

This Week in The Journal

Activity-Dependent Pruning in the Gustatory System

Chengsan Sun, Edith Hummler,
and David L. Hill

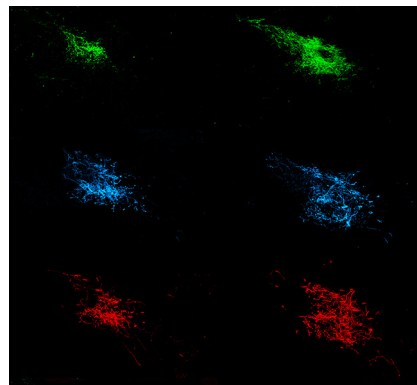
(see pages 660–672)

During development, neurons often extend exuberant axonal arbors that are later refined by pruning. Pruning can be driven by a variety of cues, including repulsive guidance molecules and synaptic activity. In the rodent gustatory system, the three main nerves carrying taste information from taste buds to the nucleus of the solitary tract (NST) cover more area and overlap more extensively in pups than in adults. Pruning of these axons appears to occur during a developmental period when neural responses to NaCl are increasing, and severe restriction of sodium intake during this period prevents refinement of gustatory afferents in the NST. Although this suggests that pruning of gustatory terminals is driven by activity in afferents conveying salt-taste information, sodium restriction affects overall growth of pups, leaving open the possibility that alterations in gustatory nerve arborization resulted from general effects on nutritional status.

Sun et al. now confirm the importance of sodium taste input in shaping gustatory circuits. They knocked out the α subunit of the epithelial sodium channel (α ENaC) selectively in taste buds, and examined the effect on terminal arborization fields of glossopharyngeal, chorda tympani, and greater superficial petrosal nerves—which innervate taste buds in the posterior tongue, anterior tongue, and palate, respectively—in NST of adult mice. The overall organization of gustatory nerve terminals in the NST was unaffected by α ENaC knockout, but the size of the terminal fields and the amount of overlap between the arbors of different nerves was greater in mutant mice than in controls. Notably, even glossopharyngeal nerve arbors were larger than normal, although these afferents are minimally responsive to NaCl, at least in anesthetized animals.

These results support the hypothesis that activity in salt-responsive gustatory afferents drives pruning of gustatory nerve terminals in the NST. Whether all sensory

afferents are affected by the lack of salt responses remains unknown. Lack of activity in salt-responsive afferents might prevent pruning of all afferents, selectively affect salt-responsive afferents, or selectively affect axons that preferentially respond to sweet, sour, and/or bitter tastes. Future experiments should address this question, as well as determining the effects of selectively eliminating responses to other tastes.



Terminal fields of glossopharyngeal (green), chorda tympani (blue), and greater superficial petrosal (red) nerves are larger in the dorsal/caudal NST of mice lacking α ENaC (right panels) than in controls (left). See Sun et al. for details.

miR-142-3p Upregulation during Inflammation

Georgia Mandolesi, Francesca De Vito,
Alessandra Musella, Antonietta Gentile,
Silvia Bullitta, et al.

(see pages 546–561)

Multiple sclerosis (MS) is an autoimmune disease in which lymphocytes targeting myelin-associated antigens infiltrate the CNS, causing inflammation, demyelination, and neurodegeneration. Studies of experimental autoimmune encephalomyelitis (EAE), a rodent model of MS, have suggested that synaptic dysfunction triggered by inflammation can produce excitotoxicity, and this can cause neuronal loss independently of demyelination (Mandolesi et al. 2015 *Nat Rev Neurol* 1:711). Because inflammation is also thought to contribute to pathology in other neurodegenerative diseases, understanding the mechanisms linking inflammation

to synaptic dysfunction is important.

MicroRNAs are one class of molecules that might alter synaptic transmission in MS. Each of the $\sim 1,000$ microRNAs present in cells regulates expression of numerous genes by binding to mRNAs and preventing their translation, and expression of several microRNAs is elevated in MS. New work now suggests that one of these molecules, miR-142-3p, contributes to synaptic dysfunction by enhancing excitatory transmission.

Previous work by Mandolesi et al. revealed that after EAE, expression of the glutamate transporter GLAST decreases in cerebellar Bergmann glia. This leads to an increase in the duration of glutamatergic spontaneous EPSCs (sEPSCs) in Purkinje cells. The authors now show that GLAST is a target of miR-142-3p, which is strongly upregulated in cerebellum after EAE induction in mice. Notably, miR-142-3p was also elevated in CSF of MS patients with active inflammatory lesions. Moreover, treating healthy mouse cerebellar slices with CSF from these patients increased sEPSC duration. This effect was blocked by an miR-142-3p inhibitor.

