

This Week in The Journal

Doublecortin-Expressing Neurons in Adult Sheep Brain

Matteo Piumatti, Ottavia Palazzo, Chiara La Rosa, Paola Crociara, Roberta Parolisi, et al.

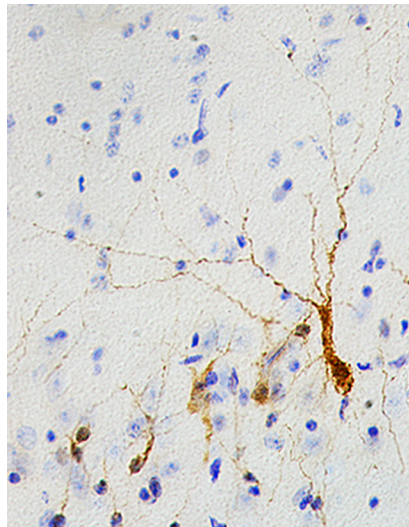
(see pages 826–842)

Although most neurons in mammalian brains are born before birth, regions of neurogenesis persist throughout life in the subgranular zone of the hippocampus and the subventricular zone of the lateral ventricle. Neurons born in these regions are incorporated into existing neural circuits in the dentate gyrus or olfactory bulb of some species, and they might contribute to circuit plasticity underlying new learning. But if adult-born neurons are important for encoding new memories, why aren't they present in all areas that store memories? One possibility is that these areas contain a population of prenatally born neurons that remain in an immature state until they are needed for circuit plasticity later in life. This hypothesis is supported by the presence of neurons expressing markers of immature neurons—particularly doublecortin and an immature, polysialylated form of neural cell adhesion molecule (PSA-NCAM)—in cortical layer II of several species. Piumatti, Palazzo, et al. identified such doublecortin-expressing neurons in adult sheep brains. These neurons were present throughout the anteroposterior and dorsoventral extents of the cortex, as well as in the external capsule, claustrum, and amygdala. Importantly, no doublecortin-expressing neurons in these areas were labeled with the proliferation marker Ki-67 or BrdU.

Most doublecortin-expressing neurons in adult brain were small, with bipolar morphologies, but some were larger with complex dendritic arbors. Although some of the neurons expressed PSA-NCAM, others expressed NeuN or HuC/D, two markers of mature neurons. Notably, NeuN was only found in doublecortin-expressing neurons that had more developed dendritic arbors. In contrast, smaller doublecortin-expressing cortical neurons often expressed Tbr1, a transcription factor found in developing glutamatergic cortical neurons and downregulated in upper-layer neurons as they mature. Finally, the number and density of

doublecortin-expressing cortical neurons was approximately four times higher in 1-week-old lambs than in adult sheep.

These data suggest that immature-looking neurons in the cortex of adult sheep are slowly maturing glutamatergic neurons. These neurons could plausibly play a role in plasticity similar to that of adult-born granule cells in the dentate gyrus. Alternatively, they might replace damaged neurons. Future work should investigate whether enriched environments or brain injuries affect the number of these neurons and determine whether selectively killing doublecortin-expressing neurons in adults affects cognitive processes.



Doublecortin-expressing neurons (brown), some of which have complex dendritic arbors, are found in layer II of sheep cortex. See Piumatti, Palazzo, et al. for details.

Role of Histone Dimethyltransferase in Cocaine Seeking

Ethan M. Anderson, Erin B. Larson, Daniel Guzman, Anne Marie Wissman, Rachael L. Neve, et al.

(see pages 803–813)

Cocaine exposure alters neural circuits involved in reward and motivation, thus promoting future drug seeking and addiction. Cocaine-induced changes include post-translational modification of histone proteins that organize DNA, causing long-term changes in gene expression. For example, repeated cocaine

administration decreases dimethylation of lysine 9 of histone H3 (H3K9me2) in the nucleus accumbens (NAc) of mice by reducing expression of the lysine dimethyltransferase G9a. Countering this change by overexpressing G9a in the NAc reduced the ability of cocaine to produce conditioned place preference and prevented cocaine-induced increases in spine density (Maze et al. 2010 Science 327:213). Thus, cocaine-induced reductions in G9a might underlie changes in neural circuitry that promote future drug seeking.

