



Cover legend: This transverse section through the neural tube of a day-old zebrafish embryo shows microtubules (green), which are elongated and orientated along the apical-basal axis of neuroepithelial cells. Microtubule destabilization in *Rgma* and *Neo1a*-depleted embryos impairs neural tube formation. Image was taken by Dr. Elim Hong and edited by Maraki Negesse. For more information, see the article by Brown et al. (pages 7465–7484).

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Articles

CELLULAR/MOLECULAR

Disruption of GpI mGluR-Dependent Cav2.3 Translation in a Mouse Model of Fragile X Syndrome

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Fragile X syndrome (FXS) is an inherited intellectual impairment that results from the loss of fragile X mental retardation protein (FMRP), an mRNA binding protein that regulates mRNA translation at synapses. The absence of FMRP leads to neuronal and circuit-level hyperexcitability that is thought to arise from the aberrant expression and activity of voltage-gated ion channels, although the identification and characterization of these ion channels have been limited. Here, we show that FMRP binds the mRNA of the R-type voltage-gated calcium channel Cav2.3 in mouse brain synaptoneurosome and represses Cav2.3 translation under basal conditions. Consequently, in hippocampal neurons from male and female FMRP KO mice, we find enhanced Cav2.3 protein expression by western blotting and abnormally large R currents in whole-cell voltage-clamp recordings. In agreement with previous studies showing that FMRP couples Group I metabotropic glutamate receptor (GpI mGluR) signaling to protein translation, we find that GpI mGluR stimulation results in increased Cav2.3 translation and R current in hippocampal neurons which is disrupted in FMRP KO mice. Thus, FMRP serves as a key translational regulator of Cav2.3 expression under basal conditions and in response to GpI mGluR stimulation. Loss of regulated Cav2.3 expression could underlie the neuronal hyperactivity and aberrant calcium spiking in FMRP KO mice and contribute to FXS, potentially serving as a novel target for future therapeutic strategies.

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DEVELOPMENT/PLASTICITY/REPAIR

Rgma-Induced Neo1 Proteolysis Promotes Neural Tube Morphogenesis

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Neuroepithelial cell (NEC) elongation is one of several key cell behaviors that mediate the tissue-level morphogenetic movements that shape the neural tube (NT), the precursor of the brain and spinal cord. However, the upstream signals that promote NEC elongation have been difficult to tease apart from those regulating apico-basal polarity and hinge point formation, due to their confounding interdependence. The Repulsive Guidance Molecule a (Rgma)/Neogenin 1 (Neo1) signaling pathway plays a conserved role in NT formation (neurulation) and is reported to regulate both NEC elongation and apico-basal polarity, through signal transduction events that have not been identified. We examine here the role of Rgma/Neo1 signaling in zebrafish (sex unknown), an organism that does not use hinge points to shape its hindbrain, thereby enabling a direct assessment of the role of this pathway in NEC elongation. We confirm that Rgma/Neo1 signaling is required for microtubule-mediated NEC elongation, and demonstrate via cell transplantation that Neo1 functions cell autonomously to promote elongation. However, in contrast to previous findings, our data do not support a role for this pathway in establishing apical junctional complexes. Last, we provide evidence that Rgma promotes Neo1 glycosylation and intramembrane proteolysis, resulting in the production of a transient, nuclear intracellular fragment (NeoICD). Partial rescue of Neo1a and Rgma knockdown embryos by overexpressing *neoICD* suggests that this proteolytic cleavage is essential for neurulation. Based on these observations, we propose that Rgma-induced NEO1 proteolysis orchestrates NT morphogenesis by promoting NEC elongation independently of the establishment of apical junctional complexes.