Remarkably, knockout mice lacking miR-142 were resistant to EAE: EAE-induction protocols failed to produce cerebellar inflammation, longer sEPSCs, and motor deficits in knockout mice. EAE-induced increases in sEPSC duration were also prevented in wild-type mice by miR-142-3p inhibitor, although the inhibitor did not reduce inflammation or motor impairment.

Together, these experiments suggest that inflammation can increase miR-142-3p in the brain, and this reduces GLAST expression. GLAST downregulation presumably reduces glutamate uptake and thus prolongs activation of excitatory synapses, which may in turn lead to excitotoxicity. Although blocking these effects did not ameliorate motor deficits in EAE, the pathway might contribute to synaptic pathology in other inflammatory diseases. Therefore, the role of miR-142-3p in other forms of inflammation-associated synaptic dysfunction should be explored.

This Week in The Journal was written by Teresa Esch, Ph.D.

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Cover legend: This painting, Trett (Tired. 1885) by Christian Krohg, portrays a woman who appears to have fallen asleep while working. Sleep is essential for maintaining cognitive performance, but the functions of sleep at the neural level are still debated. In this issue, Gina Poe discusses evidence that sleep is for forgetting (464–473) and Susan Sara presents evidence that sleep is for remembering (457–463). Public domain image found on Wikimedia Commons at <https://commons.wikimedia.org/w/index.php?curid=29841752>.

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DUAL PERSPECTIVES

Sleep to Remember

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Scientific investigation into the possible role of sleep in memory consolidation began with the early studies of Jenkins and Dallenbach (1924). Despite nearly a century of investigation with a waxing and waning of interest, the role of sleep in memory processing remains controversial and elusive. This review provides the historical background for current views and considers the relative contribution of two sleep states, rapid eye movement sleep and slow-wave sleep, to offline memory processing. The sequential hypothesis, until now largely ignored, is discussed, and recent literature supporting this view is reviewed.

The Journal of Neuroscience, • 37(3):457–463

Sleep Is for Forgetting

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It is possible that one of the essential functions of sleep is to take out the garbage, as it were, erasing and “forgetting” information built up throughout the day that would clutter the synaptic network that defines us. It may also be that this cleanup function of sleep is a general principle of neuroscience, applicable to every creature with a nervous system.

The Journal of Neuroscience, • 37(3):464–473

Articles

CELLULAR/MOLECULAR

Compensatory Activation of Cannabinoid CB2 Receptor Inhibition of GABA Release in the Rostral Ventromedial Medulla in Inflammatory Pain

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The rostral ventromedial medulla (RVM) is a relay in the descending pain modulatory system and an important site of endocannabinoid modulation of pain. Endocannabinoids inhibit GABA release in the RVM, but it is not known whether this effect persists in chronic pain states. In the present studies, persistent inflammation induced by complete Freund’s adjuvant (CFA) increased GABAergic miniature IPSCs (mIPSCs). Endocannabinoid activation of cannabinoid (CB1) receptors known to inhibit presynaptic GABA release was significantly reduced in the RVM of CFA-treated rats compared with naive rats. The reduction in CFA-treated rats correlated with decreased CB1 receptor protein expression and function in the RVM. Paradoxically, the nonselective CB1/CB2 receptor agonist WIN55212 inhibited GABAergic mIPSCs in both naive and CFA-treated rats. However, WIN55212 inhibition was reversed by the CB1 receptor antagonist rimonabant in naive rats but not in CFA-treated rats. WIN55212-mediated inhibition in CFA-treated rats was blocked by the CB2 receptor-selective antagonist SR144528, indicating that CB2 receptor function in the RVM is increased during persistent inflammation. Consistent with these results, CB2 receptor agonists AM1241 and GW405833 inhibited GABAergic mIPSC frequency only in CFA-treated rats, and the inhibition was reversed with SR144528. When administered alone, SR144528 and another CB2 receptor-selective antagonist AM630 increased mIPSC frequency in the RVM of CFA-treated rats, indicating that CB2 receptors are tonically activated by endocannabinoids. Our data provide evidence that CB2 receptor function emerges in the RVM in persistent inflammation and that selective CB2 receptor agonists may be useful for treatment of persistent inflammatory pain.

