate nuclear reorganization needed for astrocyte transformation.

The Journal of Neuroscience, February 28, 2018 • 38(9):2359 –2371

SYSTEMS/CIRCUITS

Inhalation Frequency Controls Reformatting of Mitral/Tufted Cell Odor Representations in the Olfactory Bulb

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In mammals, olfactory sensation depends on inhalation, which controls activation of sensory neurons and temporal patterning of central activity. Odor representations by mitral and tufted (MT) cells, the main output from the olfactory bulb (OB), reflect sensory input as well as excitation and inhibition from OB circuits, which may change as sniff frequency increases. To test the impact of sampling frequency on MT cell odor responses, we obtained whole-cell recordings from MT cells in anesthetized male and female mice while varying inhalation frequency via tracheotomy, allowing comparison of inhalation-linked responses across cells. We characterized frequency effects on MT cell responses during inhalation of air and odorants using inhalation pulses and also "playback" of sniffing recorded from awake mice. Inhalation-linked changes in membrane potential were well predicted across frequency from linear convolution of 1 Hz responses; and, as frequency increased, near-identical temporal responses could emerge from depolarizing, hyperpolarizing, or multiphasic MT responses. However, net excitation was not well predicted from 1 Hz responses and varied substantially across MT cells, with some cells increasing and others decreasing in spike rate. As a result, sustained odorant sampling at higher frequencies led to increasing decorrelation of the MT cell population response pattern over time. Bulk activation of sensory inputs by optogenetic stimulation affected MT cells more uniformly across frequency,

suggesting that frequency-dependent decorrelation emerges from odor-specific patterns of activity in the OB network. These results suggest that sampling behavior alone can reformat early sensory representations, possibly to optimize sensory perception during repeated sampling.
The Journal of Neuroscience, February 28, 2018 • 38(9):2189–2206

Role of Anterior Intralaminar Nuclei of Thalamus Projections to Dorsomedial Striatum in Incubation of Methamphetamine Craving

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Relapse to methamphetamine (Meth) seeking progressively increases after withdrawal from drug self-administration (incubation of Meth craving). We previously demonstrated a role of dorsomedial striatum (DMS) dopamine D1 receptors (D1Rs) in this incubation. Here, we studied the role of afferent glutamatergic projections into the DMS and local D1R– glutamate interaction in this incubation in male rats. We first measured projection-specific activation on day 30 relapse test by using cholera toxin b (retrograde tracer) + Fos (activity marker) double-labeling in projection areas. Next, we determined the effect of pharmacological reversible inactivation of lateral or medial anterior intralaminar nuclei of thalamus (AIT-L or AIT-M) on incubated Meth seeking on withdrawal day 30. We then used an anatomical asymmetrical disconnection procedure to determine whether an interaction between AIT-L→DMS glutamatergic projections and postsynaptic DMS D1Rs contributes to incubated Meth seeking. We also determined the effect of unilateral inactivation of AIT-L and D1R blockade of DMS on incubated Meth seeking, and the effect of contralateral disconnection of AIT-L→DMS projections on nonincubated Meth seeking on withdrawal day 1. Incubated Meth seeking was associated with selective activation of AIT→DMS projections; other glutamatergic projections to DMS were not activated. AIT-L (but not AIT-M) inactivation or anatomical disconnection of AIT-L→DMS projections decreased incubated Meth seeking. Unilateral inactivation of AIT-L or D1R blockade of the DMS had no effect on incubated Meth craving, and contralateral disconnection of AIT-L→DMS projections had no effect on nonincubated Meth seeking. Our results identify a novel role of AIT-L and AIT-L→DMS glutamatergic projections in incubation of drug craving and drug seeking.
The Journal of Neuroscience, February 28, 2018 • 38(9):2270–2282

Prepubertal Development of GABAergic Transmission to Gonadotropin-Releasing Hormone (GnRH) Neurons and Postsynaptic Response Are Altered by Prenatal Androgenization

