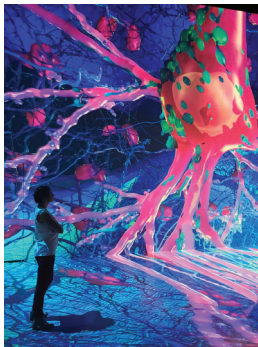


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Cover legend: In early 2019, a groundbreaking collaboration between Society for Neuroscience (SfN), ARTEHOUSE, and a team of neurobiologists led by John Morrison, PhD, was launched. It culminated in the opening of *Life of a Neuron*, a digital art installation providing an immersive experience of an actual human neuron. Pictured here inside the exhibit is Dani Dumitriu, MD, PhD, the scientist who produced the raw dataset supplied to the artists by performing a single cell microinjection with a fluorescent marker and confocal imaging. See the manuscript by Dumitriu and Morrison (pages 8075–8078) for more information. Cover image: Nikita Dumitriu.

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VIEWPOINTS

Pavlovian Fear Conditioning Is More than You Think It Is

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A common neuroscience application of Pavlovian fear conditioning is to manipulate neuron-type activity, pair a cue with foot shock, then measure cue-elicited freezing in a novel context. If the manipulation reduces freezing, the neuron type is implicated in Pavlovian fear conditioning. This application reduces Pavlovian fear conditioning to a single concept. In this Viewpoint, I describe experiments supporting the view that Pavlovian fear conditioning refers to three distinct concepts: procedure, process, and behavior. An experimenter controls procedure, observes behavior, but infers process. Distinguishing these concepts is essential because: (1) a shock-paired cue can engage numerous processes and behaviors; (2) experimenter decisions about procedure influence the processes engaged and behaviors elicited; and (3) many processes are latent, imbuing the cue with properties that only manifest outside of the original conditioning setting. This means we could understand the complete neural basis of freezing, yet know little about the neural basis of fear. Neuroscientists can choose to use a variety of procedures to study a diversity of processes and behaviors. Manipulating neuron-type activity in multiple procedures can reveal specific, general, or complex neuron-type contributions to cue-elicited processes and behaviors. The results will be a broader and more detailed neural basis of fear with greater relevance to the spectrum of symptoms defining anxiety and stressor-related disorders.

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Articles

CELLULAR/MOLECULAR

P2Y₆ Receptor-Dependent Microglial Phagocytosis of Synapses during Development Regulates Synapse Density and Memory

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During brain development, excess synapses are pruned (i.e., removed), in part by microglial phagocytosis, and dysregulated synaptic pruning can lead to behavioral deficits. The P2Y₆ receptor (P2Y₆R) is known to regulate microglial phagocytosis of neurons, and to regulate microglial phagocytosis of synapses in cell culture and *in vivo* during aging. However, currently it is unknown whether P2Y₆R regulates synaptic pruning during development. Here, we show that P2Y₆R KO mice of both sexes had strongly reduced microglial internalization of synaptic material, measured as Vglut1 within CD68-staining lysosomes of microglia at postnatal day 30 (P30), suggesting reduced microglial phagocytosis of synapses. Consistent with this, we found an increased density of synapses in the somatosensory cortex and the CA3 region and dentate gyrus of the hippocampus at P30. We also show that adult P2Y₆R KO mice have impaired short- and long-term spatial memory and impaired short- and long-term recognition memory compared with WT mice, as measured by novel location recognition, novel object recognition, and Y-maze memory tests. Overall, this indicates that P2Y₆R regulates microglial phagocytosis of synapses during development, and this contributes to memory capacity.