Anderson et al. tested this hypothesis by asking whether overexpression of G9a in the NAc reduced cocaine self-administration in rats. Surprisingly, it did not. In fact, lower doses of cocaine were required to maintain lever pressing in G9a-overexpressing rats than in controls, and G9a-overexpressing rats were willing to press a lever more times for a single cocaine injection. These effects occurred regardless of whether G9a was overexpressed during initial training or during testing. Furthermore, after rats were denied cocaine for 2 weeks and G9a levels returned to normal, delivery of intermittent foot shocks reinstated cocaine seeking to a greater extent in rats that had overexpressed G9a than in controls. Finally, G9a overexpression increased behaviors thought to model anxiety, including biting, scratching, and diarrhea, as well as avoidance of open arms of an elevated plus maze and increased latency to enter the center of an open field.

These and previous results suggest that changes in gene expression resulting from cocaine-induced reductions in histone dimethylation by G9a can enhance or inhibit cocaine seeking under different circumstances. Some of these differences might depend on the type of stress experienced, and some might depend on whether cocaine is administered acutely by the experimenter, as in conditioned place preference, or chronically and voluntarily by operant lever pressing, as in the study by Anderson et al. Such differences highlight both the complexity of motivational processes driving drug seeking and the difficulty in assigning a single role to enzymes that regulate expression of numerous genes.

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



Cover legend: This image shows immature neurons in layer II of sheep cerebral cortex. Neurons labelled in red express the cytoskeletal protein Doublecortin, typically found in immature or newly-generated cells.

The marker of mature neurons HuC/D (green) is present in several nerve cells of the same layer, and shows a faint immunoreactivity only in a subset of Doublecortin-positive cells, thus indicating the existence of different degrees of immaturity. Neurons generated embryonically but remaining immature in adults are particularly abundant in large-brained, long-living mammals such as sheep. For more information see the article by Piumatti et al. (pages 826–842).

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DUAL PERSPECTIVES

How Forces Fold the Cerebral Cortex

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Improved understanding of the factors that govern folding of the cerebral cortex is desirable for many reasons. The existence of consistent patterns in folding within and between species suggests a fundamental role in brain function. Abnormal folding patterns found in individuals affected by a diverse array of neurodevelopmental disorders underline the clinical relevance of understanding the folding process. Recent experimental and computational efforts to elucidate the biomechanical forces involved in cerebral cortical folding have converged on a consistent approach. Brain growth is modeled with two components: an expanding outer zone, destined to become the cerebral cortex, is mechanically coupled to an inner zone, destined to become white matter, that grows at a slower rate, perhaps in response to stress induced by expansion from the outer layer. This framework is consistent with experimentally observed internal forces in developing brains, and with observations of the folding process in physical models. In addition, computational simulations based on this foundation can produce folding patterns that recapitulate the characteristics of folding patterns found in gyrencephalic brains. This perspective establishes the importance of mechanical forces in our current understanding of how brains fold, and identifies realistic ranges for specific parameters in biophysical models of developing brain tissue. However, further refinement of this approach is needed. An understanding of mechanical forces that arise during brain development and their cellular-level origins is necessary to interpret the consequences of abnormal brain folding and its role in functional deficits as well as neurodevelopmental disease.

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How Cells Fold the Cerebral Cortex

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Folding of the cerebral cortex is as highly intriguing as poorly understood. At first sight, this may appear as simple tissue crumpling inside an excessively small cranium, but the process is clearly much more complex and developmentally predetermined. Whereas theoretical modeling supports a critical role for biomechanics, experimental evidence demonstrates the fundamental role of specific progenitor cell types, cellular processes, and genetic programs on cortical folding.

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Articles

CELLULAR/MOLECULAR

The Protein Tyrosine Phosphatase Shp2 Regulates Oligodendrocyte Differentiation and Early Myelination and Contributes to Timely Remyelination

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Shp2 is a nonreceptor protein tyrosine phosphatase that has been shown to influence neurogenesis, oligodendrogenesis, and oligodendrocyte differentiation. Furthermore, Shp2 is a known regulator of the Akt/mammalian target of rapamycin and ERK signaling pathways in multiple cellular contexts, including oligodendrocytes. Its role during later postnatal CNS development or in response to demyelination injury has not been examined. Based on the current studies, we hypothesize that Shp2 is a negative regulator of CNS myelination. Using transgenic mouse technology, we show that Shp2 is involved in oligodendrocyte differentiation and early myelination, but is not necessary for myelin maintenance. We also show that Shp2 regulates the timely differentiation of oligodendrocytes following lysolecithin-induced demyelination, although apparently normal remyelination occurs at a delayed time point. These data suggest that Shp2 is a relevant therapeutic target in demyelinating diseases such as multiple sclerosis.