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Gonadotropin-releasing hormone (GnRH) neurons regulate reproduction through pulsatile GnRH release. Women with polycystic ovary syndrome (PCOS) have persistently elevated luteinizing hormone release frequency, reflecting GnRH release; this exacerbates hyperandrogenemia and disrupted reproductive cycles that are characteristic of this disorder. Clinical evidence suggests that neuroendocrine features of PCOS may manifest peripubertally. Adult mice prenatally exposed to androgens (PNA) mimic several reproductive features of PCOS. GnRH neurons from these mice have increased firing activity and receive increased GABAergic transmission, which is excitatory. When changes emerge during development is unknown. To study the typical postnatal development of GABAergic transmission and the effects of PNA treatment and sex, whole-cell voltage-clamp recordings were made of GABAergic postsynaptic currents (PSCs) in GnRH neurons in brain slices from prepubertal through adult control and PNA female and male mice. GABAergic transmission was present by 1 week of age in females and males and increased in frequency, reaching adult levels at 3 and 4 weeks, respectively. GABAergic PSC frequency was elevated in 3-week-old PNA versus control females. PSC frequency in both controls and PNA mice was activity independent, suggesting that PNA induces changes in synapse organization. PNA also alters the functional response of GnRH neurons to GABA. GABA induced firing in fewer neurons from 3-week-old PNA than control females; membrane potential depolarization induced by GABA was also reduced in cells from PNA mice at this age. PNA thus induces changes during development in the presynaptic organization of the GABAergic network afferent to GnRH neurons as well as the postsynaptic GnRH neuron response, both of which may contribute to adult reproductive dysfunction.
The Journal of Neuroscience, February 28, 2018 • 38(9):2283–2293

Differential Sampling of Visual Space in Ventral and Dorsal Early Visual Cortex

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A fundamental feature of cortical visual processing is the separation of visual processing for the upper and lower visual fields. In early visual cortex (EVC), the upper visual field is processed ventrally, with the lower visual field processed dorsally. This distinction persists into several category-selective regions of occipitotemporal cortex, with ventral and lateral scene-, face-, and object-selective regions biased for the upper and lower visual fields, respectively. Here, using an elliptical population receptive field (pRF) model, we systematically tested the sampling of visual space within ventral and dorsal divisions of human EVC in both male and female participants. We found that (1) pRFs tend to be elliptical and oriented toward the fovea with distinct angular distributions for ventral and dorsal divisions of EVC, potentially reflecting a radial bias; and (2) pRFs in ventral areas were larger (~1.5×) and more elliptical (~1.2×) than those in dorsal areas. These differences potentially reflect a tendency for receptive fields in ventral temporal cortex to overlap the fovea with less emphasis on precise localization and isotropic representation of space compared with dorsal areas. Collectively, these

findings suggest that ventral and dorsal divisions of EVC sample visual space differently, likely contributing to and/or stemming from the functional differentiation of visual processing observed in higher-level regions of the ventral and dorsal cortical visual pathways.
The Journal of Neuroscience, February 28, 2018 • 38(9):2294 –2303

Timescales of Intrinsic BOLD Signal Dynamics and Functional Connectivity in Pharmacologic and Neuropathologic States of Unconsciousness

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Environmental events are processed on multiple timescales via hierarchical organization of temporal receptive windows (TRWs) in the brain. The dependence of neural timescales and TRWs on altered states of consciousness is unclear. States of reduced consciousness are marked by a shift toward slowing of neural dynamics (<1 Hz) in EEG/ECoG signals. We hypothesize that such prolongation of intrinsic timescales are also seen in blood-oxygen-level-dependent (BOLD) signals. To test this hypothesis, we measured the timescales of intrinsic BOLD signals using mean frequency (MF) and temporal autocorrelation (AC) in healthy volunteers ($n = 23$; male/female 14/9) during graded sedation with propofol. We further examined the relationship between the intrinsic timescales (local/voxel level) and its regional connectivity (across neighboring voxels; regional homogeneity, ReHo), global (whole-brain level) functional connectivity (GFC), and topographical similarity (Topo). Additional results were obtained from patients undergoing deep general anesthesia ($n = 12$; male/female: 5/7) and in patients with disorders of consciousness (DOC) ($n = 21$; male/female: 14/7). We found that MF, AC, and ReHo increased, whereas GFC and Topo decreased, during propofol sedation. The local alterations occur before changes of distant connectivity. Conversely, all of these parameters decreased in deep anesthesia and in patients with DOC. We conclude that propofol synchronizes local neuronal interactions and prolongs the timescales of intrinsic BOLD signals. These effects may impede communication among distant brain regions. Furthermore, the intrinsic timescales exhibit distinct dynamic signatures in sedation, deep anesthesia, and DOC. These results improve our understanding of the neural mechanisms of unconsciousness in pharmacologic and neuropathologic states.
The Journal of Neuroscience, February 28, 2018 • 38(9):2304 –2317

Corticosterone Production during Repeated Social Defeat Causes Monocyte Mobilization from the Bone Marrow, Glucocorticoid Resistance, and Neurovascular Adhesion Molecule Expression

