



Cover legend: This image demonstrates tau-reporter aggregation induced by exposure to misfolded tau seeds in neurons derived from induced pluripotent stem cells generated at the time of autopsy from an Alzheimer disease patient harboring the L435F allele of presenilin1. Red represents a tau aggregation sensor. Cyan represents endogenous phosphorylated tau protein. Yellow represents nuclei. For more information, see the article by Oakley et al. (pages 4335–4348). Cover image: Derek H. Oakley.

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Characterizing Cortex-Wide Dynamics with Wide-Field Calcium Imaging

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The brain functions through coordinated activity among distributed regions. Wide-field calcium imaging, combined with improved genetically encoded calcium indicators, allows sufficient signal-to-noise ratio and spatiotemporal resolution to afford a unique opportunity to capture cortex-wide dynamics on a moment-by-moment basis in behaving animals. Recent applications of this approach have been uncovering cortical dynamics at unprecedented scales during various cognitive processes, ranging from relatively simple sensorimotor integration to more complex decision-making tasks. In this review, we will highlight recent scientific advances enabled by wide-field calcium imaging in behaving mice. We then summarize several technical considerations and future opportunities for wide-field imaging to uncover large-scale circuit dynamics.

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Articles

CELLULAR/MOLECULAR

Selective Ablation of BDNF from Microglia Reveals Novel Roles in Self-Renewal and Hippocampal Neurogenesis

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Microglia, the resident immune cells of the CNS, have emerged as key regulators of neural precursor cell activity in the adult brain. However, the microglia-derived factors that mediate these effects remain largely unknown. In the present study, we investigated a role for microglial brain-derived neurotrophic factor (BDNF), a neurotrophic factor with well known effects on neuronal survival and plasticity. Surprisingly, we found that selective genetic ablation of BDNF from microglia increased the production of newborn neurons under both physiological and inflammatory conditions (e.g., LPS-induced infection and traumatic brain injury). Genetic ablation of BDNF from microglia otherwise also interfered with self-renewal/proliferation, reducing their overall density. In conclusion, we identify microglial BDNF as an important factor regulating microglia population dynamics and states, which in turn influences neurogenesis under both homeostatic and pathologic conditions.

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Synapsin Is Required for Dense Core Vesicle Capture and cAMP-Dependent Neuropeptide Release

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Release of neuropeptides from dense core vesicles (DCVs) is essential for neuromodulation. Compared with the release of small neurotransmitters, much less is known about the mechanisms and proteins contributing to neuropeptide release. By optogenetics, behavioral analysis, electrophysiology, electron microscopy, and live imaging, we show that synapsin SNN-1 is required for cAMP-dependent neuropeptide release in *Caenorhabditis elegans* hermaphrodite cholinergic motor neurons. In synapsin mutants, behaviors induced by the photoactivated adenylyl cyclase bPAC, which we previously showed to depend on ACh and neuropeptides (Steuer Costa et al., 2017), are altered as in animals with reduced cAMP. Synapsin mutants have slight alterations in synaptic vesicle (SV) distribution; however, a defect in SV mobilization was apparent after channelrhodopsin-based photostimulation. DCVs were largely affected in *snn-1* mutants: DCVs were ~30% reduced in synaptic terminals, and their contents not released following bPAC stimulation. Imaging axonal DCV trafficking, also in genome-engineered mutants in the serine-9 protein kinase A phosphorylation site, showed that synapsin captures DCVs at synapses, making them available for release. SNN-1 colocalized with immobile, captured DCVs. In synapsin deletion mutants, DCVs were more mobile and less likely to be caught at release sites, and in nonphosphorylatable SNN-1B(S9A) mutants, DCVs traffic less and accumulate, likely by enhanced SNN-1 dependent tethering. Our work establishes synapsin as a key mediator of neuropeptide release.

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The Immediate Early Gene *Arc* Is Not Required for Hippocampal Long-Term Potentiation