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SYSTEMS/CIRCUITS

Leveraging Nonhuman Primate Multisensory Neurons and Circuits in Assessing Consciousness Theory

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Both the global neuronal workspace (GNW) and integrated information theory (IIT) posit that highly complex and interconnected networks engender perceptual awareness. GNW specifies that activity recruiting frontoparietal networks will elicit a subjective experience, whereas IIT is more concerned with the functional architecture of

networks than with activity within it. Here, we argue that according to IIT mathematics, circuits converging on integrative versus convergent yet non-integrative neurons should support a greater degree of consciousness. We test this hypothesis by analyzing a dataset of neuronal responses collected simultaneously from primary somatosensory cortex (S1) and ventral premotor cortex (vPM) in nonhuman primates presented with auditory, tactile, and audio-tactile stimuli as they are progressively anesthetized with propofol. We first describe the multisensory (audio-tactile) characteristics of S1 and vPM neurons (mean and dispersion tendencies, as well as noise-correlations), and functionally label these neurons as convergent or integrative according to their spiking responses. Then, we characterize how these different pools of neurons behave as a function of consciousness. At odds with the IIT mathematics, results suggest that convergent neurons more readily exhibit properties of consciousness (neural complexity and noise correlation) and are more impacted during the loss of consciousness than integrative neurons. Last, we provide support for the GNW by showing that neural ignition (i.e., same trial coactivation of S1 and vPM) was more frequent in conscious than unconscious states. Overall, we contrast GNW and IIT within the same single-unit activity dataset, and support the GNW.

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Morphological Cell Types Projecting from V1 Layer 4B to V2 Thick and Thin Stripes

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In macaque visual cortex, different cytochrome oxidase stripes of area V2 receive segregated projections from layers (L)2/3 and 4B of the primary visual cortex (V1), and project to dorsal or ventral stream extrastriate areas. Parallel V1-to-V2 pathways suggest functionally specialized circuits, but it is unknown whether these circuits arise from distinct cell types. V1 L4B includes two morphological types of excitatory projection neurons: pyramids, which carry mixed magnocellular (M) and parvocellular (P) information to downstream areas, and spiny stellates, which carry only M information. Previous studies have shown that, overall, V2 receives ~80% of its L4B inputs from pyramids, thus receiving mixed M and P signals. However, it is unknown how pyramids and stellates distribute their outputs to the different V2 stripes, and whether different stripes receive inputs from morphologically distinct neuron types. Using viral-mediated labeling of V2-projecting L4B neurons in male macaques, we show that thick stripes receive a greater contribution of L4B inputs from M-dominated spiny stellates compared with thin stripes. Both stripe types, however, receive a much larger contribution from spiny stellates than previously shown for V2 overall, indicating that a larger amount of M information than previously thought flows into both the dorsal and ventral streams via the V2 thick and thin stripes, respectively. Moreover, we identify four types of V2-projecting L4B cells differing in size and complexity. Three such cell types project to both thin and thick stripes, but one type, the giant spiny-stellate neuron, resembling L4B neurons projecting to motion-sensitive area MT, was only found to project to thick stripes.

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GPRIN3 Controls Neuronal Excitability, Morphology, and Striatal-Dependent Behaviors in the Indirect Pathway of the Striatum

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The regulation of the striatum by the GPCR signaling through neuromodulators is essential for its physiology and physiopathology, so it is necessary to know all the compounds of these pathways. In this study, we identified a new important partner of the dopaminergic pathway: GPRIN3 (a member of the GPRIN family). GPRIN3 is highly expressed in the striatum but with undefined function. Cell sorting of medium spiny neurons (MSNs) in indirect MSNs and direct MSNs indicated the presence of the GPRIN3 gene in both populations with a preferential expression in indirect MSNs. This led us to generate GPRIN3 KO mice by CRISPR/Cas9 and test male animals to access possible alterations in morphological, electrophysiological, and behavioral parameters following its absence. 3D reconstruction analysis of MSNs revealed increased neuronal arborization in GPRIN3 KO and modified passive and active electrophysiological properties. These cellular alterations were coupled with increased motivation and cocaine-induced hyperlocomotion. Additionally, using a specific indirect MSN knockdown, we showed a preferential role for GPRIN3 in indirect MSNs related to the D₂R signaling. Together, these results show that GPRIN3 is a mediator of D₂R function in the striatum playing a major role in striatal physiology.

