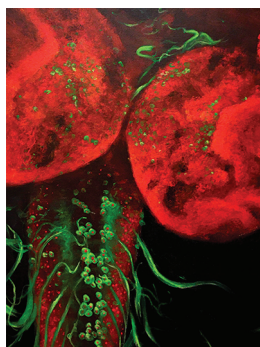


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Cover legend: This is a hand painted canvas of the *Drosophila* larval central nervous system depicting the brain lobes and the ventral nerve cord. Red represents horseradish peroxidase (HRP) and green marks some motor neurons. See the article by Wang et al. (pages 1401–1417). Cover image: Purujit Chatterjee (McGovern Medical School, Houston, TX).

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Articles

CELLULAR/MOLECULAR

Retrograde Mitochondrial Transport Is Essential for Organelle Distribution and Health in Zebrafish Neurons

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In neurons, mitochondria are transported by molecular motors throughout the cell to form and maintain functional neural connections. These organelles have many critical functions in neurons and are of high interest as their dysfunction is associated with disease. While the mechanics and impact of anterograde mitochondrial movement toward axon terminals are beginning to be understood, the frequency and function of retrograde (cell body directed) mitochondrial transport in neurons are still largely unexplored. While existing evidence indicates that some mitochondria are retrogradely transported for degradation in the cell body, the precise impact of disrupting retrograde transport on the organelles and the axon was unknown. Using long-term, *in vivo* imaging, we examined mitochondrial motility in zebrafish sensory and motor axons. We show that retrograde transport of mitochondria from axon terminals allows replacement of the axon terminal population within a day. By tracking these organelles, we show that not all mitochondria that leave the axon terminal are degraded; rather, they persist over several days. Disrupting retrograde mitochondrial flux in neurons leads to accumulation of aged organelles in axon terminals and loss of cell body mitochondria. Assays of neural circuit activity demonstrated that disrupting mitochondrial transport and function has no effect on sensory axon terminal activity but does negatively impact motor neuron axons. Taken together, our work supports a previously unappreciated role for retrograde mitochondrial transport in the maintenance of a homeostatic distribution of mitochondria in neurons and illustrates the downstream effects of disrupting this process on sensory and motor circuits.

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Differential Contribution of Cadm1–Cadm3 Cell Adhesion Molecules to Peripheral Myelinated Axons

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Cell adhesion proteins of the Cadm (SynCAM/Necl) family regulate myelination and the organization of myelinated axons. In the peripheral nervous system (PNS), intercellular contact between Schwann cells and their underlying axons is believed to be mediated by binding of glial Cadm4 to axonal Cadm3 or Cadm2. Nevertheless, given that distinct neurons express different combinations of the Cadm proteins, the identity of the functional axonal ligand for Cadm4 remains to be determined. Here, we took a genetic approach to compare the phenotype of *Cadm4* null mice, which exhibit abnormal distribution of Caspr and Kv1 potassium channels, with mice lacking different combinations of *Cadm1–Cadm3* genes. We show that in contrast to mice lacking the single *Cadm1*, *Cadm2*, or *Cadm3* genes, genetic ablation of all three phenocopies the abnormalities detected in the absence of Cadm4. Similar defects were observed in double mutant mice lacking Cadm3 and Cadm2 (i.e., *Cadm3*^{−/−}/*Cadm2*^{−/−}) or Cadm3 and Cadm1 (i.e., *Cadm3*^{−/−}/*Cadm1*^{−/−}), but not in mice lacking Cadm1 and Cadm2 (i.e., *Cadm1*^{−/−}/*Cadm2*^{−/−}). Furthermore, axonal organization abnormalities were also detected in *Cadm3* null mice that were heterozygous for the two other axonal Cadms. Our results identify Cadm3 as the main axonal ligand for glial Cadm4, and reveal that its absence could be compensated by the combined action of Cadm2 and Cadm1.