The Journal of Neuroscience, • 37(3):626–636

Promoted Interaction of C/EBP α with Demethylated *Cxcr3* Gene Promoter Contributes to Neuropathic Pain in Mice

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DNA methylation has been implicated in the pathogenesis of chronic pain. However, the specific genes regulated by DNA methylation under neuropathic pain condition remain largely unknown. Here we investigated how chemokine receptor CXCR3 is regulated by DNA methylation and how it contributes to neuropathic pain induced by spinal nerve ligation (SNL) in mice. SNL increased *Cxcr3* mRNA and protein expression in the neurons of the spinal cord. Meanwhile, the CpG (5'-cytosine-phosphate-guanine-3') island in the *Cxcr3* gene promoter region was demethylated, and the expression of DNA methyltransferase 3b (DNMT3b) was decreased. SNL also increased the binding of CCAAT (cytidine–cytidine–adenosine–adenosine–thymidine)/enhancer binding protein α (C/EBP α) with *Cxcr3* promoter and decreased the binding of DNMT3b with *Cxcr3* promoter in the spinal cord. C/EBP α expression was increased in spinal neurons after SNL, and inhibition of C/EBP α by intrathecal small interfering RNA attenuated SNL-induced pain hypersensitivity and reduced *Cxcr3* expression. Furthermore, SNL-induced mechanical allodynia and heat hyperalgesia were markedly reduced in *Cxcr3*^{−/−} mice. Spinal inhibition of *Cxcr3* by shRNA or CXCR3 antagonist also attenuated established neuropathic pain. Moreover, CXCL10, the ligand of CXCR3, was increased in spinal neurons and astrocytes after SNL. Superfusing spinal cord slices with CXCL10 enhanced spontaneous EPSCs and potentiated NMDA-induced and AMPA-induced currents of lamina II neurons. Finally, intrathecal injection of CXCL10 induced CXCR3-dependent pain hypersensitivity in naive mice. Collectively, our results demonstrated that CXCR3, increased by DNA demethylation and the enhanced interaction with C/EBP α , can be activated by CXCL10 to facilitate excitatory synaptic transmission and contribute to the maintenance of neuropathic pain.

The Journal of Neuroscience, • 37(3):685–700

DEVELOPMENT/PLASTICITY/REPAIR

Methyl-CpG-Binding Protein MBD1 Regulates Neuronal Lineage Commitment through Maintaining Adult Neural Stem Cell Identity

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Methyl-CpG-binding domain 1 (MBD1) belongs to a family of methyl-CpG-binding proteins that are epigenetic “readers” linking DNA methylation to transcriptional regulation. MBD1 is expressed in neural stem cells residing in the dentate gyrus of the adult hippocampus (aNSCs) and MBD1 deficiency leads to reduced neuronal differentiation, impaired neurogenesis, learning deficits, and autism-like behaviors in mice; however, the precise function of MBD1 in aNSCs remains unexplored. Here, we show that MBD1 is important for maintaining the integrity and stemness of NSCs, which is critical for their ability to generate neurons. MBD1 deficiency leads to the accumulation of undifferentiated NSCs and impaired transition into the neuronal lineage. Transcriptome analysis of neural stem and progenitor cells isolated directly from the dentate gyrus of MBD1 mutant (KO) and WT mice showed that gene sets related to cell differentiation, particularly astrocyte lineage genes, were upregulated in KO cells. We further demonstrated that, in NSCs, MBD1 binds and represses directly specific genes associated with differentiation. Our results suggest that MBD1 maintains the multipotency of NSCs by restraining the onset of differentiation genes and that untimely expression of these genes in MBD1-deficient stem cells may interfere with normal cell lineage commitment and cause the accumulation of undifferentiated cells. Our data reveal a novel role for MBD1 in stem cell maintenance and provide insight into how epigenetic regulation contributes to adult neurogenesis and the potential impact of its dysregulation.

The Journal of Neuroscience, • 37(3):523–536

Selective Deletion of Sodium Salt Taste during Development Leads to Expanded Terminal Fields of Gustatory Nerves in the Adult Mouse Nucleus of the Solitary Tract

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Neuronal activity plays a key role in the development of sensory circuits in the mammalian brain. In the gustatory system, experimental manipulations now exist, through genetic manipulations of specific taste transduction processes, to examine how specific taste qualities (i.e., basic tastes) impact the functional and structural development of gustatory circuits. Here, we used a mouse knock-out model in which the transduction component used to discriminate sodium salts from other taste stimuli was deleted in taste bud cells throughout development. We used this model to test the hypothesis that the lack of activity elicited by sodium salt taste impacts the terminal field organization of nerves that carry taste information from taste buds to the nucleus of the solitary tract (NST) in the medulla. The glossopharyngeal, chorda tympani, and greater superficial petrosal nerves were labeled to examine their terminal fields in adult control mice and in adult mice in which the α -subunit of the epithelial sodium channel was conditionally deleted in taste buds (α ENaC knockout). The terminal fields of all three nerves in the NST were up to 2.7 times greater in α ENaC knock-out mice compared with the respective field volumes in control mice. The shapes of the fields were similar between the two groups; however, the density and spread of labels were

greater in α ENaC knock-out mice. Overall, our results show that disruption of the afferent taste signal to sodium salts disrupts the normal age-dependent “pruning” of all terminal fields, which could lead to alterations in sensory coding and taste-related behaviors.