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Repeated social defeat (RSD) stress promotes the release of bone marrow-derived monocytes into circulation that are recruited to the brain, where they augment neuroinflammation and cause prolonged anxiety-like behavior. Physiological stress activates the sympathetic nervous system and hypothalamic-pituitary-adrenal gland (HPA) axis, and both of these systems play a role in the physiological, immunological, and behavioral responses to stress. The purpose of this study was to delineate the role of HPA activation and corticosterone production in the immunological responses to stress in male C57BL/6 mice. Here, surgical (adrenalectomy) and pharmacological (metyrapone) interventions were used to abrogate corticosterone signaling during stress. We report that both adrenalectomy and metyrapone attenuated the stress-induced release of monocytes into circulation. Neither intervention altered the production of monocytes during stress, but both interventions enhanced retention of these cells in the bone marrow. Consistent with this observation, adrenalectomy and metyrapone also prevented the stress-induced reduction of a key retention factor, CXCL12, in the bone marrow. Corticosterone depletion with metyrapone also abrogated the stress-induced glucocorticoid resistance of myeloid cells. In the brain, these corticosterone-associated interventions attenuated stress-induced microglial remodeling, neurovascular expression of the adhesion molecule intercellular cell adhesion molecule-1, prevented monocyte accumulation and neuroinflammatory signaling. Overall, these results indicate that HPA activation and corticosterone production during repeated social defeat stress are critical for monocyte release into circulation, glucocorticoid resistance of myeloid cells, and enhanced neurovascular cell adhesion molecule expression.
The Journal of Neuroscience, February 28, 2018 • 38(9):2328 –2340

Saliency Detection as a Reactive Process: Unexpected Sensory Events Evoke Corticomuscular Coupling

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Survival in a fast-changing environment requires animals not only to detect unexpected sensory events, but also to react. In humans, these salient sensory events generate large electrocortical responses, which have been traditionally interpreted within the sensory domain. Here we describe a basic physiological mechanism coupling saliency-related cortical responses with motor output. In four experiments conducted on 70 healthy participants, we show that salient substartle sensory stimuli modulate isometric force exertion by human participants, and that this modulation is tightly coupled with electrocortical activity elicited by the same stimuli. We obtained four main results. First, the force modulation follows a complex triphasic pattern consisting of alternating decreases and increases of force,

time-locked to stimulus onset. Second, this modulation occurs regardless of the sensory modality of the eliciting stimulus. Third, the magnitude of the force modulation is predicted by the amplitude of the electrocortical activity elicited by the same stimuli. Fourth, both neural and motor effects are not reflexive but depend on contextual factors. Together, these results indicate that sudden environmental stimuli have an immediate effect on motor processing, through a tight corticomuscular coupling. These observations suggest that saliency detection is not merely perceptive but reactive, preparing the animal for subsequent appropriate actions.
The Journal of Neuroscience, February 28, 2018 • 38(9):2385–2397

BEHAVIORAL/COGNITIVE

An Interaction between Serotonin Receptor Signaling and Dopamine Enhances Goal-Directed Vigor and Persistence in Mice

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The functionally selective 5-HT2C receptor ligand SB242084 can increase motivation and have rapid onset anti– depressant-like effects. We sought to identify the specific behavioral effects of SB242084 treatment and elucidate the mechanism in female and male mice. Using a quantitative behavioral approach, we determined that SB242084 increases the vigor and persistence of goal-directed activity across different types of physical work, particularly when work requirements are demanding. We found this influence of SB242084 on effort, rather than reward to be reflected in striatal DA measured during behavior. Using *in vivo* fast scan cyclic voltammetry, we found that SB242084 has no effect on reward-related phasic DA release in the NAc. Using *in vivo* microdialysis to measure tonic changes in extracellular DA, we also found no changes in the NAc. In contrast, SB242084 treatment increases extracellular DA in the dorsomedial striatum, an area that plays a key role in response vigor. These findings have several implications. At the behavioral level, this work shows that the capacity to work in demanding situations can be increased, without a generalized increase in motor activity or reward value. At the circuit level, we identified a pathway restricted potentiation of DA release and showed that this was the reason for the increased response vigor. At the cellular level, we show that a specific serotonin receptor cross talks to the DA system. Together, this information provides promise for the development of treatments for apathy, a serious clinical condition that can afflict patients with psychiatric and neurological disorders.
The Journal of Neuroscience, February 28, 2018 • 38(9):2149 –2162

Antagonistic Interactions Between Microsaccades and Evidence Accumulation Processes During Decision Formation