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DEVELOPMENT/PLASTICITY/REPAIR

miR-218 Promotes Dopaminergic Differentiation and Controls Neuron Excitability and Neurotransmitter Release through the Regulation of a Synaptic-Related Genes Network

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In the brain, microRNAs (miRNAs) are believed to play a role in orchestrating synaptic plasticity at a higher level by acting as an additional mechanism of translational regulation, alongside the mRNA/polysome system. Despite extensive research, our understanding of the specific contribution of individual miRNA to the function of dopaminergic neurons (DAN) remains limited. By performing a dopaminergic-specific miRNA screening, we have identified miR-218 as a critical regulator of DAN activity in male and female mice. We have found that miR-218 is specifically expressed in mesencephalic DAN and is able to promote dopaminergic differentiation of embryonic stem cells and functional maturation of transdifferentiated induced DA neurons. Midbrain-specific deletion of both genes encoding for miR-218 (referred to as miR-218-1 and miR-218-2) affects the expression of a cluster of synaptic-related mRNAs and alters the intrinsic excitability of DAN, as it increases instantaneous frequencies of evoked action potentials, reduces rheobase current, affects the ionic current underlying the action potential after hyperpolarization phase, and reduces dopamine efflux in response to a single electrical stimulus. Our findings provide a comprehensive understanding of the involvement of miR-218 in the dopaminergic system and highlight its role as a modulator of dopaminergic transmission.

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Motor Activity-Induced White Matter Repair in White Matter Stroke

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Subcortical white matter stroke (WMS) is a progressive disorder which is demarcated by the formation of small ischemic lesions along white matter tracts in the CNS. As lesions accumulate, patients begin to experience severe motor and cognitive decline. Despite its high rate of incidence in the human population, our understanding of the cause and outcome of WMS is extremely limited. As such, viable therapies for WMS remain to be seen. This study characterizes myelin recovery following stroke and motor learning-based rehabilitation in a mouse model of subcortical WMS. Following WMS, a transient increase in differentiating oligodendrocytes occurs within the peri-infarct in young male adult mice, which is completely abolished in male aged mice. Compound action potential recording demonstrates a decrease in conduction velocity of myelinated axons at the peri-infarct. Animals were then tested on one of three distinct motor learning-based rehabilitation strategies (skilled reach, restricted access to a complex running wheel, and unrestricted access to a complex running wheel) for their capacity to induce repair. These studies determined that unrestricted access to a complex running wheel alone increases the density of differentiating oligodendrocytes in infarcted white matter in young adult male mice, which is abolished in aged male mice. Unrestricted access to a complex running wheel was also able to enhance conduction velocity of myelinated axons at the peri-infarct to a speed comparable to naive controls suggesting functional recovery. However, there was no evidence of motor rehabilitation-induced remyelination or myelin protection.

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SYSTEMS/CIRCUITS

The Structure of Hippocampal CA1 Interactions Optimizes Spatial Coding across Experience

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Although much is known about how single neurons in the hippocampus represent an animal's position, how circuit interactions contribute to spatial coding is less well understood. Using a novel statistical estimator and theoretical modeling, both developed in the framework of maximum entropy models, we reveal highly structured CA1 cell-cell interactions in male rats during open field exploration. The statistics of these interactions depend on whether the animal is in a familiar or novel environment. In both conditions the circuit interactions optimize the encoding of spatial information, but for regimes that differ in the informativeness of their spatial inputs. This structure facilitates linear decodability, making the information easy to read out by downstream circuits. Overall, our findings suggest that the efficient coding hypothesis is not only applicable to individual neuron properties in the sensory periphery, but also to neural interactions in the central brain.