The Journal of Neuroscience, • 37(3):660–672

Target-Dependent Compartmentalization of the Corelease of Glutamate and GABA from the Mossy Fibers

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The mossy fibers (MFs) corelease glutamate and GABA onto pyramidal cells of CA3 during development, until the end of the third postnatal week. However, the major target cells of the MF are the interneurons of CA3. Therefore, it has been shown that the interneurons of the hilus and stratum lucidum receive this dual monosynaptic input on MF stimulation. Because the plasticity of glutamatergic transmission from the different terminals of the MF is target specific, we here asked whether the corelease of glutamate and GABA was also subjected to a target-dependent compartmentalization. We analyzed the occurrence and plasticity of MF simultaneous glutamatergic–GABAergic signaling onto interneurons of the different strata of CA3 in rats during the third postnatal week. We show the coexistence of time-locked, glutamate receptor and GABA receptor-mediated mono synaptic responses evoked by MF stimulation in interneurons from stratum lucidum and stratum radiatum, but not in interneurons from stratum lacunosum-moleculare. As expected from the transmission of MF origin, MF GABAergic responses were depressed by the activation of metabotropic glutamate receptors. Strikingly, while MF glutamatergic responses underwent LTD, the simultaneous MF GABAergic responses of stratum lucidum interneurons, but not of stratum radiatum interneurons, displayed a Hebbian form of LTP that was mimicked by PKC activation. PKA activation potentiated MF glutamatergic responses of stratum radiatum interneurons, whereas in stratum lucidum interneurons only GABAergic responses were potentiated. We here disclose that the corelease of glutamate and GABA, as well as their plasticity are compartmentalized in a target-dependent manner, showing counterbalanced compensatory plasticity of two neurotransmitters released by different terminals of the same pathway.

The Journal of Neuroscience, • 37(3):701–714

SYSTEMS/CIRCUITS

Control of Spike Transfer at Hippocampal Mossy Fiber Synapses *In Vivo* by GABA_A and GABA_B Receptor-Mediated Inhibition

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Despite extensive studies in hippocampal slices and incentive from computational theories, the synaptic mechanisms underlying information transfer at mossy fiber (mf) connections between the dentate gyrus (DG) and CA3 neurons *in vivo* are still elusive. Here we used an optogenetic approach in mice to selectively target and control the activity of DG granule cells (GCs) while performing whole-cell and juxtacellular recordings of CA3 neurons *in vivo*. In CA3 pyramidal cells (PCs), mf–CA3 synaptic responses consisted predominantly of an IPSP at low stimulation frequency (0.05 Hz). Upon increasing the frequency of stimulation, a biphasic response was observed consisting of a brief mf EPSP followed by an inhibitory response lasting on the order of 100 ms. Spike transfer at DG–CA3 interneurons recorded in the juxtacellular mode was efficient at low presynaptic stimulation frequency and appeared insensitive to an increased frequency of GC activity. Overall, this resulted in a robust and slow feedforward inhibition of spike transfer at mf–CA3 pyramidal cell synapses. Short-term plasticity of EPSPs with increasing frequency of presynaptic activity allowed inhibition to be overcome to reach spike discharge in CA3 PCs. Whereas the activation of GABA_A receptors was responsible for the direct inhibition of light-evoked spike responses, the slow inhibition of spiking activity required the activation of GABA_B receptors in CA3 PCs. The slow inhibitory response defined an optimum frequency of presynaptic activity for spike transfer at ~10 Hz. Altogether these properties define the temporal rules for efficient information transfer at DG–CA3 synaptic connections in the intact circuit.