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Despite their small size, microsaccades can impede stimulus detections if executed at inopportune times. Although it has been shown that microsaccades evoke both inhibitory and excitatory responses across different visual regions, their impact on the higher-level neural decision processes that bridge sensory responses to action selection has yet to be examined. Here, we show that when human observers monitor stimuli for subtle feature changes, the occurrence of microsaccades long after (up to 800 ms) change onset predicts slower reaction times and this is accounted for by momentary suppression of neural signals at each key stage of decision formation: visual evidence encoding, evidence accumulation, and motor preparation. Our data further reveal that, independent of the timing of the change events, the onset of neural decision formation coincides with a systematic inhibition of microsaccade production, persisting until the perceptual report is executed. Our combined behavioral and neural measures highlight antagonistic interactions between microsaccade occurrence and evidence accumulation during visual decision-making tasks.
The Journal of Neuroscience, February 28, 2018 • 38(9):2163–2176

Altered Baseline and Nicotine-Mediated Behavioral and Cholinergic Profiles in ChAT-Cre Mouse Lines

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The recent development of transgenic rodent lines expressing cre recombinase in a cell-specific manner, along with advances in engineered viral vectors, has permitted in-depth investigations into circuit function. However, emerging evidence has begun to suggest that genetic modifications may introduce unexpected caveats. In the current studies, we sought to extensively characterize male and female mice from both the $ChAT_{(BAC)}$-Cre mouse line, created with the bacterial artificial chromosome (BAC) method, and $ChAT_{(IRES)}$-Cre mouse line, generated with the internal ribosome entry site (IRES) method. $ChAT_{(BAC)}$-Cre transgenic and wild-type mice did not differ in general locomotor behavior, anxiety measures, drug-induced cataplexy, nicotine-mediated hypolocomotion, or operant food training. However, $ChAT_{(BAC)}$-Cre transgenic mice did exhibit significant deficits in intravenous nicotine self-administration, which paralleled an increase in vesicular acetylcholine transporter and choline acetyltransferase (ChAT) hippocampal expression. For the $ChAT_{(IRES)}$-Cre line, transgenic mice exhibited deficits in baseline locomotor, nicotine-mediated hypolocomotion, and operant food training compared with wild-type and hemizygous littermates. No differences among $ChAT_{(IRES)}$-Cre wild-type, hemizygous, and transgenic littermates were found in anxiety measures, drug-induced cataplexy, and nicotine self-administration. Given that increased cre expression was present in the $ChAT_{(IRES)}$-Cre transgenic mice, as well as a decrease in ChAT expression in the hippocampus, altered neuronal function may underlie behavioral phenotypes. In contrast, $ChAT_{(IRES)}$-Cre hemizygous mice were more similar to wild-type mice in both protein expression and the majority of behavioral assessments. As such, interpretation of data derived from ChAT-Cre rodents must consider potential limitations dependent on the line and/or genotype used in research investigations.

The Journal of Neuroscience, February 28, 2018 • 38(9):2177–2188

A Collaborator's Reputation Can Bias Decisions and Anxiety under Uncertainty

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Informational social influence theory posits that under conditions of uncertainty, we are inclined to look to others for advice. This leaves us remarkably vulnerable to being influenced by others' opinions or advice. Rational agents, however, do not blindly seek and act on arbitrary information, but often consider the quality of its source before committing to a course of action. Here, we ask the question of whether a collaborator's reputation can increase their social influence and, in turn, bias perception and anxiety under changing levels of uncertainty. Human male and female participants were asked to provide estimations of dot direction using the random dot motion (RDM) perceptual discrimination task and were paired with transient collaborators of high or low reputation whom provided their own estimations. The RDM varied in degrees of uncertainty and joint performance accuracy was linked to risk of an electric shock. Despite providing identical information, we show that collaborating with a high reputation compared with a low reputation partner, led to significantly more conformity during the RDM task for uncertain perceptual decisions. Consequently, high reputation partners decreased the subjects' anxiety during the anticipatory shock periods. fMRI data showed that parametric changes in conformity resulted in increased activity in the ventromedial PFC, whereas dissent was associated with increased in activity in the dorsal anterior cingulate cortex (dACC). Furthermore, the dACC and insula, regions involved in anticipatory pain, were significantly more active when collaborating with a low reputation partner. These results suggest that information about reputation can influence both cognitive and affective processes and in turn alter the neural circuits that underlie decision-making and emotion.