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DEVELOPMENT/PLASTICITY/REPAIR

Structural and Functional Synaptic Plasticity Induced by Convergent Synapse Loss in the *Drosophila* Neuromuscular Circuit

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Throughout the nervous system, the convergence of two or more presynaptic inputs on a target cell is commonly observed. The question we ask here is to what extent converging inputs influence each other's structural and functional synaptic plasticity. In complex circuits, isolating individual inputs is difficult because postsynaptic cells can receive thousands of inputs. An ideal model to address this question is the *Drosophila* larval neuromuscular junction (NMJ) where each postsynaptic muscle cell receives inputs from two glutamatergic types of motor neurons (MNs), known as 1b and 1s MNs. Notably, each muscle is unique and receives input from a different combination of 1b and 1s MNs; we surveyed multiple muscles for this reason. Here, we identified a cell-specific promoter that allows ablation of 1s MNs postinnervation and measured structural and functional responses of convergent 1b NMJs using microscopy and electrophysiology. For all muscles examined in both sexes, ablation of 1s MNs resulted in NMJ expansion and increased spontaneous neurotransmitter release at corresponding 1b NMJs. This demonstrates that 1b NMJs can compensate for the loss of convergent 1s MNs. However, only a subset of 1b NMJs showed compensatory evoked neurotransmission, suggesting target-specific plasticity. Silencing 1s MNs led to similar plasticity at 1b NMJs, suggesting that evoked neurotransmission from 1s MNs contributes to 1b synaptic plasticity. Finally, we genetically blocked 1s innervation in male larvae and robust 1b synaptic plasticity was eliminated, raising the possibility that 1s NMJ formation is required to set up a reference for subsequent synaptic perturbations.

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Evidence for Subcortical Plasticity after Paired Stimulation from a Wearable Device

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Existing non-invasive stimulation protocols can generate plasticity in the motor cortex and its corticospinal projections; techniques for inducing plasticity in subcortical circuits and alternative descending pathways such as the reticulospinal tract (RST) are less well developed. One possible approach developed by this laboratory pairs electrical muscle stimulation with auditory clicks, using a wearable device to deliver stimuli during normal daily activities. In this study, we applied a variety of electrophysiological assessments to male and female healthy human volunteers during a morning and evening laboratory visit. In the intervening time (~6 h), subjects wore the stimulation device, receiving three different protocols, in which clicks and stimulation of the biceps muscle were paired at either low or high rate, or delivered at random. Paired stimulation: (1) increased the extent of reaction time shortening by a loud sound (the StartReact effect); (2) decreased the suppression of responses to transcranial magnetic brain stimulation (TMS) following a loud sound; (3) enhanced muscle responses elicited by a TMS coil oriented to induce anterior-posterior (AP) current, but not posterior-anterior (PA) current, in the brain. These measurements have all been suggested to be sensitive to subcortical, possibly reticulospinal, activity. Changes were similar for either of the two paired stimulus rates tested, but absent after unpaired (control) stimulation. Taken together, these results suggest that pairing clicks and muscle stimulation for long periods does indeed induce plasticity in subcortical systems such as the RST.

The Journal of Neuroscience, February 17, 2021 • 41(7):1418–1428

SYSTEMS/CIRCUITS

An Angiotensin-Responsive Connection from the Lamina Terminalis to the Paraventricular Nucleus of the Hypothalamus Evokes Vasopressin Secretion to Increase Blood Pressure in Mice

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Blood pressure is controlled by endocrine, autonomic, and behavioral responses that maintain blood volume and perfusion pressure at levels optimal for survival. Although it is clear that central angiotensin type 1a receptors (AT1aR; encoded by the *Agtr1a* gene) influence these processes, the neuronal circuits mediating these effects are incompletely understood. The present studies characterize the structure and function of AT1aR neurons in the lamina terminalis (containing the median preoptic nucleus and organum vasculosum of the lamina terminalis), thereby evaluating their roles in blood pressure control. Using male *Agtr1a*-Cre mice, neuroanatomical studies reveal that AT1aR neurons in the area are largely glutamatergic and send projections to the paraventricular nucleus of the hypothalamus (PVN) that appear to synapse onto vasopressin-synthesizing neurons. To evaluate the functionality of these lamina terminalis AT1aR neurons, we virally delivered light-sensitive opsins and then optogenetically excited or inhibited the neurons while evaluating cardiovascular parameters or fluid intake. Optogenetic excitation robustly elevated blood pressure, water intake, and sodium intake, while optogenetic inhibition produced the opposite effects. Intriguingly, optogenetic excitation of these AT1aR neurons of the lamina terminalis also resulted in Fos induction in vasopressin neurons within the PVN and supraoptic nucleus. Further, within the PVN, selective optogenetic stimulation of afferents that arise from these lamina terminalis AT1aR neurons induced glutamate release onto magnocellular neurons and was sufficient to increase blood pressure. These cardiovascular effects were attenuated by systemic pretreatment with a vasopressin-1a-receptor antagonist. Collectively, these data indicate that excitation of lamina terminalis AT1aR neurons induces neuroendocrine and behavioral responses that increase blood pressure.