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Transplanted Cells Are Essential for the Induction But Not the Expression of Cortical Plasticity

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Transplantation of even a small number of embryonic inhibitory neurons from the medial ganglionic eminence (MGE) into postnatal visual cortex makes it lose responsiveness to an eye deprived of vision when the transplanted neurons reach the age of the normal critical period of activity-dependent ocular dominance (OD) plasticity. The transplant might induce OD plasticity in the host circuitry or might instead construct a parallel circuit of its own to suppress cortical responses to the deprived eye. We transplanted MGE neurons expressing either archaerhodopsin or channelrhodopsin into the visual cortex of both male and female mice, closed one eyelid for 4–5 d, and,

as expected, observed transplant-induced OD plasticity. This plasticity was evident even when the activity of the transplanted cells was suppressed or enhanced optogenetically, demonstrating that the plasticity was produced by changes in the host visual cortex.

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BEHAVIORAL/COGNITIVE

Temporal Coding of Reward Value in Monkey Ventral Striatal Tonicly Active Neurons

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The rostromediodorsal striatum is critical for behavior dependent on evaluating rewards. We asked what contribution tonically active neurons (TANs), the putative striatal cholinergic interneurons, make in coding reward value in this part of the striatum. Two female monkeys were given the option to accept or reject an offered reward in each trial, the value of which was signaled by a visual cue. Forty-five percent of the TANs use temporally modulated activity to encode information about discounted value. These responses were significantly better represented using principal component analysis than by just counting spikes. The temporal coding is straightforward: the spikes are distributed according to a sinusoidal envelope of activity that changes gain, ranging from positive to negative according to discounted value. Our results show that the information about the relative value of an offered reward is temporally encoded in neural spike trains of TANs. This temporal coding may allow well tuned, coordinated behavior to emerge.

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Dopamine D_{2L} Receptor Deficiency Causes Stress Vulnerability through 5-HT_{1A} Receptor Dysfunction in Serotonergic Neurons

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Mental disorders are caused by genetic and environmental factors. We here show that deficiency of an isoform of dopamine D₂ receptor (D₂R), D_{2L}R, causes stress vulnerability in mouse. This occurs through dysfunction of serotonin [5-hydroxytryptamine (5-HT)] 1A receptor (5-HT_{1A}R) on serotonergic neurons in the mouse brain. Exposure to forced swim stress significantly increased anxiety- and depressive-like behaviors in D_{2L}R knock-out (KO) male mice compared with wild-type mice. Treatment with 8-OH-DPAT, a 5-HT_{1A}R agonist, failed to alleviate the stress-induced behaviors in D_{2L}R-KO mice. In forced swim-stressed D_{2L}R-KO mice, 5-HT efflux in the medial prefrontal cortex was elevated and the expression of genes related to 5-HT levels was upregulated by the transcription factor PET1 in the dorsal raphe nucleus. Notably, D_{2L}R formed a heteromer with 5-HT_{1A}R in serotonergic neurons, thereby suppressing 5-HT_{1A}R-activated G-protein-activated inwardly rectifying potassium conductance in D_{2L}R-KO serotonergic neurons. Finally, D_{2L}R overexpression in serotonergic neurons in the dorsal raphe nucleus alleviated stress vulnerability observed in D_{2L}R-KO mice. Together, we conclude that disruption of the negative feedback regulation by the D_{2L}R/5-HT_{1A}R heteromer causes stress vulnerability.

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Semantic Context Enhances the Early Auditory Encoding of Natural Speech

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Speech perception involves the integration of sensory input with expectations based on the context of that speech. Much debate surrounds the issue of whether or not prior knowledge feeds back to affect early auditory encoding in the lower levels of the speech processing hierarchy, or whether perception can be best explained as a purely feedforward process. Although there has been compelling evidence on both sides of this debate, experiments involving naturalistic speech stimuli to address these questions have been lacking. Here, we use a recently introduced method for quantifying the semantic context of speech and relate it to a commonly used method for indexing low-level auditory encoding of speech. The relationship between these measures is taken to be an indication of how semantic context leading up to a word influences how its low-level acoustic and phonetic features are processed. We record EEG from human participants (both male and female) listening to continuous natural speech and find that the early cortical tracking of a word's speech envelope is enhanced by its semantic similarity to its sentential context. Using a forward modeling approach, we find that

prediction accuracy of the EEG signal also shows the same effect. Furthermore, this effect shows distinct temporal patterns of correlation depending on the type of speech input representation (acoustic or phonological) used for the model, implicating a top-down propagation of information through the processing hierarchy. These results suggest a mechanism that links top-down prior information with the early cortical entrainment of words in natural, continuous speech.