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Memory consolidation is thought to occur through protein synthesis-dependent synaptic plasticity mechanisms such as long-term potentiation (LTP). Dynamic changes in gene expression and epigenetic modifications underlie the maintenance of LTP. Similar mechanisms may mediate the storage of memory. Key plasticity genes, such as the immediate early gene *Arc*, are induced by learning and by LTP induction. Mice that lack *Arc* have severe deficits in memory consolidation, and *Arc* has been implicated in numerous other forms of synaptic plasticity, including long-term depression and cell-to-cell signaling. Here, we take a comprehensive approach to determine if *Arc* is necessary for hippocampal LTP in male and female mice. Using a variety of *Arc* knock-out (KO) lines, we found that germline *Arc* KO mice show no deficits in CA1 LTP induced by high-frequency stimulation and enhanced LTP induced by theta-burst stimulation. Temporally restricting the removal of *Arc* to adult animals and spatially restricting it to the CA1 using *Arc* conditional KO mice did not have an effect on any form of LTP. Similarly, acute application of *Arc* antisense oligodeoxynucleotides had no effect on hippocampal CA1 LTP. Finally, the maintenance of *in vivo* LTP in the dentate gyrus of *Arc* KO mice was normal. We conclude that *Arc* is not necessary for hippocampal LTP and may mediate memory consolidation through alternative mechanisms.

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SYSTEMS/CIRCUITS

Cell-Type-Specific Dynamics of Calcium Activity in Cortical Circuits over the Course of Slow-Wave Sleep and Rapid Eye Movement Sleep

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Sleep shapes cortical network activity, fostering global homeostatic downregulation of excitability while maintaining or even upregulating excitability in selected networks in a manner that supports memory consolidation. Here, we used two-photon calcium imaging of cortical layer 2/3 neurons in sleeping male mice to examine how these seemingly opposing dynamics are balanced in cortical networks. During slow-wave sleep (SWS) episodes, mean calcium activity of excitatory pyramidal (Pyr) cells decreased. Simultaneously, however, variance in Pyr population calcium activity increased, contradicting the notion of a homogenous downregulation of network activity. Indeed, we identified a subpopulation of Pyr cells distinctly upregulating calcium activity during SWS, which were highly active during sleep spindles known to support mnemonic processing. Rapid eye movement (REM) episodes following SWS were associated with a general downregulation of Pyr cells, including the subpopulation of Pyr cells active during spindles, which persisted into following stages of sleep and wakefulness. Parvalbumin-positive inhibitory interneurons (PV-In) showed an increase in calcium activity during SWS episodes, while activity remained unchanged during REM sleep episodes. This supports the view that downregulation of Pyr calcium activity during SWS results from increased somatic inhibition via PV-In, whereas downregulation during REM sleep is achieved independently of such inhibitory activity. Overall, our findings show that SWS enables upregulation of select cortical circuits (likely those which were involved in mnemonic processing) through a spindle-related process, whereas REM sleep mediates general downregulation, possibly through synaptic re-normalization.

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Distinct Functional and Structural Connectivity of the Human Hand-Knob Supported by Intraoperative Findings

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Fine motor skills rely on the control of hand muscles exerted by a region of primary motor cortex (M1) that has been extensively investigated in monkeys. Although neuroimaging enables the exploration of this system also in humans, indirect measurements of brain activity prevent causal definitions of hand motor representations, which can be achieved using data obtained during brain mapping in tumor patients. High-frequency direct electrical stimulation delivered at rest (HF-DES-Rest) on the hand-knob region of the precentral gyrus has identified two sectors showing differences in cortical excitability. Using quantitative analysis of motor output elicited with HF DES-Rest, we characterized two sectors based on their excitability, higher in the posterior and lower in the anterior sector. We studied whether the different cortical excitability of these two regions reflected differences in functional connectivity (FC) and structural connectivity (SC). Using healthy adults from the Human Connectome Project (HCP), we computed FC and SC of the anterior and the posterior hand-knob sectors identified within a large cohort of patients. The comparison of FC of the two seeds showed that the anterior hand-knob, relative to the posterior hand-knob, showed stronger functional connections with a bilateral set of parietofrontal areas responsible for integrating perceptual and cognitive hand-related sensorimotor processes necessary for goal-related actions. This was reflected in different patterns of SC between the two sectors. Our results suggest that the human hand-knob is a functionally and structurally heterogeneous region organized along a motor-cognitive gradient.

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BEHAVIORAL/COGNITIVE

Examining the Coding Strength of Object Identity and Nonidentity Features in Human Occipito-Temporal Cortex and Convolutional Neural Networks

