



Cover legend: Hand laminated wood sculpture by Paméla Simard created from fluorescent microscopy images generated by Hunter S. Shaw. The piece named, Bdl, represents the visual system of the fruit fly brain, and more precisely, the contributions of adhesion molecules to photoreceptor synaptic development. This collaboration between artist and scientist as part of the Convergence Initiative explores the similarities between the processes involved in artistic creativity and in scientific research. Photography by Alex Tran. (pages 6817–6828).

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- Erratum:** The article "Hyperexcitability and Hyperplasticity Disrupt Cerebellar Signal Transfer in the *IB2* KO Mouse Model of Autism" by Teresa Soda, Lisa Mapelli, Francesca Locatelli, Laura Botta, Mitchell Goldfarb, Francesca Prestori, and Egidio Ugo D'Angelo, appeared on pages 2383–2397 of the March 27, 2019 issue. An erratum for this article appears on p. 7029.

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Articles

CELLULAR/MOLECULAR

The Conserved IgSF9 Protein Borderless Regulates Axonal Transport of Presynaptic Components and Color Vision in *Drosophila*

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Normal brain function requires proper targeting of synaptic-vesicle (SV) and active-zone components for presynaptic assembly and function. Whether and how synaptogenic signals (e.g., adhesion) at axo-dendritic contact sites promote axonal transport of presynaptic components for synapse formation, however, remain unclear. In this study, we show that Borderless (Bdl), a member of the conserved IgSF9-family trans-synaptic cell adhesion molecules, plays a novel and specific role in regulating axonal transport of SV components. Loss of *bdl* disrupts axonal transport of SV components in photoreceptor R8 axons, but does not affect the transport of mitochondria. Genetic mosaic analysis, transgene rescue and cell-type-specific knockdown indicate that Bdl is required both presynaptically and postsynaptically for delivering SV components in R8 axons. Consistent with a role for Bdl in R8 axons, loss of *bdl* causes a failure of R8-dependent phototaxis response to green light. *bdl* interacts genetically with *imac* encoding for a member of the UNC-104/Imac/KIF1A-family motor proteins, and is required for proper localization of Imac in R8 presynaptic terminals. Our results support a model in which Bdl mediates specific axo-dendritic interactions in a homophilic manner, which upregulates the Imac motor in promoting axonal transport of SV components for R8 presynaptic assembly and function.

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Differences between Dorsal Root and Trigeminal Ganglion Nociceptors in Mice Revealed by Translational Profiling

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Nociceptors located in the trigeminal ganglion (TG) and DRG are the primary sensors of damaging or potentially damaging stimuli for the head and body, respectively, and are key drivers of chronic pain states. While nociceptors in these two tissues show a high degree of functional similarity, there are important differences in their development lineages, their functional connections to the CNS, and recent genome-wide analyses of gene expression suggest that they possess some unique genomic signatures. Here, we used translating ribosome affinity purification to comprehensively characterize and compare mRNA translation in *Scn10a*-positive nociceptors in the TG and DRG of male and female mice. This unbiased method independently confirms several findings of differences between TG and DRG nociceptors described in the literature but also suggests preferential utilization of key signaling pathways. Most prominently, we provide evidence that translational efficiency in mechanistic target of rapamycin (mTOR)-related genes is higher in the TG compared with DRG, whereas several genes associated with the negative regulator of mTOR, AMP-activated protein kinase, have higher translational efficiency in DRG nociceptors. Using capsaicin as a sensitizing stimulus, we show that behavioral responses are greater in the TG region and this effect is completely reversible with mTOR inhibition. These findings have implications for the relative capacity of these nociceptors to be sensitized upon injury. Together, our data provide a comprehensive, comparative view of transcriptome and translational activity in TG and DRG nociceptors that enhances our understanding of nociceptor biology.