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Negative Memory Engrams in the Hippocampus Enhance the Susceptibility to Chronic Social Defeat Stress

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The hippocampus has been highly implicated in depression symptoms. Recent findings suggest that the expression and susceptibility of depression symptoms are related to the enhanced functioning of the hippocampus. We reasoned that hippocampal engrams, which represent ensembles of neurons with increased activity after memory formation, could underlie some contributions of the hippocampus to depression symptoms. Using the chronic social defeat stress model, we examined social defeat-related hippocampal engrams in mice that are either susceptible or resilient to the stressor. *TetTag* mice were used to label social defeat-related hippocampal ensembles by LacZ. Engram cells correspond to ensembles that were reactivated by the same stressor. Compared with resilient and nonstressed control mice, susceptible mice exhibited a higher reactivation of social defeat-related LacZ-labeled cells (i.e., engram cells) in both the dorsal and ventral hippocampal CA1 regions. The density of CA1 engram cells correlated with the level of social avoidance. Using DREADD and optogenetic approaches to activate and inactivate social defeat-related CA1 engram cells enhanced and suppressed social avoidance, respectively. Increased engram cells in susceptible mice could not be found in the dentate gyrus. Susceptible mice exhibited more negative stimuli-related, but not neutral stimuli-related, CA1 engram cells than resilient mice in the dorsal hippocampus. Finally, chronic, but not a short and subthreshold, social defeat protocol was necessary to increase CA1 engram cell density. The susceptibility to chronic social defeat stress is regulated by hippocampal CA1 engrams for negative memory. Hippocampal negative memory engrams may underlie the vulnerability and expression of cognitive symptoms in depression.

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Probing the Neural Mechanisms for Distractor Filtering and Their History-Contingent Modulation by Means of TMS

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In visual search, the presence of a salient, yet task-irrelevant, distractor in the stimulus array interferes with target selection and slows down performance. Neuroimaging data point to a key role of the frontoparietal dorsal attention network in dealing with visual distractors; however, the respective roles of different nodes within the network and their hemispheric specialization are still unresolved. Here, we used transcranial magnetic stimulation (TMS) to evaluate the causal role of two key regions of the dorsal attention network in resisting attentional capture by a salient singleton distractor: the frontal eye field (FEF) and the cortex within the intraparietal sulcus (IPS). The task of the participants (male/female human volunteers) was to discriminate the pointing direction of a target arrow while ignoring a task-irrelevant salient distractor. Immediately after stimulus onset, triple-pulse 10 Hz TMS was delivered either to IPS or FEF on either side of the brain. Results indicated that TMS over the right FEF significantly reduced the behavioral cost engendered by the salient distractor relative to left FEF stimulation. No such effect was obtained with stimulation of IPS on either side of brain. Interestingly, this FEF-dependent reduction in distractor interference interacted with the contingent trial history, being maximal when no distractor was present on the previous trial relative to when there was one. Our results provide direct causal evidence that the right FEF houses key mechanisms for distractor filtering, pointing to a pivotal role of the frontal cortex of the right hemisphere in limiting interference from an irrelevant but attention-grabbing stimulus.

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NEUROBIOLOGY OF DISEASE

Altered Synaptic Drive onto Birthdated Dentate Granule Cells in Experimental Temporal Lobe Epilepsy

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Dysregulated adult hippocampal neurogenesis occurs in many temporal lobe epilepsy (TLE) models. Most dentate granule cells (DGCs) generated in response to an epileptic insult develop features that promote increased excitability, including ectopic location, persistent hilar basal dendrites (HBDs), and mossy fiber sprouting.