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A visual object is characterized by multiple visual features, including its identity, position and size. Despite the usefulness of identity and nonidentity features in vision and their joint coding throughout the primate ventral visual processing pathway, they have so far been studied relatively independently. Here in both female and male human participants, the coding of identity and nonidentity features was examined together across the human ventral visual pathway. The nonidentity features tested included two Euclidean features (position and size) and two non-Euclidean features (image statistics and spatial frequency (SF) content of an image). Overall, identity representation increased and nonidentity feature representation decreased along the ventral visual pathway, with identity outweighing the non-Euclidean but not the Euclidean features at higher levels of visual processing. In 14 convolutional neural networks (CNNs) pretrained for object categorization with varying architecture, depth, and with/without recurrent processing, nonidentity feature representation showed an initial large increase from early to mid-stage of processing, followed by a decrease at later stages of processing, different from brain responses. Additionally, from lower to higher levels of visual processing, position became more underrepresented and image statistics and SF became more overrepresented compared with identity in CNNs than in the human brain. Similar results were obtained in a CNN trained with stylized images that emphasized shape representations. Overall, by measuring the coding strength of object identity and nonidentity features together, our approach provides a new tool for characterizing feature coding in the human brain and the correspondence between the brain and CNNs.

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Longitudinal Analysis of Sleep Spindle Maturation from Childhood through Late Adolescence

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Sleep spindles are intermittent bursts of 11–15 Hz EEG waves that occur during non-rapid eye movement sleep. Spindles are believed to help maintain sleep and to play a role in sleep-dependent memory consolidation. Here we applied an automated sleep spindle detection program to our large longitudinal sleep EEG dataset (98 human subjects, 6–18 years old, >2000 uninterrupted nights) to evaluate maturational trends in spindle wave frequency, density, amplitude, and duration. This large dataset enabled us to apply nonlinear as well as linear age models, thereby extending the findings of prior cross-sectional studies that used linear models. We found that spindle wave frequency increased with remarkable linearity across the age range. Central spindle density increased nonlinearly to a peak at age 15.1 years. Central spindle wave amplitude declined in a sigmoidal pattern with the age of fastest decline at 13.5 years. Spindle duration decreased linearly with age. Of the four measures, only spindle amplitude showed a sex difference in dynamics such that the age of most rapid decline in females preceded that in males by 1.4 years. This amplitude pattern, including the sex difference in timing, paralleled the maturational pattern for δ (1–4 Hz) wave power. We interpret these age-related changes in spindle characteristics as indicators of maturation of thalamocortical circuits and changes in sleep depth. These robust age-effects could facilitate the search for cognitive-behavioral correlates of spindle waveforms and might also help guide basic research on EEG mechanisms and postnatal brain maturation.

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A Signaled Locomotor Avoidance Action Is Fully Represented in the Neural Activity of the Midbrain Tegmentum

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Animals, including humans, readily learn to avoid harmful and threatening situations by moving in response to cues that predict the threat (e.g., fire alarm, traffic light). During a negatively reinforced sensory-guided locomotor action, known as signaled active avoidance, animals learn to avoid a harmful unconditioned stimulus (US) by moving away when signaled by a harmless conditioned stimulus (CS) that predicts the threat. CaMKII-expressing neurons in the pedunculopontine tegmentum area (PPT) of the midbrain locomotor region have been shown to play a critical role in the expression of this learned behavior, but the activity of these neurons during learned behavior is unknown. Using calcium imaging fiber photometry in freely behaving mice, we show that PPT neurons sharply activate during presentation of the auditory CS that predicts the threat before onset of avoidance movement. PPT neurons activate further during the succeeding CS-driven avoidance movement, or during the faster US-driven escape movement. PPT neuron activation was weak during slow spontaneous movements but correlated sharply with movement speed and, therefore, with the urgency of the behavior. Moreover, using optogenetics, we found that these neurons must discharge during the signaled avoidance interval for naive mice to effectively learn the active avoidance behavior. As an essential hub for signaled active avoidance, neurons in the midbrain tegmentum process the conditioned cue that predicts the threat and discharge sharply relative to the speed or apparent urgency of the avoidance (learned) and escape (innate) responses.

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Interoception Primes Emotional Processing: Multimodal Evidence from Neurodegeneration

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Recent frameworks in cognitive neuroscience and behavioral neurology underscore interoceptive priors as core modulators of negative emotions. However, the field lacks experimental designs manipulating the priming of emotions via interoception and exploring their multimodal signatures in neurodegenerative models. Here, we designed a novel task that involves interoceptive and control-exteroceptive priming conditions followed by post-interoception and post-exteroception facial emotion recognition (FER). We recruited 114 participants, including healthy controls (HCs) as well as patients with behavioral variant frontotemporal dementia (bvFTD), Parkinson's disease (PD), and Alzheimer's disease (AD). We measured online EEG modulations of the heart-evoked potential (HEP), and associations with both brain structural and resting-state functional connectivity patterns. Behaviorally, post-interoception negative FER was enhanced in HCs but selectively disrupted in bvFTD and PD, with AD presenting generalized disruptions across emotion types. Only bvFTD presented impaired interoceptive accuracy. Increased HEP modulations during post-interoception negative FER was observed in HCs and AD, but not in bvFTD or PD patients. Across all groups, post-interoception negative FER correlated with the volume of the insula and the ACC. Also, negative FER was associated with functional connectivity along the (a) salience network in the post-interoception condition, and along the (b) executive network in the post-exteroception condition. These patterns were selectively disrupted in bvFTD (a) and PD (b), respectively. Our approach underscores the multidimensional impact of interoception on emotion, while revealing a specific pathophysiological marker of bvFTD. These findings inform a promising theoretical and clinical agenda in the fields of interoception, emotion, allostasis, and neurodegeneration.