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Spatial and Temporal Arrangement of Recurrent Inhibition in the Primate Upper Limb

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Renshaw cells mediate recurrent inhibition between motoneurons within the spinal cord. The function of this circuit is not clear; we previously suggested based on computational modeling that it may cancel oscillations in muscle activity around 10 Hz, thereby reducing physiological tremor. Such tremor is especially problematic for dexterous hand movements, yet knowledge of recurrent inhibitory function is sparse for the control of the primate upper limb, where no direct measurements have been made to date. In this study, we made intracellular penetrations into 89 motoneurons in the cervical enlargement of four terminally anesthetized female macaque monkeys, and recorded recurrent IPSPs in response to antidromic stimulation of motor axons. Recurrent inhibition was strongest to motoneurons innervating shoulder muscles and elbow extensors, weak to wrist and digit extensors, and almost absent to the intrinsic muscles of the hand. Recurrent inhibitory connections often spanned joints, for example from motoneurons innervating wrist and digit muscles to those controlling the shoulder and elbow. Wrist and digit flexor motoneurons sometimes inhibited the corresponding extensors, and vice versa. This complex connectivity presumably reflects the flexible usage of the primate upper limb. Using trains of stimuli to motor nerves timed as a Poisson process and coherence analysis, we also examined the temporal properties of recurrent inhibition. The recurrent feedback loop effectively carried frequencies up to 100 Hz, with a coherence peak around 20 Hz. The coherence phase validated predictions from our previous computational model, supporting the idea that recurrent inhibition may function to reduce tremor.

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Laminar Origin of Corticostriatal Projections to the Motor Putamen in the Macaque Brain

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In the macaque brain, projections from distant, interconnected cortical areas converge in specific zones of the striatum. For example, specific zones of the motor putamen are targets of projections from frontal motor, inferior parietal, and ventrolateral prefrontal hand-related areas and thus are integral part of the so-called “lateral grasping network.” In the present study, we analyzed the laminar distribution of corticostriatal neurons projecting to different parts of the motor putamen. Retrograde neural tracers were injected in different parts of the putamen in 3 *Macaca mulatta* (one male) and the laminar distribution of the labeled corticostriatal neurons was analyzed quantitatively. In frontal motor areas and frontal operculum, where most labeled cells were located, almost everywhere the proportion of corticostriatal labeled neurons in layers III and/or VI was comparable or even stronger than in layer V. Furthermore, within these regions, the laminar distribution pattern of corticostriatal labeled neurons largely varied independently from their density and from the projecting area/sector, but likely according to the target striatal zone. Accordingly, the present data show that cortical areas may project in different ways to different striatal zones, which can be targets of specific combinations of signals originating from the various cortical layers of the areas of a given network. These observations extend current models of corticostriatal interactions, suggesting more complex modes of information processing in the basal ganglia for different motor and nonmotor functions and opening new questions on the architecture of the corticostriatal circuitry.

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Functional Differentiation of Mouse Visual Cortical Areas Depends upon Early Binocular Experience

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The mammalian visual cortex contains multiple retinotopically defined areas that process distinct features of the visual scene. Little is known about what guides the functional differentiation of visual cortical areas during development. Recent studies in mice have revealed that visual input from the two eyes provides spatiotemporally distinct signals to primary visual cortex (V1), such that contralateral eye-dominated V1 neurons respond to higher spatial frequencies than ipsilateral eye-dominated neurons. To test whether binocular visual input drives the differentiation of visual cortical areas, we used two-photon calcium imaging to characterize the effects of juvenile monocular deprivation (MD) on the responses of neurons in V1 and two higher visual areas, LM (lateromedial) and PM (posteromedial). In adult mice of either sex, we find that MD prevents the emergence of distinct spatiotemporal tuning in V1, LM, and PM. We also find that, within each of these areas, MD reorganizes the distinct spatiotemporal tuning properties driven by the two eyes. Moreover, we find a relationship between speed tuning and ocular dominance in all three areas that MD preferentially disrupts in V1, but not in LM or PM. Together, these results reveal that balanced binocular vision during development is essential for driving the functional differentiation of visual cortical areas. The higher visual areas of mouse visual cortex may provide a useful platform for investigating the experience-dependent mechanisms that set up the specialized processing within neocortical areas during postnatal development.