The Journal of Neuroscience, November 29, 2023 • 43(48):8140–8156

Cortical Synchrony and Information Flow during Transition from Wakefulness to Light Non-Rapid Eye Movement Sleep

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Sleep is a highly stereotyped phenomenon, requiring robust spatiotemporal coordination of neural activity. Understanding how the brain coordinates neural activity with sleep onset can provide insights into the physiological functions subserved by sleep and the pathologic phenomena associated with sleep onset. We quantified whole-brain network changes in synchrony and information flow during the transition from wakefulness to light non-rapid eye movement (NREM) sleep, using MEG imaging in a convenient sample of 14 healthy human participants (11 female; mean 63.4 years [SD 11.8 years]). We furthermore performed computational modeling to infer excitatory and inhibitory properties of local neural activity. The transition from wakefulness to light NREM was identified to be encoded in spatially and temporally specific patterns of long-range synchrony. Within the delta band, there was a global increase in connectivity from wakefulness to light NREM, which was highest in frontoparietal regions. Within the theta band, there was an increase in connectivity in fronto-parieto-occipital regions and a decrease in temporal regions from wakefulness to Stage 1 sleep. Patterns of information flow revealed that mesial frontal regions receive hierarchically organized inputs from broad cortical regions upon sleep onset, including direct inflow from occipital regions and indirect inflow via parieto-temporal regions within the delta frequency band. Finally, biophysical neural mass modeling demonstrated changes in the anterior-to-posterior distribution of cortical excitation-to-inhibition with increased excitation-to-inhibition model parameters in anterior regions in light NREM compared with wakefulness. Together, these findings uncover whole-brain corticocortical structure and the orchestration of local and long-range, frequency-specific cortical interactions in the sleep-wake transition.

The Journal of Neuroscience, November 29, 2023 • 43(48):8157–8171

Hypersensitivity to Distractors in Fragile X Syndrome from Loss of Modulation of Cortical VIP Interneurons

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Attention deficit is one of the most prominent and disabling symptoms in Fragile X syndrome (FXS). Hypersensitivity to sensory stimuli contributes to attention difficulties by overwhelming and/or distracting affected individuals, which disrupts activities of daily living at home and learning at school. We find that auditory or visual distractors selectively impair visual discrimination performance in humans and mice with FXS but not in typically developing controls. In both species, males and females were examined. Vasoactive intestinal polypeptide (VIP) neurons were significantly modulated by incorrect responses in the poststimulus period during early distractor trials in WT mice, consistent with their known role as error signals. Strikingly, however, VIP cells from *Fmr1*^{−/−} mice showed little modulation in error trials, and this correlated with their poor performance on the distractor task. Thus, VIP interneurons and their reduced modulatory influence on pyramidal cells could be a potential therapeutic target for attentional difficulties in FXS.

The Journal of Neuroscience, November 29, 2023 • 43(48):8172–8188

BEHAVIORAL/COGNITIVE

Intonation Units in Spontaneous Speech Evoke a Neural Response

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Spontaneous speech is produced in chunks called intonation units (IUs). IUs are defined by a set of prosodic cues and presumably occur in all human languages. Recent work has shown that across different grammatical and sociocultural conditions IUs form rhythms of ~1 unit per second. Linguistic theory suggests that IUs pace the flow of information in the discourse. As a result, IUs provide a promising and hitherto unexplored theoretical framework for studying the neural mechanisms of communication. In this article, we identify a neural response unique to the boundary defined by the IU. We measured the EEG of human participants (of either sex), who listened to different speakers recounting an emotional life event. We analyzed the speech stimuli linguistically and modeled the EEG response at word offset using a GLM approach. We find that the EEG response to IU-final words differs from the response to IU-nonfinal words even when equating acoustic boundary strength. Finally, we relate our findings to the body of research on rhythmic brain mechanisms in speech processing. We study the unique contribution of IUs and acoustic boundary strength in predicting delta-band EEG. This analysis suggests that IU-related neural activity, which is tightly linked to the classic Closure Positive Shift (CPS), could be a time-locked component that captures the previously characterized delta-band neural speech tracking.