However, some appear to integrate normally and even exhibit reduced excitability compared to other DGCs. To examine the relationship between DGC birthdate, morphology, and network integration in a model of TLE, we retrovirally birthdated either early-born [EB; postnatal day (P)7] or adult-born (AB; P60) DGCs. Male rats underwent pilocarpine-induced status epilepticus (SE) or sham treatment at P56. Three to six months after SE or sham treatment, we used whole-cell patch-clamp and fluorescence microscopy to record spontaneous excitatory and inhibitory currents from birthdated DGCs. We found that both AB and EB populations of DGCs recorded from epileptic rats received increased excitatory input compared with age-matched controls. Interestingly, when AB populations were separated into normally integrated (normotopic) and aberrant (ectopic or HBD-containing) subpopulations, only the aberrant populations exhibited a relative increase in excitatory input (amplitude, frequency, and charge transfer). The ratio of excitatory-to-inhibitory input was most dramatically upregulated for ectopically localized DGCs. These data provide definitive physiological evidence that aberrant integration of post-SE, AB DGCs contributes to increased synaptic drive and support the idea that ectopic DGCs serve as putative hub cells to promote seizures.

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Increased Expression of Fibronectin Leucine-Rich Transmembrane Protein 3 in the Dorsal Root Ganglion Induces Neuropathic Pain in Rats

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Neuropathic pain is a chronic condition that occurs frequently after nerve injury and induces hypersensitivity or allodynia characterized by aberrant neuronal excitability in the spinal cord dorsal horn. Fibronectin leucine-rich transmembrane protein 3 (FLRT3) is a modulator of neurite outgrowth, axon pathfinding, and cell adhesion, which is upregulated in the dorsal horn following peripheral nerve injury. However, the function of FLRT3 in adults remains unknown. Therefore, we aimed to investigate the involvement of spinal FLRT3 in neuropathic pain using rodent models. In the dorsal horns of male rats, FLRT3 protein levels increased at day 4 after peripheral nerve injury. In the DRG, FLRT3 was expressed in activating transcription factor 3-positive, injured sensory neurons. Peripheral nerve injury stimulated *Flrt3* transcription in the DRG but not in the spinal cord. Intrathecal administration of FLRT3 protein to naive rats induced mechanical allodynia and GluN2B phosphorylation in the spinal cord. DRG-specific FLRT3 overexpression using adeno-associated virus also produced mechanical allodynia. Conversely, a function-blocking FLRT3 antibody attenuated mechanical allodynia after partial sciatic nerve ligation. Therefore, FLRT3 derived from injured DRG neurons increases dorsal horn excitability and induces mechanical allodynia.

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Female Sex and Brain-Selective Estrogen Benefit α -Synuclein Tetramerization and the PD-like Motor Syndrome in 3K Transgenic Mice

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Many studies report a higher risk for Parkinson's disease (PD) and younger age of onset in men. This, and the fact that the neuropathological process underlying PD symptoms may begin before menopause, suggests that estrogen-based hormone therapy could modify this higher risk in males. However, the effects of female sex or estrogen on α -synuclein (α S) homeostasis and related PD neuropathology remain unknown. Here, we used an α S tetramer-abrogating mouse model of PD (3K) that amplifies the familial E46K PD mutation to investigate the effects of female sex and brain-selective estrogen treatment on α S tetramerization and solubility, formation of vesicle-rich α S⁺ aggregates, dopaminergic and cortical fiber integrity, and associated motor deficits. In male 3K mice, the motor phenotype became apparent at ~10 weeks and increased to age 6 months, paralleled by PD-like neuropathology, whereas 3K females showed a significant delay in onset. At 6 months, this beneficial phenotypic effect in 3K females was associated with a higher α S tetramer-to-monomer ratio and less decrease in dopaminergic and cortical fiber length and quantity. Brain-selective estrogen treatment in symptomatic 3K mice significantly increased the tetramer-to-monomer ratio, turnover by autophagy of aggregate-prone monomers, and neurite complexity of surviving DAergic and cortical neurons, in parallel with benefits in motor performance. Our findings support an upstream role for α S tetramer loss in PD phenotypes and a role for estrogen in mitigating PD-like neuropathology *in vivo*. Brain-selective estrogen therapy may be useful in delaying or reducing PD symptoms in men and postmenopausal women.

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