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Photoreceptive Ganglion Cells Drive Circuits for Local Inhibition in the Mouse Retina

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Intrinsically photosensitive retinal ganglion cells (ipRGCs) exhibit melanopsin-dependent light responses that persist in the absence of rod and cone photoreceptor-mediated input. In addition to signaling anterogradely to the brain, ipRGCs signal retrogradely to intraretinal circuitry via gap junction-mediated electrical synapses with amacrine cells (ACs). However, the targets and functions of these intraretinal signals remain largely unknown. Here, in mice of both sexes, we identify circuitry that enables M5 ipRGCs to locally inhibit retinal neurons via electrical synapses with a nonspiking GABAergic AC. During pharmacological blockade of rod- and cone-mediated input, whole-cell recordings of corticotropin-releasing hormone-expressing (CRH⁺) ACs reveal persistent visual responses that require both melanopsin expression and gap junctions. In the developing retina, ipRGC-mediated input to CRH⁺ ACs is weak or absent before eye opening, indicating a primary role for this input in the mature retina (i.e., in parallel with rod- and cone-mediated input). Among several ipRGC types, only M5 ipRGCs exhibit consistent anatomical and physiological coupling to CRH⁺ ACs. Optogenetic stimulation of local CRH⁺ ACs directly drives IPSCs in M4 and M5, but not M1-M3, ipRGCs. CRH⁺ ACs also inhibit M2 ipRGC-coupled spiking ACs, demonstrating direct interaction between discrete networks of ipRGC-coupled interneurons. Together, these results demonstrate a functional role for electrical synapses in translating ipRGC activity into feedforward and feedback inhibition of local retinal circuits.

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BEHAVIORAL/COGNITIVE

Memory Load Alters Perception-Related Neural Oscillations during Multisensory Integration

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Integrating information across different senses is a central feature of human perception. Previous research suggests that multisensory integration is shaped by a context-dependent and largely adaptive interplay between stimulus-driven bottom-up and top-down endogenous influences. One critical question concerns the extent to which this interplay is sensitive to the amount of available cognitive resources. In the present study, we investigated the influence of limited cognitive resources on audiovisual integration by measuring high-density electroencephalography (EEG) in healthy participants performing the sound-induced flash illusion (SIFI) and a verbal *n*-back task (0-back, low load and 2-back, high load) in a dual-task design. In the SIFI, the integration of a flash with two rapid beeps can induce the illusory perception of two flashes. We found that high compared with low load increased illusion susceptibility and modulated neural oscillations underlying illusion-related crossmodal interactions. Illusion perception under high load was associated with reduced early β power (18–26 Hz, ~70 ms) in auditory and motor areas, presumably reflecting an early mismatch signal and subsequent top-down influences including increased frontal θ power (7–9 Hz, ~120 ms) in mid-anterior cingulate cortex (ACC) and a later β power suppression (13–22 Hz, ~350 ms) in prefrontal and auditory cortex. Our study demonstrates that integrative crossmodal interactions underlying the SIFI are sensitive to the amount of available cognitive resources and that multisensory integration engages top-down θ and β oscillations when cognitive resources are scarce.

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Learning to Synchronize: Midfrontal Theta Dynamics during Rule Switching

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In recent years, several hierarchical extensions of well-known learning algorithms have been proposed. For example, when stimulus-action mappings vary across time or context, the brain may learn two or more stimulus-action mappings in separate modules, and additionally (at a hierarchically higher level) learn to appropriately switch between those modules. However, how the brain mechanistically coordinates neural communication to implement such hierarchical learning remains unknown. Therefore, the current study tests a recent computational model that proposed how midfrontal theta oscillations implement such hierarchical learning via the principle of binding by synchrony (Sync model). More specifically, the Sync model uses bursts at theta frequency to flexibly bind appropriate task modules by synchrony. The 64-channel EEG signal was recorded while 27 human subjects (female: 21, male: 6) performed a probabilistic reversal learning task. In line with the Sync model, postfeedback theta power showed a linear relationship with negative prediction errors, but not with positive prediction errors. This relationship was especially pronounced for subjects with better behavioral fit (measured via Akaike information criterion) of the Sync model. Also consistent with Sync model simulations, theta phase-coupling between midfrontal electrodes and temporoparietal electrodes was stronger after negative feedback. Our data suggest that the brain uses theta power and synchronization for flexibly switching between task rule modules, as is useful, for example, when multiple stimulus-action mappings must be retained and used.