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ELMOD1 Stimulates ARF6-GTP Hydrolysis to Stabilize Apical Structures in Developing Vestibular Hair Cells

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Sensory hair cells require control of physical properties of their apical plasma membranes for normal development and function. Members of the ADP-ribosylation factor (ARF) small GTPase family regulate membrane trafficking and cytoskeletal assembly in many cells. We identified ELMO domain-containing protein 1 (ELMOD1), a guanine nucleoside triphosphatase activating protein (GAP) for ARF6, as the most highly enriched ARF regulator in hair cells. To characterize ELMOD1 control of trafficking, we analyzed mice of both sexes from a strain lacking functional ELMOD1 [roundabout (*rda*)]. In *rda/rda* mice, cuticular plates of utricle hair cells initially formed normally, then degenerated after postnatal day 5; large numbers of vesicles invaded the compromised cuticular plate. Hair bundles initially developed normally, but the cell's apical membrane lifted away from the cuticular plate, and stereocilia elongated and fused. Membrane trafficking in type I hair cells, measured by FM1-43 dye labeling, was altered in *rda/rda* mice. Consistent with the proposed GAP role for ELMOD1, the ARF6 GTP/GDP ratio was significantly elevated in *rda/rda* utricles compared with controls, and the level of ARF6-GTP was correlated with the severity of the *rda/rda* phenotype. These results suggest that conversion of ARF6 to its GDP-bound form is necessary for final stabilization of the hair bundle.

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Orai1 Plays a Crucial Role in Central Sensitization by Modulating Neuronal Excitability

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Pathological pain is a common and debilitating condition that is often poorly managed. Central sensitization is an important mechanism underlying pathological pain. However, candidate molecules involved in central sensitization remain unclear. Store-operated calcium channels (SOCs) mediate important calcium signals in nonexcitable and excitable cells. SOCs have been implicated in a wide variety of human pathophysiological conditions, including immunodeficiency, occlusive vascular diseases, and cancer. However, the role of SOCs in CNS disorders has been relatively unexplored. Orai1, a key component of SOCs, is expressed in the human and rodent spinal cord dorsal horn, but its functional significance in dorsal horn neurons is poorly understood. Here we sought to explore a potential role of Orai1 in the modulation of neuronal excitability and A-type potassium channels involved in pain plasticity. Using both male and female Orai1 knock-out mice, we found that activation of Orai1 increased neuronal excitability and reduced A-type potassium channels via the protein kinase C–extracellular signal-regulated protein kinase (PKC–ERK) pathway in dorsal horn neurons. Orai1 deficiency significantly decreased acute pain induced by noxious stimuli, nearly eliminated the second phase of formalin-induced nociceptive response, markedly attenuated carrageenan-induced ipsilateral pain hypersensitivity and abolished carrageenan-induced contralateral mechanical allodynia. Consistently, carrageenan-induced increase in neuronal excitability was abolished in the dorsal horn from Orai1 mutant mice. These findings uncover a novel signaling pathway involved in the pain process and central sensitization. Our study also reveals a novel link among Orai1, ERK, A-type potassium channels, and neuronal excitability.

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Proteolytic Processing of Neurexins by Presenilins Sustains Synaptic Vesicle Release

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Proteolytic processing of synaptic adhesion components can accommodate the function of synapses to activity-dependent changes. The adhesion system formed by neurexins (Nrxns) and neuroligins (Nlgns) bidirectionally orchestrate the function of presynaptic and postsynaptic terminals. Previous studies have shown that presenilins (PS), components of the gamma-secretase complex frequently mutated in familial Alzheimer's disease, clear from glutamatergic terminals the accumulation of Nrxn C-terminal fragments (Nrxn-CTF) generated by ectodomain shedding. Here, we characterized the synaptic consequences of the proteolytic processing of Nrxns in cultured hippocampal neurons from mice and rats of both sexes. We show that activation of presynaptic Nrxns with postsynaptic Nlg1 or inhibition of ectodomain shedding in axonal Nrxn1- β increases presynaptic release at individual terminals, likely reflecting an increase in the number of functional release sites. Importantly, inactivation of PS inhibits presynaptic release downstream of Nrxn activation, leaving synaptic vesicle recruitment unaltered. Glutamate-receptor signaling initiates the activity-dependent generation of Nrxn-CTF, which accumulate at presynaptic terminals lacking PS function. The sole expression of Nrxn-CTF decreases presynaptic release and calcium flux, recapitulating the deficits due to loss of PS function. Our data indicate that inhibition of Nrxn processing by PS is deleterious to glutamatergic function.