The Journal of Neuroscience, • 37(3):587–598

Three Small-Receptive-Field Ganglion Cells in the Mouse Retina Are Distinctly Tuned to Size, Speed, and Object Motion

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Retinal ganglion cells (RGCs) are frequently divided into functional types by their ability to extract and relay specific features from a visual scene, such as the capacity to discern local or global motion, direction of motion, stimulus orientation, contrast or uniformity, or the presence of large or small objects. Here we introduce three previously uncharacterized, nondirection-selective ON–OFF RGC types that represent a distinct set of feature detectors in the mouse retina. The three high-definition (HD) RGCs possess small receptive-field centers and strong surround suppression. They respond selectively to objects of specific sizes, speeds, and types of motion. We present comprehensive morphological characterization of the HD RGCs and physiological recordings of their light responses, receptive-field size and structure, and synaptic mechanisms of surround suppression. We also explore the similarities and differences between the HD RGCs and a well characterized RGC with a comparably small receptive field, the local edge detector, in response to moving objects and textures. We model populations of each RGC type to study how they differ in their performance tracking a moving object. These results, besides introducing three new RGC types that together constitute a substantial fraction of mouse RGCs, provide insights into the

role of different circuits in shaping RGC receptive fields and establish a foundation for continued study of the mechanisms of surround suppression and the neural basis of motion detection.

The Journal of Neuroscience, • 37(3):610–625

End-Stopping Predicts Curvature Tuning along the Ventral Stream

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Neurons in primate inferotemporal cortex (IT) are clustered into patches of shared image preferences. Functional imaging has shown that these patches are activated by natural categories (e.g., faces, body parts, and places), artificial categories (numerals, words) and geometric features (curvature and real-world size). These domains develop in the same cortical locations across monkeys and humans, which raises the possibility of common innate mechanisms. Although these commonalities could be high-level template-based categories, it is alternatively possible that the domain locations are constrained by low-level properties such as end-stopping, eccentricity, and the shape of the preferred images. To explore this, we looked for correlations among curvature preference, receptive field (RF) end-stopping, and RF eccentricity in the ventral stream. We recorded from sites in V1, V4, and posterior IT (PIT) from six monkeys using microelectrode arrays. Across all visual areas, we found a tendency for end-stopped sites to prefer curved over straight contours. Further, we found a progression in population curvature preferences along the visual hierarchy, where, on average, V1 sites preferred straight Gabors, V4 sites preferred curved stimuli, and many PIT sites showed a preference for curvature that was concave relative to fixation. Our results provide evidence that high-level functional domains may be mapped according to early rudimentary properties of the visual system.

The Journal of Neuroscience, • 37(3):648–659

Decision-Related Activity in Macaque V2 for Fine Disparity Discrimination Is Not Compatible with Optimal Linear Readout

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Fine judgments of stereoscopic depth rely mainly on relative judgments of depth (relative binocular disparity) between objects, rather than judgments of the distance to where the eyes are fixating (absolute disparity). In macaques, visual area V2 is the earliest site in the visual processing hierarchy for which neurons selective for relative disparity have been observed (Thomas et al., 2002). Here, we found that, in macaques trained to perform a fine disparity discrimination task, disparity-selective neurons in V2 were highly selective for the task, and their activity correlated with the animals' perceptual decisions (unexplained by the stimulus). This may partially explain similar correlations reported in downstream areas. Although compatible with a perceptual role of these neurons for the task, the interpretation of such decision-related activity is complicated by the effects of interneuronal “noise” correlations between sensory neurons. Recent work has developed simple predictions to differentiate decoding schemes (Pitkow et al., 2015) without needing measures of noise correlations, and found that data from early sensory areas were compatible with optimal linear readout of populations with information-limiting correlations. In contrast, our data here deviated significantly from these predictions. We additionally tested this prediction for previously reported results of decision-related activity in V2 for a related task, coarse disparity discrimination (Nienborg and Cumming, 2006), thought to rely on absolute disparity. Although these data followed the predicted pattern, they violated the prediction quantitatively. This suggests that optimal linear decoding of sensory signals is not generally a good predictor of behavior in simple perceptual tasks.

The Journal of Neuroscience, • 37(3):715–725

BEHAVIORAL/COGNITIVE

Does the Superior Colliculus Control Perceptual Sensitivity or Choice Bias during Attention? Evidence from a Multialternative Decision Framework

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Distinct networks in the forebrain and the midbrain coordinate to control spatial attention. The critical involvement of the superior colliculus (SC)—the central structure in the midbrain network—in visuospatial attention has been shown by four seminal, published studies in monkeys (*Macaca mulatta*) performing multialternative tasks. However, due to the lack of a mechanistic framework for interpreting behavioral data in such tasks, the nature of the SC's contribution to attention remains unclear. Here we present and validate a novel decision framework for analyzing behavioral data in multialternative attention tasks. We apply this framework to re-examine the behavioral evidence from these published studies. Our model is a multidimensional extension to signal detection theory that distinguishes between two major classes of attentional mechanisms: those that alter the quality of sensory information or “sensitivity,” and those that alter the selective gating of sensory information or “choice bias.” Model-based simulations and model-based analyses of data from these published studies revealed a converging pattern of results that indicated that choice-bias changes, rather than sensitivity changes, were the primary outcome of SC manipulation. Our results suggest that the SC contributes to attentional performance predominantly by generating a spatial choice bias for stimuli at a selected location, and that this bias operates downstream of forebrain mechanisms that enhance sensitivity. The findings lead to a testable mechanistic framework of how the midbrain and forebrain networks interact to control spatial attention.