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Basal Ganglia Output Has a Permissive Non-Driving Role in a Signaled Locomotor Action Mediated by the Midbrain

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The basal ganglia are important for movement and reinforcement learning. Using mice of either sex, we found that the main basal ganglia GABAergic output in the midbrain, the substantia nigra pars reticulata (SNr), shows movement-related neural activity during the expression of a negatively reinforced signaled locomotor action known as signaled active avoidance; this action involves mice moving away during a warning signal to avoid a threat. In particular, many SNr neurons deactivate during active avoidance responses. However, whether SNr deactivation has an essential role driving or regulating active avoidance responses is unknown. We found that optogenetic excitation of SNr or striatal GABAergic fibers that project to an area in the pedunculo-pontine tegmentum (PPT) within the midbrain locomotor region abolishes signaled active avoidance responses, while optogenetic inhibition of SNr cells (mimicking the SNr deactivation observed during an active avoidance behavior) serves as an effective conditioned stimulus signal to drive avoidance responses by disinhibiting PPT neurons. However, preclusion of SNr deactivation, or direct inhibition of SNr fibers in the PPT, does not impair the expression of signaled active avoidance, indicating that SNr output does not drive the expression of a signaled locomotor action mediated by the midbrain. Consistent with a permissive regulatory role, SNr output provides information about the state of the ongoing action to downstream structures that mediate the action.

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Granulocyte-Colony Stimulating Factor Reduces Cocaine-Seeking and Downregulates Glutamatergic Synaptic Proteins in Medial Prefrontal Cortex

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Psychostimulant use disorder is a major public health issue, and despite the scope of the problem there are currently no Food and Drug Administration (FDA)-approved treatments. There would be tremendous utility in development of a treatment that could help patients both achieve and maintain abstinence. Previous work from our group has identified granulocyte-colony stimulating factor (G-CSF) as a neuroactive cytokine that alters behavioral response to cocaine, increases synaptic dopamine release, and enhances cognitive flexibility. Here, we investigate the role of G-CSF in affecting extinction and reinstatement of cocaine-seeking and perform detailed characterization of its proteomic effects in multiple limbic substructures. Male Sprague Dawley rats were injected with PBS or G-CSF during (1) extinction or (2) abstinence from cocaine self-administration, and drug seeking behavior was measured. Quantitative assessment of changes in the proteomic landscape in the nucleus accumbens (NAc) and medial prefrontal cortex (mPFC) were performed via data-independent acquisition (DIA) mass spectrometry analysis. Administration of G-CSF during extinction accelerated the rate of extinction, and administration during abstinence attenuated cue-induced cocaine-seeking. Analysis of global protein expression demonstrated that G-CSF regulated proteins primarily in mPFC that are critical to glutamate signaling and synapse maintenance. Taken together, these findings support G-CSF as a viable translational research target with the potential to reduce drug craving or seeking behaviors. Importantly, recombinant G-CSF exists as an FDA-approved medication which may facilitate rapid clinical translation. Additionally, using cutting-edge multiregion discovery proteomics analyses, these studies identify a novel mechanism underlying G-CSF effects on behavioral plasticity.

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Corticosterone Attenuates Reward-Seeking Behavior and Increases Anxiety via D2 Receptor Signaling in Ventral Tegmental Area Dopamine Neurons