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Macrophage Toll-like Receptor 9 Contributes to Chemotherapy-Induced Neuropathic Pain in Male Mice

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Chemotherapy-induced peripheral neuropathy (CIPN) remains a pressing clinical problem; however, our understanding of sexual dimorphism in CIPN remains unclear. Emerging studies indicate a sex-dimorphic role of Toll-like receptor 4 (TLR4) in driving neuropathic pain. In this study, we examined the role of TLR9 in CIPN induced by paclitaxel in WT and *Tlr9* mutant mice of both sexes. Baseline pain sensitivity was not affected in either *Tlr9* mutant male or female mice. Intraplantar and intrathecal injection of the TLR9 agonist ODN 1826 induced mechanical allodynia in both sexes of WT and *Tlr4* KO mice but failed to do so in *Tlr9* mutant mice. Moreover, *Trpv1* KO or C-fiber blockade by resiniferatoxin failed to affect intraplantar ODN 1826-induced mechanical allodynia. Interestingly, the development of paclitaxel-evoked mechanical allodynia was attenuated by TLR9 antagonism or *Tlr9* mutation only in male mice. Paclitaxel-induced CIPN caused macrophage infiltration to DRGs in both sexes, and this infiltration was not affected by *Tlr9* mutation. Paclitaxel treatment also upregulated TNF and CXCL1 in macrophage cultures and DRG tissues in both sexes, but these

changes were compromised by *Tlr9* mutation in male animals. Intraplantar adoptive transfer of paclitaxel-activated macrophages evoked mechanical allodynia in both sexes, which was compromised by *Tlr9* mutation or by treatment with TLR9 inhibitor only in male animals. Finally, TLR9 antagonism reduced paclitaxel-induced mechanical allodynia in female nude mice (T-cell and B-cell deficient). Together, these findings reveal sex-dimorphic macrophage TLR9 signaling in chemotherapy-induced neuropathic pain.

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DEVELOPMENT/PLASTICITY/REPAIR

Distinct Heterosynaptic Plasticity in Fast Spiking and Non-Fast-Spiking Inhibitory Neurons in Rat Visual Cortex

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Inhibition in neuronal networks of the neocortex serves a multitude of functions, such as balancing excitation and structuring neuronal activity in space and time. Plasticity of inhibition is mediated by changes at both inhibitory synapses, as well as excitatory synapses on inhibitory neurons. Using slices from visual cortex of young male rats, we describe a novel form of plasticity of excitatory synapses on inhibitory neurons, weight-dependent heterosynaptic plasticity. Recordings from connected pyramid-to-interneuron pairs confirm that postsynaptic activity alone can induce long-term changes at synapses that were not presynaptically active during the induction, i.e., heterosynaptic plasticity. Moreover, heterosynaptic changes can accompany homosynaptic plasticity induced in inhibitory neurons by conventional spike-timing-dependent plasticity protocols. In both fast-spiking (FS) and non-FS neurons, heterosynaptic changes were weight-dependent, because they correlated with initial paired-pulse ratio (PPR), indicative of initial strength of a synapse. Synapses with initially high PPR, indicative of low release probability (“weak” synapses), had the tendency to be potentiated, while synapses with low initial PPR (“strong” synapses) tended to depress or did not change. Interestingly, the net outcome of heterosynaptic changes was different in FS and non-FS neurons. FS neurons expressed balanced changes, with gross average ($n = 142$) not different from control. Non-FS neurons ($n = 66$) exhibited net potentiation. This difference could be because of higher initial PPR in the non-FS neurons. We propose that weight-dependent heterosynaptic plasticity may counteract runaway dynamics of excitatory inputs imposed by Hebbian-type learning rules and contribute to fine-tuning of distinct aspects of inhibitory function mediated by FS and non-FS neurons in neocortical networks.

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SYSTEMS/CIRCUITS

Divergent Auditory Nerve Encoding Deficits Between Two Common Etiologies of Sensorineural Hearing Loss

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Speech intelligibility can vary dramatically between individuals with similar clinically defined severity of hearing loss based on the audiogram. These perceptual differences, despite equal audiometric-threshold elevation, are often assumed to reflect central-processing variations. Here, we compared peripheral-processing in auditory nerve (AN) fibers of male chinchillas between two prevalent hearing loss etiologies: metabolic hearing loss (MHL) and noise-induced hearing loss (NIHL). MHL results from age-related reduction of the endocochlear potential due to atrophy of the stria vascularis. MHL in the present study was induced using furosemide, which provides a validated model of age-related MHL in young animals by reversibly inhibiting the endocochlear potential. Effects of MHL on peripheral processing were assessed using Wiener–kernel (system identification) analyses of single AN fiber responses to broadband noise, for direct comparison to previously published AN responses from animals with NIHL. Wiener–kernel analyses show that even mild NIHL causes grossly abnormal coding of low-frequency stimulus components. In contrast, for MHL the same abnormal coding was only observed with moderate to severe loss. For equal sensitivity loss, coding impairment was substantially less severe with MHL than with NIHL, probably due to greater preservation of the tip-to-tail ratio of cochlear frequency tuning with MHL compared with NIHL rather than different intrinsic AN properties. Differences in peripheral neural coding between these two pathologies—the more severe of which, NIHL, is preventable—likely contribute to individual speech perception differences. Our results underscore the need to minimize noise overexposure and for strategies to personalize diagnosis and treatment for individuals with sensorineural hearing loss.