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Temporally Specific Roles of Ventral Tegmental Area Projections to the Nucleus Accumbens and Prefrontal Cortex in Attention and Impulse Control

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Deficits in impulse control and attention are prominent in the symptomatology of mental disorders such as attention deficit hyperactivity disorder (ADHD), substance addiction, schizophrenia, and bipolar disorder, yet the underlying mechanisms are incompletely understood. Frontostriatal structures, such as the nucleus accumbens (NAc), the medial prefrontal cortex (mPFC), and their dopaminergic innervation from the ventral tegmental area (VTA) have been implicated in impulse control and attention. What remains unclear is how the temporal pattern of activity of these VTA projections contributes to these processes. Here, we optogenetically stimulated VTA dopamine (DA) cells, as well as VTA projections to the NAc core (NAcC), NAc shell (NAcS), and the mPFC in male rats performing the 5-choice serial reaction time task (5-CSRTT). Our data show that stimulation of VTA DA neurons, and VTA projections to the NAcC and the mPFC immediately before presentation of the stimulus cue, impaired attention but spared impulse control. Importantly, in addition to reducing attention, activation of VTA-NAcS also increased impulsivity when tested under a longer intertrial interval (ITI), to provoke impulsive behavior. Optogenetic stimulation at the beginning of the ITI only partially replicated these effects. In sum, our data show how attention and impulsivity are modulated by neuronal activity in distinct ascending output pathways from the VTA in a temporally specific manner. These findings increase our understanding of the intricate mechanisms by which mesocorticolimbic circuits contribute to cognition.

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NEUROBIOLOGY OF DISEASE

mTOR Attenuation with Rapamycin Reverses Neurovascular Uncoupling and Memory Deficits in Mice Modeling Alzheimer's Disease

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Vascular dysfunction is a universal feature of aging and decreased cerebral blood flow has been identified as an early event in the pathogenesis of Alzheimer's disease (AD). Cerebrovascular dysfunction in AD includes deficits in neurovascular coupling (NVC), a mechanism that ensures rapid delivery of energy substrates to active neurons through the blood supply. The mechanisms underlying NVC impairment in AD, however, are not well understood. We have previously shown that mechanistic/mammalian target of rapamycin (mTOR) drives cerebrovascular dysfunction in models of AD by reducing the activity of endothelial nitric oxide synthase (eNOS), and that attenuation of mTOR activity with rapamycin is sufficient to restore eNOS-dependent cerebrovascular function. Here we show mTOR drives NVC impairments in an AD model through the inhibition of neuronal NOS (nNOS)- and non-NOS-dependent components of NVC, and that mTOR attenuation with rapamycin is sufficient to restore NVC and even enhance it above WT responses. Restoration of NVC and concomitant reduction of cortical amyloid- β levels effectively treated memory deficits in 12-month-old hAPP(J20) mice. These data indicate that mTOR is a critical driver of NVC dysfunction and underlies cognitive impairment in an AD model. Together with our previous findings, the present studies suggest that mTOR promotes cerebrovascular dysfunction in AD, which is associated with early disruption of nNOS activation, through its broad negative impact on nNOS as well as on non-NOS components of NVC. Our studies highlight the potential of mTOR attenuation as an efficacious treatment for AD and potentially other neurologic diseases of aging.