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Neuronal Glutamate Transporters Control Dopaminergic Signaling and Compulsive Behaviors

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There is an ongoing debate on the contribution of the neuronal glutamate transporter EAAC1 to the onset of compulsive behaviors. Here, we used behavioral, electrophysiological, molecular, and viral approaches in male and female mice to identify the molecular and cellular mechanisms by which EAAC1 controls the execution of repeated motor behaviors. Our findings show that, in the striatum, a brain region implicated with movement execution, EAAC1 limits group I metabotropic glutamate receptor (mGluRI) activation, facilitates D1 dopamine receptor (D1R) expression, and ensures long-term synaptic plasticity. Blocking mGluRI in slices from mice lacking EAAC1 restores D1R expression and synaptic plasticity. Conversely, activation of intracellular signaling pathways coupled to mGluRI in D1R-containing striatal neurons of mice expressing EAAC1 leads to reduced D1R protein level and increased stereotyped movement execution. These findings identify new molecular mechanisms by which EAAC1 can shape glutamatergic and dopaminergic signals and control repeated movement execution.

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DEVELOPMENT/PLASTICITY/REPAIR

Synaptic Regulator α -Synuclein in Dopaminergic Fibers Is Essentially Required for the Maintenance of Subependymal Neural Stem Cells

Ana Perez-Villalba,^{1,2,3} M. Salomé Sirerol-Piquer,^{1,2,3} Germán Belenguer,^{1,2,3} Raúl Soriano-Cantón,^{1,2,3} Ana Belén Muñoz-Manchado,^{1,4,5} Javier Villadiego,^{1,4,5} Diana Alarcón-Arís,^{6,7,8} Federico N. Soria,^{9,10} Benjamin Dehay,^{9,10} Erwan Bezard,^{9,10} Miquel Vila,^{1,11,12} Analía Bortolozzi,^{6,7,8} Juan José Toledo-Aral,^{1,4,5} Francisco Pérez-Sánchez,^{1,2,3} and Isabel Fariñas^{1,2,3}

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Synaptic protein α -synuclein (α -SYN) modulates neurotransmission in a complex and poorly understood manner and aggregates in the cytoplasm of degenerating neurons in Parkinson's disease. Here, we report that α -SYN present in dopaminergic nigral afferents is essential for the normal cycling and maintenance of neural stem cells (NSCs) in the brain subependymal zone of adult male and female mice. We also show that premature senescence of adult NSCs into non-neurogenic astrocytes in mice lacking α -SYN resembles the effects of dopaminergic fiber degeneration resulting from chronic exposure to 1-methyl-4-phenyl-1,2,3,6-tetra-hydropyridine or intranigral inoculation of aggregated toxic α -SYN. Interestingly, NSC loss in α -SYN-deficient mice can be prevented by viral delivery of human α -SYN into their substantia nigra or by treatment with L-DOPA, suggesting that α -SYN regulates dopamine availability to NSCs. Our data indicate that α -SYN, present in dopaminergic nerve terminals supplying the subependymal zone, acts as a niche component to sustain the neurogenic potential of adult NSCs and identify α -SYN and DA as potential targets to ameliorate neurogenic defects in the aging and diseased brain.

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Non-Newly Generated, “Immature” Neurons in the Sheep Brain Are Not Restricted to Cerebral Cortex

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A newly proposed form of brain structural plasticity consists of non-newly generated, “immature” neurons of the adult cerebral cortex. Similar to newly generated neurons, these cells express the cytoskeletal protein Doublecortin (DCX), yet they are generated prenatally and then remain in a state of immaturity for long periods. In rodents, the immature neurons are restricted to the paleocortex, whereas in other mammals, they are also found in neocortex. Here, we analyzed the DCX-expressing cells in the whole sheep brain of both sexes to search for an indicator of structural plasticity at a cellular level in a relatively large-brained, long-living mammal. Brains from adult and

newborn sheep (injected with BrdU and analyzed at different survival times) were processed for DCX, cell proliferation markers (Ki-67, BrdU), pallial/subpallial developmental origin (*Tbr1*, *Sp8*), and neuronal/glial antigens for phenotype characterization. We found immature-like neurons in the whole sheep cortex and in large populations of DCX-expressing cells within the external capsule and the surrounding gray matter (claustrum and amygdala). BrdU and Ki-67 detection at neonatal and adult ages showed that all of these DCX⁺ cells were generated during embryogenesis, not after birth. These results show that the adult sheep, unlike rodents, is largely endowed with non-newly generated neurons retaining immature features, suggesting that such plasticity might be particularly important in large-brained, long-living mammals.