The Journal of Neuroscience, • 37(3):480–511

Neural Tuning to Numerosity Relates to Perceptual Tuning in 3–6-Year-Old Children

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Neural representations of approximate numerical value, or numerosity, have been observed in the intraparietal sulcus (IPS) in monkeys and humans, including children. Using functional magnetic resonance imaging, we show that children as young as 3–4 years old exhibit neural tuning to cardinal numerosities in the IPS and that their neural responses are accounted for by a model of numerosity coding that has been used to explain neural responses in the adult IPS. We also found that the sensitivity of children's neural tuning to number in the right IPS was comparable to their numerical discrimination sensitivity observed behaviorally, outside of the scanner. Children's neural tuning curves in the right IPS were significantly sharper than in the left IPS, indicating that numerical representations are more precise and mature more rapidly in the right hemisphere than in the left. Further, we show that children's perceptual sensitivity to numerosity can be predicted by the development of their neural sensitivity to numerosity. This research provides novel evidence of developmental continuity in the neural code underlying numerical representation and demonstrates that children's neural sensitivity to numerosity is related to their cognitive development.

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Selectivity in Postencoding Connectivity with High-Level Visual Cortex Is Associated with Reward-Motivated Memory

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Reward motivation has been demonstrated to enhance declarative memory by facilitating systems-level consolidation. Although high-reward information is often intermixed with lower reward information during an experience, memory for high value information is prioritized. How is this selectivity achieved? One possibility is that postencoding consolidation processes bias memory strengthening to those representations associated with higher reward. To test this hypothesis, we investigated the influence of differential reward motivation on the selectivity of postencoding markers of systems-level memory consolidation. Human participants encoded intermixed, trial-unique memoranda that were associated with either high or low-value during fMRI acquisition. Encoding was interleaved with periods of rest, allowing us to investigate experience-dependent changes in connectivity as they related to later memory. Behaviorally, we found that reward motivation enhanced 24 h associative memory. Analysis of patterns of postencoding connectivity showed that, even though learning trials were intermixed, there was significantly greater connectivity with regions of high-level, category-selective visual cortex associated with high-reward trials. Specifically, increased connectivity of category-selective visual cortex with both the VTA and the anterior hippocampus predicted associative memory for high- but not low-reward memories. Critically, these results were independent of encoding-related connectivity and univariate activity measures. Thus, these findings support a model by which the selective stabilization of memories for salient events is supported by postencoding interactions with sensory cortex associated with reward.

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Action Categories in Lateral Occipitotemporal Cortex Are Organized Along Sociality and Transitivity

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How neural specificity for distinct conceptual knowledge categories arises is central for understanding the organization of semantic memory in the human brain. Although there is a large body of research on the neural processing of distinct object categories, the organization of action categories remains largely unknown. In particular, it is unknown whether different action categories follow a specific topographical organization on the cortical surface analogously to the category-specific organization of object knowledge. Here, we tested whether the neural representation of action knowledge is organized in terms of nonsocial versus social and object-unrelated versus object-related actions (sociality and transitivity, respectively, hereafter). We hypothesized a major distinction of sociality and transitivity along dorsal and ventral lateral occipitotemporal cortex (LOTC), respectively. Using fMRI-based multivoxel pattern analysis, we identified neural representations of action information associated with sociality and transitivity in bilateral LOTC. Representational similarity analysis revealed a dissociation between dorsal and ventral LOTC. We found that action representations in dorsal LOTC are segregated along features of sociality, whereas action representations in ventral LOTC are segregated along features of transitivity. In addition, representations of sociality and transitivity features were found more anteriorly in LOTC than representations of specific subtypes of actions, suggesting a posterior–anterior gradient from concrete to abstract action features. These findings elucidate how the neural representations of perceptually and conceptually diverse actions are organized in distinct subsystems in the LOTC.