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High Dietary Fat Consumption Impairs Axonal Mitochondrial Function *In Vivo*

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Peripheral neuropathy (PN) is the most common complication of prediabetes and diabetes. PN causes severe morbidity for Type 2 diabetes (T2D) and prediabetes patients, including limb pain followed by numbness resulting from peripheral nerve damage. PN in T2D and prediabetes is associated with dyslipidemia and elevated circulating lipids; however, the molecular mechanisms underlying PN development in prediabetes and T2D are unknown. Peripheral nerve sensory neurons rely on axonal mitochondria to provide energy for nerve impulse conduction under homeostatic conditions. Models of dyslipidemia

in vitro demonstrate mitochondrial dysfunction in sensory neurons exposed to elevated levels of exogenous fatty acids. Herein, we evaluated the effect of dyslipidemia on mitochondrial function and dynamics in sensory axons of the saphenous nerve of a male high-fat diet (HFD)-fed murine model of prediabetes to identify mitochondrial alterations that correlate with PN pathogenesis *in vivo*. We found that the HFD decreased mitochondrial membrane potential (MMP) in axonal mitochondria and reduced the ability of sensory neurons to conduct at physiological frequencies. Unlike mitochondria in control axons, which dissipated their MMP in response to increased impulse frequency (from 1 to 50 Hz), HFD mitochondria dissipated less MMP in response to axonal energy demand, suggesting a lack of reserve capacity. The HFD also decreased sensory axonal Ca^{2+} levels and increased mitochondrial lengthening and expression of PGC1 α , a master regulator of mitochondrial biogenesis. Together, these results suggest that mitochondrial dysfunction underlies an imbalance of axonal energy and Ca^{2+} levels and impairs impulse conduction within the saphenous nerve in prediabetic PN.

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Continuous Monitoring of Tau-Induced Neurotoxicity in Patient-Derived iPSC-Neurons

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Tau aggregation within neurons is a critical feature of Alzheimer's disease (AD) and related tauopathies. It is believed that soluble pathologic tau species seed the formation of tau aggregates in a prion-like manner and propagate through connected neurons during the progression of disease. Both soluble and aggregated forms of tau are thought to have neurotoxic properties. In addition, different strains of misfolded tau may cause differential neurotoxicity. In this work, we present an accelerated human neuronal model of tau-induced neurotoxicity that incorporates both soluble tau species and tau aggregation. Using patient-derived induced pluripotent stem cell (iPSC) neurons expressing a tau aggregation biosensor, we develop a cell culture system that allows continuous assessment of both induced tau aggregation and neuronal viability at single-cell resolution for periods of >1 week. We show that exogenous tau "seed" uptake, as measured by tau repeat domain (TauRD) reporter aggregation, increases the risk for subsequent neuronal death *in vitro*. These results are the first to directly visualize neuronal TauRD aggregation and subsequent cell death in single human iPSC neurons. Specific morphologic strains or patterns of TauRD aggregation are then identified and associated with differing neurotoxicity. Furthermore, we demonstrate that familial AD iPSC neurons expressing the PSEN1 L435F mutation exhibit accelerated TauRD aggregation kinetics and a tau strain propagation bias when compared with control iPSC neurons.

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Temporal Contribution of Myeloid-Lineage TLR4 to the Transition to Chronic Pain: A Focus on Sex Differences

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Complex regional pain syndrome (CRPS) is a chronic pain disorder with a clear acute-to-chronic transition. Preclinical studies demonstrate that toll-like receptor 4 (TLR4), expressed by myeloid-lineage cells, astrocytes, and neurons, mediates a sex-dependent transition to chronic pain; however, evidence is lacking on which exact TLR4-expressing cells are responsible. We used complementary pharmacologic and transgenic approaches in mice to more specifically manipulate myeloid-lineage TLR4 and outline its contribution to the transition from acute-to-chronic CRPS based on three key variables: location (peripheral vs central), timing (prevention vs treatment), and sex (male vs female). We demonstrate that systemic TLR4 antagonism is more effective at improving chronic allodynia trajectory when administered at the time of injury (early) in the tibial fracture model of CRPS in both sexes. In order to clarify the contribution of myeloid-lineage cells peripherally (macrophages) or centrally (microglia), we rigorously characterize a novel spatiotemporal transgenic mouse line, *Cx3CR1-Cre^{ERT2-eYFP};TLR4^{fl/fl}* (TLR4 cKO) to specifically knock out TLR4 only in microglia and no other myeloid-lineage cells. Using this transgenic mouse, we find that early TLR4 cKO results in profound improvement in chronic, but not acute, allodynia in males, with a significant but less robust effect in females. In contrast, late TLR4 cKO results in partial improvement in allodynia in both sexes, suggesting that downstream cellular or molecular TLR4-independent events may have already been triggered. Overall, we find that the contribution of TLR4 is time- and microglia-dependent in both sexes; however, females also rely on peripheral myeloid-lineage (or other TLR4-expressing) cells to trigger chronic pain.

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