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SYSTEMS/CIRCUITS

Early Procedural Pain Is Associated with Regionally-Specific Alterations in Thalamic Development in Preterm Neonates

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Very preterm human neonates are exposed to numerous invasive procedures as part of life-saving care. Evidence suggests that repetitive neonatal procedural pain precedes long-term alterations in brain development. However, to date the link between pain and brain development has limited temporal and anatomic specificity. We hypothesized that early exposure to painful stimuli during a period of rapid brain development, before pain modulatory systems reach maturity, will predict pronounced changes in thalamic development, and thereby cognitive and motor function. In a prospective cohort study, 155 very preterm neonates (82 males, 73 females) born 24–32 weeks' gestation underwent two MRIs at median postmenstrual ages 32 and 40 weeks that included structural, metabolic, and diffusion imaging. Detailed day-by-day clinical data were collected. Cognitive and motor abilities were assessed at 3 years, corrected age. The association of early (skin breaks, birth–Scan 1) and late pain (skin breaks, Scans 1–2) with thalamic volumes and *N*-acetylaspartate (NAA)/choline (Cho), and fractional anisotropy of white-matter pathways was assessed. Early pain was associated with slower thalamic macrostructural growth, most pronounced in extremely premature neonates. Deformation-based morphometry analyses confirmed early pain-related volume losses were localized to somatosensory regions. In extremely preterm neonates early pain was associated with decreased thalamic NAA/Cho and microstructural alterations in thalamocortical pathways. Thalamic growth was in turn related to cognitive and motor outcomes. We observed regionally-specific alterations in the lateral thalamus and thalamocortical pathways in extremely preterm neonates exposed to more procedural pain. Findings suggest a sensitive period leading to lasting alterations in somatosensory-system development.

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A Unifying Motif for Spatial and Directional Surround Suppression

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In the visual system, the response to a stimulus in a neuron's receptive field can be modulated by stimulus context, and the strength of these contextual influences vary with stimulus intensity. Recent work has shown how a theoretical model, the stabilized supralinear network (SSN), can account for such modulatory influences, using a small set of computational mechanisms. Although the predictions of the SSN have been confirmed in primary visual cortex (V1), its computational principles apply with equal validity to any cortical structure. We have therefore tested the generality of the SSN by examining modulatory influences in the middle temporal area (MT) of the macaque visual cortex, using electrophysiological recordings and pharmacological manipulations. We developed a novel stimulus that can be adjusted parametrically to be larger or smaller in the space of all possible motion directions. We found, as predicted by the SSN, that MT neurons integrate across motion directions for low-contrast stimuli, but that they exhibit suppression by the same stimuli when they are high in contrast. These results are analogous to those found in visual cortex when stimulus size is varied in the space domain. We further tested the mechanisms of inhibition using pharmacological manipulations of inhibitory efficacy. As predicted by the SSN, local manipulation of inhibitory strength altered firing rates, but did not change the strength of surround suppression. These results are consistent with the idea that the SSN can account for modulatory influences along different stimulus dimensions and in different cortical areas.

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Causal Evidence for Learning-Dependent Frontal Lobe Contributions to Cognitive Control

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The lateral prefrontal cortex (LPFC) plays a central role in the prioritization of sensory input based on task relevance. Such top-down control of perception is of fundamental importance in goal-directed behavior, but can also be costly when deployed excessively, necessitating a mechanism that regulates control engagement to align it with changing environmental demands. We have recently introduced the “flexible control model” (FCM), which explains this regulation as resulting from a self-adjusting reinforcement-learning mechanism that infers latent statistical structure in dynamic task environments to predict forthcoming states. From this perspective, LPFC-based control is engaged as a function of anticipated cognitive demand, a notion for which we previously obtained correlative neuroimaging evidence. Here, we put this hypothesis to a rigorous, causal test by combining the FCM with a transcranial magnetic stimulation (TMS) intervention that transiently perturbed the LPFC. Human participants (male and female) completed a nonstationary version of the Stroop task with dynamically changing probabilities of conflict between task-relevant and task-irrelevant stimulus features. TMS was given on each trial before stimulus onset either over the LPFC or over a control site. In the control condition, we observed adaptive performance fluctuations consistent with demand predictions that were inferred from recent and remote trial history and effectively captured by our model. Critically, TMS over the LPFC eliminated these fluctuations while leaving basic cognitive and motor functions intact. These results provide causal evidence for a learning-based account of cognitive control and delineate the nature of the signals that regulate top-down biases over stimulus processing.