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Robust Associative Learning Is Sufficient to Explain the Structural and Dynamical Properties of Local Cortical Circuits

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The ability of neural networks to associate successive states of network activity lies at the basis of many cognitive functions. Hence, we hypothesized that many ubiquitous structural and dynamical properties of local cortical networks result from associative learning. To test this hypothesis, we trained recurrent networks of excitatory and inhibitory neurons on memories composed of varying numbers of associations and compared the resulting network properties with those observed experimentally. We show that, when the network is robustly loaded with near-maximum amount of associations it can support, it develops properties that are consistent with the observed probabilities of excitatory and inhibitory connections, shapes of connection weight distributions, overexpression of specific 2- and 3-neuron motifs, distributions of connection numbers in clusters of 3–8 neurons, sustained, irregular, and asynchronous firing activity, and balance of excitation and inhibition. In addition, memories loaded into the network can be retrieved, even in the presence of noise that is comparable with the baseline variations in the postsynaptic potential. The confluence of these results suggests that many structural and dynamical properties of local cortical networks are simply a byproduct of associative learning. We predict that overexpression of excitatory–excitatory bidirectional connections observed in many cortical systems must be accompanied with underexpression of bidirectionally connected inhibitory–excitatory neuron pairs.

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Differential Inhibitory Configurations Segregate Frequency Selectivity in the Mouse Inferior Colliculus

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Receptive fields and tuning curves of sensory neurons represent the neural substrates that allow animals to efficiently detect and distinguish external stimuli. They are progressively refined to create diverse sensitivity and selectivity for neurons along ascending central pathways. However, the neural circuitry mechanisms have not been directly determined for such fundamental qualities in relation to sensory neurons' functional organizations, because of the technical difficulty of correlating neurons' input and output. Here, we obtained spike outputs and synaptic inputs from the same neurons within characteristically defined neural ensembles, to determine the synaptic mechanisms driving their diverse frequency selectivity in the mouse inferior colliculus. We find that the synaptic strength and timing of excitatory and inhibitory inputs are configured differently and independently within individual neurons' receptive fields, which segregate sensitive and selective neurons and endow neural populations with broad receptive fields and sharp frequency tuning. By computationally modeling spike outputs from integrating synaptic inputs and comparing them with real spike responses of the same neurons, we show that space-clamping errors did not qualitatively affect the estimation of spike responses derived from synaptic currents in *in vivo* voltage-clamp recordings. These data suggest that heterogeneous inhibitory circuits coexist locally for a parallel but differentiated representation of incoming signals.

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Efferent Inputs Are Required for Normal Function of Vestibular Nerve Afferents

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A group of vestibular afferent nerve fibers with irregular-firing resting discharges are thought to play a prominent role in responses to fast head movements and vestibular plasticity. We show that, in C57BL/6 mice (either sex, 4–5 weeks old), normal activity in the efferent vestibular pathway is required for function of these irregular afferents. Thermal inhibition of efferent fibers results in a profound inhibition of irregular afferents' resting discharges, rendering them inadequate for signaling head movements. In this way, efferent inputs adjust the contribution of the peripheral irregular afferent pathway that plays a critical role in peripheral vestibular signaling and plasticity.

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BEHAVIORAL/COGNITIVE

In a Temporally Segmented Experience Hippocampal Neurons Represent Temporally Drifting Context But Not Discrete Segments

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There is widespread agreement that episodic memory is organized into a timeline of past experiences. Recent work suggests that the hippocampus may parse the flow of experience into discrete episodes separated by event boundaries. A complementary body of work suggests that context changes gradually as experience unfolds. We recorded from hippocampal neurons as male Long–Evans rats performed 6 blocks of an object discrimination task in sets of 15 trials. Each block was separated by removal

from the testing chamber for a delay to enable segmentation. The reward contingency reversed from one block to the next to incentivize segmentation. We expected animals to hold two distinct, recurring representations of context to match the two distinct rule contingencies. Instead, we found that overtrained rats began each block neither above nor below chance but by guessing randomly. While many units had clear firing fields selective to the conjunction of objects in places, a significant population also reflected a continuously drifting code both within block and across blocks. Despite clear boundaries between blocks, we saw no neural evidence for event segmentation in this experiment. Rather, the hippocampal ensemble drifted continuously across time. This continuous drift in the neural representation was consistent with the lack of segmentation observed in behavior.