The Journal of Neuroscience, February 28, 2018 • 38(9):2262–2269

Dynamic Interactions between Top–Down Expectations and Conscious Awareness

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It is well known that top– down expectations affect perceptual processes. Yet, remarkably little is known about the relationship between expectations and conscious awareness. We address three crucial outstanding questions: (1) how do expectations affect the likelihood of conscious stimulus perception?; (2) does the brain register violations of expectations nonconsciously?; and (3) do expectations need to be conscious to influence perceptual decisions? Using human participants, we performed three experiments in which we manipulated stimulus predictability within the attentional blink paradigm, while combining visual psychophysics with electrophysiological recordings. We found that valid stimulus expectations increase the likelihood of conscious access of stimuli. Furthermore, our findings suggest a clear dissociation in the interaction between expectations and consciousness: conscious awareness seems crucial for the implementation of top– down expectations, but not for the generation of bottom-up stimulus-evoked prediction errors. These results constrain and update influential theories about the role of consciousness in the predictive brain.

The Journal of Neuroscience, February 28, 2018 • 38(9):2318 –2327

Progranulin Gene Therapy Improves Lysosomal Dysfunction and Microglial Pathology Associated with Frontotemporal Dementia and Neuronal Ceroid Lipofuscinosis

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Loss-of-function mutations in progranulin, a lysosomal glycoprotein, cause neurodegenerative disease. Progranulin haploinsufficiency causes frontotemporal dementia (FTD) and complete progranulin deficiency causes *CLN11* neuronal ceroid lipofuscinosis (NCL). Progranulin replacement is a rational therapeutic strategy for these disorders, but there are critical unresolved mechanistic questions about a progranulin gene therapy approach, including its potential to reverse existing pathology. Here, we address these issues using an AAV vector (AAV-*Grn*) to deliver progranulin in *Grn*$^{-/-}$ mice (both male and female), which model aspects of NCL and FTD pathology, developing lysosomal dysfunction, lipofuscinosis, and microgliosis. We first tested whether AAV-*Grn* could improve preexisting pathology. Even with treatment after onset of pathology, AAV-*Grn* reduced lipofuscinosis in several brain regions of *Grn*$^{-/-}$ mice. AAV-*Grn* also reduced microgliosis in brain regions distant from the injection site. AAV-expressed progranulin was only detected in neurons, not in microglia, indicating that the microglial activation in progranulin deficiency can be improved by targeting neurons and thus may be driven at least in part by neuronal dysfunction. Even areas with sparse transduction and almost undetectable progranulin showed improvement, indicating that low-level replacement may be sufficiently effective. The beneficial effects of AAV-*Grn* did not require progranulin binding to sortilin. Finally, we tested whether AAV-*Grn* improved lysosomal function. AAV-derived progranulin was delivered to the lysosome, ameliorated the accumulation of LAMP-1 in *Grn*$^{-/-}$ mice, and corrected abnormal cathepsin D activity. These data shed light on progranulin biology and support progranulin-boosting therapies for NCL and FTD due to *GRN* mutations.

The Journal of Neuroscience, February 28, 2018 • 38(9):2341–2358

Endoplasmic Reticulum Stress Contributes to the Loss of Newborn Hippocampal Neurons after Traumatic Brain Injury

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Adult hippocampal neurogenesis has been shown to be required for certain types of cognitive function. For example, studies have shown that these neurons are critical for pattern separation, the ability to store similar experiences as distinct memories. Although traumatic brain injury (TBI) has been shown to cause the loss of newborn hippocampal neurons, the signaling pathway(s) that triggers their death is unknown. Endoplasmic reticulum (ER) stress activates the PERK-eIF2α pathway that acts to restore ER function and improve cell survival. However, unresolved/intense ER stress activates C/EBP homologous protein (CHOP), leading to cell death. We show that TBI causes the death of hippocampal newborn neurons via CHOP. Using CHOP KO mice, we show that loss of CHOP markedly reduces newborn neuron loss after TBI. Injured CHOP mice performed significantly better in a context fear discrimination task compared with injured wild-type mice. In contrast, the PERK inhibitor GSK2606414 exacerbated doublecortin cell loss and worsened contextual discrimination. Administration of guanabenz (which reduces ER stress) to injured male rats reduced the loss of newborn neurons and improved one-trial contextual fear memory. Interestingly, we also found that the surviving newborn neurons in brain-injured animals had dendritic loss, which was not observed in injured CHOP KO mice or in animals treated with guanabenz. These results indicate that ER stress plays a key role in the death of newborn neurons after TBI. Further, these findings indicate that ER stress can alter dendritic arbors, suggesting a role for ER stress in neuroplasticity and dendritic pathologies.

The Journal of Neuroscience, February 28, 2018 • 38(9):2372–2384