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A Computational Account of Optimizing Social Predictions Reveals That Adolescents Are Conservative Learners in Social Contexts

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As adolescents transition to the complex world of adults, optimizing predictions about others’ preferences becomes vital for successful social interactions. Mounting evidence suggests that these social learning processes are affected by ongoing brain development across adolescence. A mechanistic understanding of how adolescents optimize social predictions and how these learning strategies are implemented in the brain is lacking. To fill this gap, we combined computational modeling with functional neuroimaging. In a novel social learning task, male and female human adolescents and adults predicted the preferences of peers and could update their predictions based on trial-by-trial feedback about the peers’ actual preferences. Participants also rated their own preferences for the task items and similar additional items. To describe how participants optimize their inferences over time, we pitted simple reinforcement learning models against more specific “combination” models, which describe inferences based on a combination of reinforcement learning from past feedback and participants’ own preferences. Formal model comparison revealed that, of the tested models, combination models best described how adults and adolescents update predictions of others. Parameter estimates of the best-fitting model differed between age groups, with adolescents showing more conservative updating. This developmental difference was accompanied by a shift in encoding predictions and the errors thereof within the medial prefrontal and fusiform cortices. In the adolescent group, encoding of own preferences and prediction errors scaled with parent-reported social traits, which provides additional external validity for our learning task and the winning computational model. Our findings thus help to specify adolescent-specific social learning processes.

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NEUROBIOLOGY OF DISEASE

Overexpression of the Histone Dimethyltransferase G9a in Nucleus Accumbens Shell Increases Cocaine Self-Administration, Stress-Induced Reinstatement, and Anxiety

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Repeated exposure to cocaine induces lasting epigenetic changes in neurons that promote the development and persistence of addiction. One epigenetic alteration involves reductions in levels of the histone dimethyltransferase G9a in nucleus accumbens (NAc) after chronic cocaine administration. This reduction in G9a may enhance cocaine reward because overexpressing G9a in the NAc decreases cocaine-conditioned place preference. Therefore, we hypothesized that HSV-mediated G9a overexpression in the NAc shell (NAcSh) would attenuate cocaine self-administration (SA) and cocaine-seeking behavior. Instead, we found that G9a overexpression, and the resulting increase in histone 3 lysine 9 dimethylation (H3K9me2), increases sensitivity to cocaine reinforcement and enhances motivation for cocaine in self-administering male rats.

Moreover, when G9a overexpression is limited to the initial 15 d of cocaine SA training, it produces an enduring postexpression enhancement in cocaine SA and prolonged (over 5 weeks) increases in reinstatement of cocaine seeking induced by foot-shock stress, but in the absence of continued global elevations in H3K9me2. The increase in stress-induced reinstatement is paralleled by heightened anxiety measures, suggesting that countering the cocaine-induced decreases in endogenous G9a with ectopic G9a overexpression leads to lasting anxiogenic effects. Finally, we found an enduring reduction in phosphorylated cAMP-response element binding protein levels in the NAcSh that could account for the increased anxiety. These data demonstrate a novel role for G9a in promoting comorbid cocaine addiction and anxiety and suggest that increased epigenetic repression of transcription through H3K9 during cocaine use can have long-lasting and unexpected negative consequences on behavior.