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Learning What Is Irrelevant or Relevant: Expectations Facilitate Distractor Inhibition and Target Facilitation through Distinct Neural Mechanisms

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It is well known that attention can facilitate performance by top-down biasing processing of task-relevant information in advance. Recent findings from behavioral studies suggest that distractor inhibition is not under similar direct control but strongly dependent on expectations derived from previous experience. Yet, how expectations about distracting information influence distractor inhibition at the neural level remains unclear. The current study addressed this outstanding question in three experiments in which search displays with repeating distractor or target locations across trials allowed human observers (male and female) to learn which location to selectively suppress or boost. Behavioral findings demonstrated that both distractor and target location learning resulted in more efficient search, as indexed by faster response times. Crucially, distractor learning benefits were observed without target location foreknowledge, unaffected by the number of possible target locations, and could not be explained by priming alone. To determine how distractor location expectations facilitated performance, we applied a spatial encoding model to EEG data to reconstruct activity in neural populations tuned to distractor or target locations. Target location learning increased neural tuning to target locations in advance, indicative of preparatory biasing. This sensitivity increased after target presentation. By contrast, distractor expectations did not change preparatory spatial tuning. Instead, distractor expectations reduced distractor-specific processing, as reflected in the disappearance of the Pd event-related potential component, a neural marker of distractor inhibition, and decreased decoding accuracy. These findings suggest that the brain may no longer process expected distractors as distractors, once it has learned they can safely be ignored.

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Binding During Sequence Learning Does Not Alter Cortical Representations of Individual Actions

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As a sequence of movements is learned, serially ordered actions get bound together into sets to reduce computational complexity during planning and execution. Here, we investigated how actions become naturally bound over the course of learning and how this learning affects cortical representations of individual actions. Across 5 weeks of practice, neurologically healthy human subjects learned either a complex 32-item sequence of finger movements (trained group, $n = 9$; 3 female) or randomly ordered actions (control group, $n = 9$; 3 female). Over the course of practice, responses during sequence production in the trained group became temporally correlated, consistent with responses being bound together under a common command. These behavioral changes, however, did not coincide with plasticity in the multivariate representations of individual finger movements, assessed using fMRI, at any level of the cortical motor hierarchy. This suggests that the representations of individual actions remain stable, even as the execution of those same actions become bound together in the context of producing a well learned sequence.

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Monosynaptic Hippocampal-Prefrontal Projections Contribute to Spatial Memory Consolidation in Mice

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Time locking between neocortical sleep slow oscillations, thalamo-cortical spindles, and hippocampal sharp-wave ripples has convincingly been shown to be a key element of systems consolidation. Here we investigate the role of monosynaptic projections from ventral/intermediate hippocampus to medial prefrontal cortex (mPFC) in

sleep-dependent memory consolidation in male mice. Following acquisition learning in the Barnes maze, we optogenetically silenced the axonal terminals of hippocampal projections within mPFC during slow-wave sleep. This silencing during SWS selectively impaired recent but not remote memory in the absence of effects on error rate and escape latencies. Furthermore, it prevented the development of the most efficient search strategy and sleep spindle time-locking to slow oscillation. An increase in post-learning sleep sharp-wave ripple (SPWR) density and reduced time locking of learning-associated SPWR activity to sleep spindles may be a less specific response. Our results demonstrate that monosynaptic projections from hippocampus to mPFC contribute to sleep-dependent memory consolidation, potentially by affecting the temporal coupling of sleep-associated electrophysiological events.