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Visual Sampling Predicts Hippocampal Activity

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Eye movements serve to accumulate information from the visual world, contributing to the formation of coherent memory representations that support cognition and behavior. The hippocampus and the oculomotor network are well connected anatomically through an extensive set of polysynaptic pathways. However, the extent to which visual sampling behavior is related to functional responses in the hippocampus during encoding has not been studied directly in human neuroimaging. In the current study, participants engaged in a face processing task while brain responses were recorded with fMRI and eye movements were monitored simultaneously. The number of gaze fixations that a participant made on a given trial was correlated significantly with hippocampal activation such that more fixations were associated with stronger hippocampal activation. Similar results were also found in the fusiform face area, a face-selective perceptual processing region. Notably, the number of fixations was associated with stronger hippocampal activation when the presented faces were novel, but not when the faces were repeated. Increases in fixations during viewing of novel faces also led to larger repetition-related suppression in the hippocampus, indicating that this fixation–hippocampal relationship may reflect the ongoing development of lasting representations. Together, these results provide novel empirical support for the idea that visual exploration and hippocampal binding processes are inherently linked.

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Independent Neural Computation of Value from Other People's Confidence

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Expectation of reward can be shaped by the observation of actions and expressions of other people in one's environment. A person's apparent confidence in the likely reward of an action, for instance, makes qualities of their evidence, not observed directly, socially accessible. This strategy is computationally distinguished from associative learning methods that rely on direct observation, by its use of inference from indirect evidence. In twenty-three healthy human subjects, we isolated effects of first-hand experience, other people's choices, and the mediating effect of their confidence, on decision-making and neural correlates of value within ventromedial prefrontal cortex (vmPFC). Value derived from first-hand experience and other people's choices (regardless of confidence) were indiscriminately represented across vmPFC. However, value computed from agent choices weighted by their associated confidence was represented with specificity for ventromedial area 10. This pattern corresponds to shifts of connectivity and overlapping cognitive processes along a posterior-anterior vmPFC axis. Task behavior and self-reported self-reliance for decision-making in other social contexts correlated. The tendency to conform in other social contexts corresponded to increased activation in cortical regions previously shown to respond to social conflict in proportion to subsequent conformity (Campbell-Meiklejohn et al., 2010). The tendency to self-monitor predicted a selectively enhanced response to accordance with others in the right temporoparietal junction (rTPJ). The findings anatomically decompose vmPFC value representations according to computational requirements and provide biological insight into the social transmission of preference and reassurance gained from the confidence of others.

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NEUROBIOLOGY OF DISEASE

miR-142-3p Is a Key Regulator of IL-1 β -Dependent Synaptopathy in Neuroinflammation

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MicroRNAs (miRNA) play an important role in post-transcriptional gene regulation of several physiological and pathological processes. In multiple sclerosis (MS), a chronic inflammatory and degenerative disease of the CNS, and in its mouse model, the experimental autoimmune encephalomyelitis (EAE), miRNA dysregulation has been mainly related to immune system dysfunction and white matter (WM) pathology. However, little is known about their role in gray matter pathology. Here, we explored miRNA involvement in the inflammation-driven alterations of synaptic structure and function, collectively known as synaptopathy, a neuropathological process contributing to excitotoxic neurodegeneration in MS/EAE. Particularly, we observed that miR-142-3p is increased in the CSF of patients with active MS and in EAE brains. We propose miR-142-3p as a molecular mediator of the IL-1 β -dependent downregulation of the glial glutamate-aspartate transporter (GLAST), which causes an enhancement of the glutamatergic transmission in the EAE cerebellum. The synaptic abnormalities mediated by IL-1 β and the clinical and neuropathological manifestations of EAE disappeared in *miR-142* knock-out mice. Furthermore, we observed that *in vivo* miR-142-3p inhibition, either by a preventive and local treatment or by a therapeutic and

systemic strategy, abolished IL-1 β - and GLAST-dependent synaptopathy in EAE wild-type mice. Consistently, miR-142-3p was responsible for the glutamatergic synaptic alterations caused by CSF of patients with MS, and CSF levels of miR-142-3p correlated with prospective MS disease progression. Our findings highlight miR-142-3p as key molecular player in IL-1 β -mediated synaptic dysfunction, possibly leading to excitotoxic damage in both EAE and MS diseases. Inhibition of miR-142-3p could be neuroprotective in MS.