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Miz1 Controls Schwann Cell Proliferation via H3K36^{me2} Demethylase Kdm8 to Prevent Peripheral Nerve Demyelination

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Schwann cell differentiation and myelination depends on chromatin remodeling, histone acetylation, and methylation, which all affect Schwann cell proliferation. We previously reported that the deletion of the POZ (POxvirus and Zinc finger) domain of the transcription factor Miz1 (Myc-interacting zinc finger protein; encoded by *Zbtb17*) in mouse Schwann cells (*Miz1ΔPOZ*) causes a neuropathy at 90 d after birth [postnatal day (P) 90], with a subsequent spontaneous regeneration. Here we show that RNA sequencing from *Miz1ΔPOZ* and control animals at P30 revealed a set of upregulated genes with a strong correlation to cell-cycle regulation. Consistently, a subset of Schwann cells did not exit the cell cycle as observed in control animals and the growth fraction increased over time. From the RNAseq gene list, two direct Miz1 target genes were identified, one of which encodes the histone H3K36^{me2} demethylase Kdm8. We show that the expression of *Kdm8* is repressed by Miz1 and that its release in *Miz1ΔPOZ* cells induces a decrease of H3K36^{me2}, especially in deregulated cell-cycle-related genes. The linkage between elevated *Kdm8* expression, hypomethylation of H3K36 at cell-cycle-relevant genes, and the subsequent re-entering of adult Schwann cells into the cell cycle suggests that the release of *Kdm8* repression in the absence of a functional Miz1 is a central issue in the development of the *Miz1ΔPOZ* phenotype.

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Common Pathophysiology in Multiple Mouse Models of Pitt–Hopkins Syndrome

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Mutations or deletions of the transcription factor *TCF4* are linked to Pitt–Hopkins syndrome (PTHS) and schizophrenia, suggesting that the precise pathogenic mutations dictate cellular, synaptic, and behavioral consequences. Here, we generated two novel mouse models of PTHS, one that mimics the most common pathogenic *TCF4* point mutation (human R580W, mouse R579W) and one that deletes three pathogenic arginines, and explored phenotypes of these lines alongside models of pan-cellular or CNS-specific heterozygous *Tcf4* disruption. We used mice of both sexes to show that impaired *Tcf4* function results in consistent microcephaly, hyperactivity, reduced anxiety, and deficient spatial learning. All four PTHS mouse models demonstrated exaggerated hippocampal long-term potentiation (LTP), consistent with deficits in hippocampus-mediated behaviors. We further examined R579W mutant mice and mice with pan-cellular *Tcf4* heterozygosity and found that they exhibited hippocampal NMDA receptor hyperfunction, which likely drives the enhanced LTP. Together, our data pinpoint convergent neurobiological features in PTHS mouse models and provide a foundation for preclinical studies and a rationale for testing whether NMDAR antagonists might be used to treat PTHS.

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Combined Active Humoral and Cellular Immunization Approaches for the Treatment of Synucleinopathies

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Dementia with Lewy bodies, Parkinson's disease, and Multiple System Atrophy are age-related neurodegenerative disorders characterized by progressive accumulation of α -synuclein (α -syn) and jointly termed synucleinopathies. Currently, no disease-modifying treatments are available for these disorders. Previous preclinical studies demonstrate that active and passive immunizations targeting α -syn partially ameliorate behavioral deficits and α -syn accumulation; however, it is unknown whether combining humoral and cellular immunization might act synergistically to reduce inflammation and improve microglial-mediated α -syn clearance. Since combined delivery of antigen plus rapamycin (RAP) in nanoparticles is known to induce antigen-specific regulatory T cells (Tregs), we adapted this approach to α -syn using the antigen-presenting cell-targeting glucan microparticle (GP) vaccine delivery system. PDGF- α -syn transgenic (tg) male and female mice were immunized with GP-alone, GP- α -syn (active humoral immunization), GP+RAP, or GP+RAP/ α -syn (combined active humoral and Treg) and analyzed using neuropathological and biochemical markers. Active immunization resulted in higher serological total IgG, IgG1, and IgG2a anti- α -syn levels. Compared with mice immunized with GP-alone or GP- α -syn, mice vaccinated with GP+RAP or GP+RAP/ α -syn

displayed increased numbers of CD25-, FoxP3-, and CD4-positive cells in the CNS. GP- α -syn or GP+RAP/ α -syn immunizations resulted in a 30–45% reduction in α -syn accumulation, neuroinflammation, and neurodegeneration. Mice immunized with GP+RAP/ α -syn further rescued neurons and reduced neuroinflammation. Levels of TGF- β 1 were increased with GP+RAP/ α -syn immunization, while levels of TNF- α and IL-6 were reduced. We conclude that the observed effects of GP+RAP/ α -syn immunization support the hypothesis that cellular immunization may enhance the effects of active immunotherapy for the treatment of synucleinopathies.