The Journal of Neuroscience, November 29, 2023 • 43(48):8189–8200

Distinct ACC Neural Mechanisms Underlie Authentic and Transmitted Anxiety Induced by Maternal Separation in Mice

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It is known that humans and rodents are capable of transmitting stress to their naive partners via social interaction. However, a comprehensive understanding of transmitted stress, which may differ from authentic stress, thus revealing unique neural mechanisms of social interaction resulting from transmitted stress and the associated anxiety, is missing. We used, in the present study, maternal separation (MS) as a stress model to investigate whether MS causes abnormal behavior in adolescence. A key concern in the analysis of stress transmission is whether the littermates of MS mice who only witness MS stress ("Partners") exhibit behavioral abnormalities similar to those of MS mice themselves. Of special interest is the establishment of the neural mechanisms underlying transmitted stress and authentic stress. The results show that Partners, similar to MS mice, exhibit anxiety-like behavior and hyperalgesia after witnessing littermates being subjected to early-life repetitive MS. Electrophysiological analysis revealed that mice subjected to MS demonstrate a reduction in both the excitatory and inhibitory synaptic activities of parvalbumin interneurons (PVINs) in the anterior cingulate cortex (ACC). However, Partners differed from MS mice in showing an increase in the number and excitability of GABAergic PVINs in the ACC and in the ability of chemogenetic PVIN inactivation to eliminate abnormal behavior. Furthermore, the social transfer of anxiety-like behavior required intact olfactory, but not visual, perception. This study suggests a functional involvement of ACC PVINs in mediating the distinct neural basis of transmitted anxiety.

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The Representation of Observed Actions at the Subordinate, Basic, and Superordinate Level

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Actions can be planned and recognized at different hierarchical levels, ranging from very specific (e.g., to swim backstroke) to very broad (e.g., locomotion). Understanding the corresponding neural representation is an important prerequisite to reveal how our brain flexibly assigns meaning to the world around us. To address this question, we conducted an event-related fMRI study in male and female human participants in which we examined distinct representations of observed actions at the subordinate, basic and superordinate level. Using multiple regression representational similarity analysis (RSA) in predefined regions of interest, we found that the three different taxonomic levels were best captured by patterns of activations in bilateral lateral occipitotemporal cortex (LOTc), showing the highest similarity with the basic level model. A whole-brain multiple regression RSA revealed that information unique to the basic level was captured by patterns of activation in dorsal and ventral portions of the LOTc and in parietal regions. By contrast, the unique information for the subordinate level was limited to bilateral occipitotemporal cortex, while no single cluster was obtained that captured unique information for the superordinate level. The behaviorally established action space was best captured by patterns of activation in the LOTc and superior parietal cortex, and the corresponding neural patterns of activation showed the highest similarity with patterns of activation corresponding to the basic level model. Together, our results suggest that occipitotemporal cortex shows a preference for the basic level model, with flexible access across the subordinate and the basic level.

The Journal of Neuroscience, November 29, 2023 • 43(48):8219–8230

NEUROBIOLOGY OF DISEASE

The Role of Retinal Dopamine D1 Receptors in Ocular Growth and Myopia Development in Mice

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Dopamine is a key neurotransmitter in the signaling cascade controlling ocular refractive development, but the exact role and site of action of dopamine D1 receptors (D1Rs) involved in myopia remains unclear. Here, we determine whether retinal D1Rs exclusively mediate the effects of endogenous dopamine and systemically delivered D1R agonist or antagonist in the mouse form deprivation myopia (FDM) model. Male C57BL/6 mice subjected to unilateral FDM or unobstructed vision were divided into the following four groups: one noninjected and three groups that received intraperitoneal injections of a vehicle, D1R agonist SKF38393 (18 and 59 nmol/g), or D1R antagonist SCH39166 (0.1 and 1 nmol/g). The effects of these drugs on FDM were further assessed in *Drd1*-knock-out (*Drd1*-KO), retina-specific conditional *Drd1*-KO (*Drd1*-CKO) mice, and corresponding wild-type littermates. In the visually unobstructed group, neither SKF38393 nor SCH39166 affected normal refractive development, whereas myopia development was attenuated by SKF38393 and enhanced by SCH39166 injections. In *Drd1*-KO or *Drd1*-CKO mice, however, these drugs had no effect on FDM development, suggesting that activation of retinal D1Rs is pertinent to myopia suppression by the D1R agonist. Interestingly, the development of myopia was unchanged by either *Drd1*-KO or *Drd1*-CKO, and neither