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NEUROBIOLOGY OF DISEASE

Tuning of Glutamate, But Not GABA, Release by an Intrasyntaptic Vesicle APP Domain Whose Function Can Be Modulated by β - or α -Secretase Cleavage

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APP, whose mutations cause familial Alzheimer's disease (FAD), modulates neurotransmission via interaction of its cytoplasmic tail with the synaptic release machinery. Here we identified an intravesicular domain of APP, called intraluminal SV-APP interacting domain (ISVAID), which interacts with glutamatergic, but not GABAergic, synaptic vesicle proteins. ISVAID contains the β - and α -secretase cleavage sites of APP: proteomic analysis of the interactome of ISVAID suggests that β - and α -secretase cleavage of APP cuts inside the interaction domain of ISVAID and destabilizes protein–protein interactions. We have tested the functional significance of the ISVAID and of β -/ α -secretase-processing of APP using various ISVAID-derived peptides in competition experiments on both female and male mouse and rats hippocampal slices. A peptide encompassing the entire ISVAID facilitated glutamate, but not GABA, release acting as dominant negative inhibitor of the functions of this APP domain in acute hippocampal slices. In contrast, peptides representing the product of β -/ α -secretase-processing of ISVAID did not alter excitatory neurotransmitter release. These findings suggest that cleavage of APP by either β - or α -secretase may inactivate the ISVAID, thereby enhancing glutamate release. Our present data support the notion that APP tunes glutamate release, likely through intravesicular and extravesicular interactions with synaptic vesicle proteins and the neurotransmitter release machinery, and that β -/ α cleavage of APP facilitates the release of excitatory neurotransmitter.

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SIV-Mediated Synaptic Dysfunction Is Associated with an Increase in Synapsin Site 1 Phosphorylation and Impaired PP2A Activity

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Although the reduction of viral loads in people with HIV undergoing combination antiretroviral therapy has mitigated AIDS-related symptoms, the prevalence of neurological impairments has remained unchanged. HIV-associated CNS dysfunction includes impairments in memory, attention, memory processing, and retrieval. Here, we show a significant site-specific increase in the phosphorylation of Syn I serine 9, site 1, in the frontal cortex lysates and synaptosome preparations of male rhesus macaques infected with simian immunodeficiency virus (SIV) but not in uninfected or SIV-infected antiretroviral therapy animals. Furthermore, we found that a lower protein phosphatase 2A (PP2A) activity, a phosphatase responsible for Syn I (S9) dephosphorylation, is primarily associated with the higher S9 phosphorylation in the frontal cortex of SIV-infected macaques. Comparison of brain sections confirmed higher Syn I (S9) in the frontal cortex and greater coexpression of Syn I and PP2A A subunit, which was observed as perinuclear aggregates in the somata of the frontal cortex of SIV-infected macaques. Synaptosomes from SIV-infected animals were physiologically tested using a synaptic vesicle endocytosis assay and FM4–64 dye showing a significantly higher baseline depolarization levels in synaptosomes of SIV⁺-infected than uninfected control or antiretroviral therapy animals. A PP2A-activating FDA-approved drug, FTY720, decreased the higher synaptosome depolarization in SIV-infected animals. Our results suggest that an impaired distribution and lower activity of serine/threonine phosphatases in the context of HIV infection may cause an indirect effect on the phosphorylation levels of essential proteins involving in synaptic transmission, supporting the occurrence of specific impairments in the synaptic activity during SIV infection.

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Targeting Seizure-Induced Neurogenesis in a Clinically Relevant Time Period Leads to Transient But Not Persistent Seizure Reduction

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Mesial temporal lobe epilepsy (mTLE), the most common form of medically refractory epilepsy in adults, is usually associated with hippocampal pathophysiology. Using rodent models of mTLE, many studies including work from our laboratory have shown that new neurons born around the onset of severe acute seizures known as status epilepticus (SE) are crucial for the process of epileptogenesis and targeting seizure-induced neurogenesis either genetically or pharmacologically can impact the frequency

of chronic seizures. However, these studies are limited in their clinical relevance as none of them determines the potential of blocking new neurons generated after the epileptogenic insult to alleviate the development of chronic seizures. Therefore, using a pilocarpine-induced SE model of mTLE in mice of either sex, we show that >4 weeks of continuous and concurrent ablation of seizure-induced neurogenesis after SE can reduce the formation of spontaneous recurrent seizures by 65%. We also found that blocking post-SE neurogenesis does not lead to long-term seizure reduction as the effect was observed only transiently for 10 d with >4 weeks of continuous and concurrent ablation of seizure-induced neurogenesis. Thus, these findings provide evidence that seizure-induced neurogenesis when adequately reduced in a clinically relevant time period has the potential to transiently suppress recurrent seizures, but additional mechanisms need to be targeted to permanently prevent epilepsy development.

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