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Insulin-Like Growth Factor II Targets the mTOR Pathway to Reverse Autism-Like Phenotypes in Mice

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Autism spectrum disorder (ASD) is a developmental disability characterized by impairments in social interaction and repetitive behavior, and is also associated with cognitive deficits. There is no current treatment that can ameliorate most of the ASD symptomatology; thus, identifying novel therapies is urgently needed. We used male BTBR $T^{+} Itpr3^{fl/y}$ (BTBR) mice, a model that reproduces most of the core behavioral phenotypes of ASD, to test the effects of systemic administration of insulin-like growth factor II (IGF-II), a polypeptide that crosses the blood–brain barrier and acts as a cognitive enhancer. We show that systemic IGF-II treatments reverse the typical defects in social interaction, cognitive/executive functions, and repetitive behaviors reflective of ASD-like phenotypes. In BTBR mice, IGF-II, via IGF-II receptor, but not via IGF-I receptor, reverses the abnormal levels of the AMPK–mTOR–S6K pathway and of active translation at synapses. Thus, IGF-II may represent a novel potential therapy for ASD.

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FK506-Binding Protein 12.6/1b, a Negative Regulator of $[Ca^{2+}]$, Rescues Memory and Restores Genomic Regulation in the Hippocampus of Aging Rats

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Hippocampal overexpression of FK506-binding protein 12.6/1b (*FKBP1b*), a negative regulator of ryanodine receptor Ca^{2+} release, reverses aging-induced memory impairment and neuronal Ca^{2+} dysregulation. Here, we tested the hypothesis that *FKBP1b* also can protect downstream transcriptional networks from aging-induced dysregulation. We gave hippocampal microinjections of *FKBP1b*-expressing viral vector to male rats at either 13 months of age (long-term, LT) or 19 months of age (short-term, ST) and tested memory performance in the Morris water maze at 21 months of age. Aged rats treated ST or LT with *FKBP1b* substantially outperformed age-matched vector controls and performed similarly to each other and young controls (YCs). Transcriptional profiling in the same animals identified 2342 genes with hippocampal expression that was upregulated/downregulated in aged controls (ACs) compared with YCs (the aging effect). Of these aging-dependent genes, 876 (37%) also showed altered expression in aged *FKBP1b*-treated rats compared with ACs, with *FKBP1b* restoring expression of essentially all such genes (872/876, 99.5%) in the direction opposite the aging effect and closer to levels in YCs. This inverse relationship between the aging and *FKBP1b* effects suggests that the aging effects arise from *FKBP1b* deficiency. Functional category analysis revealed that genes downregulated with aging and restored by *FKBP1b* were associated predominantly with diverse brain structure categories, including cytoskeleton, membrane channels, and extracellular region. Conversely, genes upregulated with aging but not restored by *FKBP1b* associated primarily with glial–neuroinflammatory, ribosomal, and lysosomal categories. Immunohistochemistry confirmed aging-induced rarefaction and *FKBP1b*-mediated restoration of neuronal microtubular structure. Therefore, a previously unrecognized genomic network modulating diverse brain structural processes is dysregulated by aging and restored by *FKBP1b* overexpression.

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Lack of Parkin Anticipates the Phenotype and Affects Mitochondrial Morphology and mtDNA Levels in a Mouse Model of Parkinson's Disease

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PARK2 is the most common gene mutated in monogenic recessive familial cases of Parkinson's disease (PD). Pathogenic mutations cause a loss of function of the encoded protein Parkin. ParkinKO mice, however, poorly represent human PD symptoms as they only exhibit mild motor phenotypes, minor dopamine metabolism abnormalities, and no signs of dopaminergic neurodegeneration. Parkin has been shown to participate in mitochondrial turnover, by targeting damaged mitochondria with low membrane potential to mitophagy. We studied the role of Parkin on mitochondrial quality control *in vivo* by knocking out Parkin in the PD-mito-*PstI* mouse (males), where the mitochondrial DNA (mtDNA) undergoes double-strand breaks only in dopaminergic neurons. The lack of Parkin promoted earlier onset of dopaminergic neurodegeneration and motor defects in the PD-mito-*PstI* mice, but it did not worsen the pathology. The lack of Parkin affected mitochondrial morphology in dopaminergic axons and was associated with an increase in mtDNA levels (mutant and wild type). Unexpectedly, it did not cause a parallel increase in mitochondrial mass or mitophagy. Our results suggest that Parkin affects mtDNA levels in a mitophagy-independent manner.

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