SKF38393 nor SCH39166 injections, nor *Drd1*-KO, affected the retinal or vitreal dopamine and the dopamine metabolite DOPAC levels. Effects on axial length were less marked than effects on refraction. Therefore, activation of D1Rs, specifically retinal D1Rs, inhibits myopia development in mice. These results also suggest that multiple dopamine D1R mechanisms play roles in emmetropization and myopia development.

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Hyperexcitability in the Olfactory Bulb and Impaired Fine Odor Discrimination in the *Fmr1* KO Mouse Model of Fragile X Syndrome

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Fragile X syndrome (FXS) is the single most common monogenetic cause of autism spectrum disorders (ASDs) in humans. FXS is caused by loss of expression of the fragile X mental retardation protein (FMRP), an mRNA-binding protein encoded on the X chromosome involved in suppressing protein translation. Sensory processing deficits have been a major focus of studies of FXS in both humans and rodent models of FXS, but olfactory deficits remain poorly understood. Here, we conducted experiments in wild-type (WT) and *Fmr1* knock-out (KO; *Fmr1*^{-/-}) mice (males) that lack expression of the gene encoding FMRP to assess olfactory circuit and behavioral abnormalities. In patch-clamp recordings conducted in slices of the olfactory bulb, output mitral cells (MCs) in *Fmr1* KO mice displayed greatly enhanced excitation under baseline conditions, as evidenced by a much higher rate of occurrence of spontaneous network-level events known as long-lasting depolarizations (LLDs). The higher probability of spontaneous LLDs (sLLDs), which appeared to be because of a decrease in GABAergic synaptic inhibition in glomeruli leading to more feedforward excitation, caused a reduction in the reliability of stimulation-evoked responses in MCs. In addition, in a go/no-go operant discrimination paradigm, we found that *Fmr1* KO mice displayed impaired discrimination of odors in difficult tasks that involved odor mixtures but not altered discrimination of monomolecular odors. We suggest that the *Fmr1* KO-induced reduction in MC response reliability is one plausible mechanism for the impaired fine odor discrimination.

The Journal of Neuroscience, November 29, 2023 • 43(48):8243–8258

Extracellular ATP Neurotransmission and Nicotine Sex-Specifically Modulate Habenular Neuronal Activity in Adolescence

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The recent increase in the use of nicotine products by teenagers has revealed an urgent need to better understand the impact of nicotine on the adolescent brain. Here, we sought to examine the actions of extracellular ATP as a neurotransmitter and to investigate whether ATP and nicotinic signaling interact during adolescence. With the GRAB_{ATP} (G-protein-coupled receptor activation-based ATP sensor), we first demonstrated that nicotine induces extracellular ATP release in the medial habenula, a brain region involved in nicotine aversion and withdrawal. Using patch-clamp electrophysiology, we then demonstrated that activation of the ATP receptors P2X or P2Y₁ increases the neuronal firing of cholinergic neurons. Surprisingly, contrasting interactive effects were observed with nicotine exposure. For the P2X receptor, activation had no observable effect on acute nicotine-mediated activity, but during abstinence after 10 d of nicotine exposure, coexposure to nicotine and the P2X agonist potentiated neuronal activity in female, but not male, neurons. For P2Y₁ signaling, a potentiated effect of the agonist and nicotine was observed with acute exposure, but not following extended nicotine exposure. These data reveal a complex interactive effect between nicotinic and ATP signaling in the adolescent brain and provide mechanistic insights into extracellular ATP signaling with sex-specific alterations of neuronal responses based on prior drug exposure.

The Journal of Neuroscience, November 29, 2023 • 43(48):8259–8270