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Epilepsy-Associated KCNQ2 Channels Regulate Multiple Intrinsic Properties of Layer 2/3 Pyramidal Neurons

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KCNQ2 potassium channels are critical for normal brain function, as both loss-of-function and gain-of-function KCNQ2 variants can lead to various forms of neonatal epilepsy. Despite recent progress, the full spectrum of consequences as a result of KCNQ2 dysfunction in neocortical pyramidal neurons is still unknown. Here, we report that conditional ablation of *Kcnq2* from mouse neocortex leads to hyperexcitability of layer 2/3 (L2/3) pyramidal neurons, exhibiting an increased input resistance and action potential frequency, as well as a reduced medium afterhyperpolarization (mAHP), a conductance partly mediated by KCNQ2 channels. Importantly, we show that introducing the KCNQ2 loss-of-function variant KCNQ2^{L205V} into L2/3 pyramidal neurons using *in utero* electroporation also results in a hyperexcitable phenotype similar to the conditional knock-out. KCNQ2^{L205V} has a right-shifted conductance-to-voltage relationship, suggesting loss of KCNQ2 channel activity at subthreshold membrane potentials is sufficient to drive large changes in L2/3 pyramidal neuronal excitability even in the presence of an intact mAHP. We also found that the changes in excitability following *Kcnq2* ablation are accompanied by alterations at action potential properties, including action potential amplitude in *Kcnq2*-null neurons. Importantly, partial inhibition of Na_v1.6 channels was sufficient to counteract the hyperexcitability of *Kcnq2*-null neurons. Therefore, our work shows that loss of KCNQ2 channels alters the intrinsic neuronal excitability and action potential properties of L2/3 pyramidal neurons, and identifies Na_v1.6 as a new potential molecular target to reduce excitability in patients with KCNQ2 encephalopathy.

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Disease Progression-Dependent Effects of TREM2 Deficiency in a Mouse Model of Alzheimer's Disease

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Neuroinflammation is an important contributor to Alzheimer's disease (AD) pathogenesis, as underscored by the recent identification of immune-related genetic risk factors for AD, including coding variants in the gene *TREM2* (*triggering receptor expressed on myeloid cells 2*). Understanding TREM2 function promises to provide important insights into how neuroinflammation contributes to AD pathology. However, studies so far have produced seemingly conflicting results, with reports that amyloid pathology can be both decreased and increased in TREM2-deficient AD mouse models. In this study, we unify these previous findings by demonstrating that TREM2 deficiency ameliorates amyloid pathology early, but exacerbates it late in disease progression in the APPPS1–21 mouse model of AD. We also demonstrate that TREM2 deficiency decreases plaque-associated myeloid cell accumulation by reducing cell proliferation, specifically late in pathology. In addition, TREM2 deficiency reduces myeloid cell internalization of amyloid throughout pathology, but decreases inflammation-related gene transcript levels selectively late in disease progression. Together, these results suggest that TREM2 plays distinct functional roles at different stages in AD pathology.

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Differential Vulnerability of CA1 versus CA3 Pyramidal Neurons After Ischemia: Possible Relationship to Sources of Zn²⁺ Accumulation and Its Entry into and Prolonged Effects on Mitochondria

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Excitotoxic mechanisms contribute to the degeneration of hippocampal pyramidal neurons after recurrent seizures and brain ischemia. However, susceptibility differs, with CA1 neurons degenerating preferentially after global ischemia and CA3 neurons after limbic seizures. Whereas most studies address contributions of excitotoxic Ca²⁺ entry, it is apparent that Zn²⁺ also contributes, reflecting accumulation in neurons either after synaptic release and entry through postsynaptic channels or upon mobilization from intracellular Zn²⁺-binding proteins such as metallothionein-III (MT-III). Using mouse hippocampal slices to study acute oxygen glucose deprivation (OGD)-triggered neurodegeneration, we found evidence for early contributions of excitotoxic Ca²⁺ and Zn²⁺ accumulation in both CA1 and CA3, as indicated by the ability of Zn²⁺ chelators or Ca²⁺ entry blockers to delay pyramidal neuronal death in both regions. However, using knock-out animals (of MT-III and vesicular Zn²⁺ transporter, ZnT3) and channel blockers revealed substantial differences in relevant Zn²⁺ sources, with critical contributions of presynaptic release and its permeation through Ca²⁺- (and Zn²⁺)-permeable AMPA channels in CA3 and Zn²⁺ mobilization from MT-III predominating in CA1. To assess the consequences of the intracellular Zn²⁺ accumu-

lation, we used OGD exposures slightly shorter than those causing acute neuronal death; under these conditions, cytosolic Zn^{2+} rises persisted for 10–30 min after OGD, followed by recovery over ~ 40 –60 min. Furthermore, the recovery appeared to be accompanied by mitochondrial Zn^{2+} accumulation (via the mitochondrial Ca^{2+} uniporter MCU) in CA1 but not in CA3 neurons and was markedly diminished in MT-III knock-outs, suggesting that it depended upon Zn^{2+} mobilization from this protein.

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