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Corticosteroids (CORT) have been widely used in anti-inflammatory medication. Chronic CORT treatment can cause mesocorticolimbic system dysfunctions, which are known to play a key role for the development of psychiatric disorders. The VTA is a critical site in the mesocorticolimbic pathway and is responsible for motivation and reward-seeking behaviors. However, the mechanism by which chronic CORT alters VTA dopamine neuronal activity is largely unknown. We treated periadolescent male mice with vehicle, 1 d, or 7 d CORT in the drinking water, examined behavioral impacts with light/dark box, elevated plus maze, operant chamber, and open field tests, measured the effects of CORT on VTA dopamine neuronal activity using patch-clamp electrophysiology and dopamine concentration using fast-scan cyclic voltammetry, and tested the effects of dopamine D2 receptor (D2R) blockade by intra-VTA infusion of a D2R antagonist. CORT treatment induced anxiety-like behavior as well as decreased food-seeking behaviors. We show that chronic CORT treatment decreased excitability and excitatory synaptic transmission onto VTA dopamine neurons. Furthermore, chronic CORT increased somatodendritic dopamine concentration. The D2R antagonist sulpiride restored decreased excitatory transmission and excitability of VTA dopamine neurons. Furthermore, sulpiride decreased anxiety-like behavior and rescued food-seeking behavior in mice with chronic CORT exposure. Together, 7 d CORT treatment induces anxiety-like behavior and impairs food-seeking in a mildly aversive environment. D2R signaling in the VTA might be a potential target to ameliorate chronic CORT-induced anxiety and reward-seeking deficits.

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A Discrete Glycinergic Neuronal Population in the Ventromedial Medulla That Induces Muscle Atonia during REM Sleep and Cataplexy in Mice

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During rapid eye movement (REM) sleep, anti-gravity muscle tone and bodily movements are mostly absent, because somatic motoneurons are inhibited by descending inhibitory pathways. Recent studies showed that glycine/GABA neurons in the ventromedial medulla (VMM; Gly^{VMM} neurons) play an important role in generating muscle atonia during REM sleep (REM-atonía). However, how these REM-atonía-inducing neurons interconnect with other neuronal populations has been unknown. In the present study, we first identified a specific subpopulation of Gly^{VMM} neurons that play an important role in induction of REM-atonía by virus vector-mediated tracing in male mice in which glycinergic neurons expressed Cre recombinase. We found these neurons receive direct synaptic input from neurons in several brain stem regions, including glutamatergic neurons in the sublaterodorsal tegmental nucleus (SLD; Glu^{SLD} neurons). Silencing this circuit by specifically expressing tetanus toxin light chain (TeTNLC) resulted in REM sleep without atonia. This manipulation also caused a marked decrease in time spent in cataplexy-like episodes (CLEs) when applied to narcoleptic *orexin-ataxin-3* mice. We also showed that Gly^{VMM} neurons play an important role in maintenance of sleep. This present study identified a population of glycinergic neurons in the VMM that are commonly involved in REM-atonía and cataplexy.

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NEUROBIOLOGY OF DISEASE

Traumatic Brain Injury Causes Chronic Cortical Inflammation and Neuronal Dysfunction Mediated by Microglia

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Traumatic brain injury (TBI) can lead to significant neuropsychiatric problems and neurodegenerative pathologies, which develop and persist years after injury. Neuroinflammatory processes evolve over this same period. Therefore, we aimed to determine the contribution of microglia to neuropathology at acute [1 d postinjury (dpi)], subacute (7 dpi), and chronic (30 dpi) time points. Microglia were depleted with PLX5622, a CSF1R antagonist, before midline fluid percussion injury (FPI) in male mice and cortical neuropathology/inflammation was assessed using a neuropathology mRNA panel. Gene expression associated with inflammation and neuropathology were robustly increased acutely after injury (1 dpi) and the majority of this expression was microglia independent. At 7 and 30 dpi, however, microglial depletion reversed TBI-related expression of genes associated with inflammation, interferon signaling, and neuropathology. Myriad suppressed genes at subacute and chronic endpoints were attributed to neurons. To understand the relationship between microglia, neurons, and other glia, single-cell RNA sequencing was completed 7 dpi, a critical time point in the evolution from acute to chronic pathogenesis. Cortical

microglia exhibited distinct TBI-associated clustering with increased type-1 interferon and neurodegenerative/damage-related genes. In cortical neurons, genes associated with dopamine signaling, long-term potentiation, calcium signaling, and synaptogenesis were suppressed. Microglial depletion reversed the majority of these neuronal alterations. Furthermore, there was reduced cortical dendritic complexity 7 dpi, reduced neuronal connectivity 30 dpi, and cognitive impairment 30 dpi. All of these TBI-associated functional and behavioral impairments were prevented by microglial depletion. Collectively, these studies indicate that microglia promote persistent neuropathology and long-term functional impairments in neuronal homeostasis after TBI.

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