

This Week in The Journal

The Acetyltransferase GCN5 Limits Diencephalon Size

Jonathan J. Wilde, Julie A. Siegenthaler, Sharon Y.R. Dent, and Lee A. Niswander

(see pages 2565–2579)

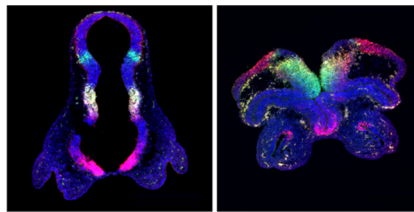
Early in development, gradients of morphogens activate different transcriptional programs along the neural plate, dividing primordial neural tissue into domains that become the telencephalon, diencephalon, midbrain, and hindbrain. Where and when morphogens and their downstream effectors are expressed must be precisely controlled to ensure that each domain forms and grows properly. Excessive or insufficient growth can prevent neural tube closure and cause neurological deficits.

The specification and growth of the diencephalon depends on localized expression of the morphogen sonic hedgehog (Shh): broader-than-normal expression of Shh leads to excessive production of diencephalic tissue. Wilde et al. have identified a molecular pathway that limits Shh expression to prevent such diencephalic expansion. They first found that the diencephalon was selectively expanded in mice in which the acetyltransferase GCN5 lacked enzymatic activity. In addition, Shh expression was expanded, and signaling by WNT, which promotes Shh expression, was increased in mutant mice. Because retinoic acid represses WNT signaling, and because GCN5 associates with retinoic acid receptor α (RAR α), the authors asked whether GCN5 regulates expression of genes controlled by retinoic acid. Indeed, GCN5 mutation decreased expression of such genes.

Previous work indicated that one target of GCN5 acetylation is TACC1, a protein that interacts with RAR α and is expressed in the developing forebrain. Wilde et al. found that in the absence of retinoic acid, wild-type GCN5, RAR α , and TACC1 formed a complex localized to retinoic acid response elements in chromatin. Addition of retinoic acid caused GCN5-

dependent acetylation of TACC1, which led to dissociation of TACC1 from the chromatin-bound complex.

These results suggest that growth of diencephalic tissue is restricted by retinoic acid, which binds to RAR α at retinoic acid response elements in DNA. This binding triggers acetylation of TACC1 by GCN5, which causes TACC1 to dissociate from DNA. This in turn allows transcription of the associated genes. These genes likely repress WNT signaling and Shh expression, thus defining the limits of diencephalic specification. Future work will need to determine how retinoic acid production is regulated to prevent excessive restriction of diencephalon growth.



Loss of GCN5 acetyltransferase activity (right) causes mispatterning and expansion of the diencephalon, as indicated by expression of two diencephalic markers (green and magenta). See Wilde et al. for details.

Orbitofrontal Cortex Encodes Updated Reward Identity

James D. Howard and Thorsten Kahnt

(see pages 2627–2638)

Many factors influence behavioral choices. What you order from a menu, for example, depends not only on what foods you like, but also on how recently you have eaten those foods and how hungry you are. All these factors must be incorporated into a neural representation of the expected value of each option before a choice is made. Evidence suggests that such expected values are encoded by activity in the orbitofrontal cortex. How values are updated to reflect current states, and how such updating influences decisions, is poorly understood, however. Therefore, Howard and Kahnt used

functional magnetic resonance imaging to investigate changes in neural representations of food-related odors before and after one odor was devalued.

Hungry participants first rated the appeal of several odors, and two appetizing odors were selected for use in a subsequent choice task, which was performed in a scanner. In each trial of the task, subjects chose whether to sniff a high or low concentration of one of the appealing odors. They then consumed a meal consisting of food associated with one of these odors, thus devaluing that odor. Finally, subjects performed the choice task again. Pattern-based analysis was then used to compare neural representations of expected rewards before and after the meal.

Before the meal, subjects chose to sniff the higher concentration of both odors; after the meal, subjects chose the lower concentration of the devalued odor, but continued to choose the high concentration of the non-devalued odor. Pattern analysis indicated that reward identity was encoded in medial and lateral aspects of the posterior orbitofrontal cortex (pOFC). While representations of both rewards changed in the medial pOFC after the meal, only the representation of the devalued reward changed in the lateral pOFC. Additional analyses indicated that functional coupling between the lateral pOFC and ventromedial prefrontal cortex (vmPFC)—an area that encodes identity-independent reward value—decreased selectively for the devalued reward after the meal. The larger this decrease, the more subjects' preference for the high concentration of the devalued odor decreased.

These results support the hypothesis that the lateral pOFC represents the predicted values of specific rewards, updates these values as conditions change, and communicates these values to vmPFC to guide decisions. How outcome representations change at the neural ensemble level remains unknown and should be investigated in future studies.

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



Cover legend: The image shows spinal cord myelinated fibers immunostained with anti- β IV Spectrin antibody to label the nodes of Ranvier (green), anti-Caspr antibody to label the paranodal region (blue), and anti-Kv1.2 antibody to visualize the juxtaparanodal area (red). Nodes are specialized myelin-free structures required for action potential regeneration and transmission along myelinated axons. New work reveals that the cytoskeletal scaffolding protein Ankyrin G is critical for proper organization, maturation, and stability of the nodes of Ranvier. For more information, see the article by Saifetiarova et al. (pages 2524–2538).

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Aptamers as Valuable Molecular Tools in Neurosciences

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Aptamers are short nucleic acids that interact with a variety of targets with high affinity and specificity. They have been shown to inhibit biological functions of cognate target proteins, and they are identifiable by an *in vitro* selection process, also termed SELEX (Systematic Evolution of Ligands by EXponential enrichment). Being nucleic acids, aptamers can be synthesized chemically or enzymatically. The latter renders RNA aptamers compatible with the cell's own transcription machinery and, thus, expressible inside cells. The synthesis of aptamers by chemical approaches opens up the possibility of producing aptamers on a large scale and enables a straightforward access to introduce modifications in a site-specific manner (e.g., fluorophores or photo-labile groups). These characteristics make aptamers broadly applicable (e.g., as an analytical, diagnostic, or separation tool). In this *TechSight*, we provide a brief overview on aptamer technology and the potential of aptamers as valuable research tools in neurosciences.

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Articles

CELLULAR/MOLECULAR

Early and Late Loss of the Cytoskeletal Scaffolding Protein, Ankyrin G Reveals Its Role in Maturation and Maintenance of Nodes of Ranvier in Myelinated Axons

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The mechanisms that govern node of Ranvier organization, stability, and long-term maintenance remain to be fully elucidated. One of the molecular components of the node is the cytoskeletal scaffolding protein, ankyrin G (AnkG), which interacts with multiple members of the nodal complex. The role of AnkG in nodal organization and maintenance is still not clearly defined as to whether AnkG functions as an initial nodal organizer or whether it functions as a nodal stabilizer after the nodal complex has been assembled. Using a mouse model system, we report here that perinatal and juvenile neuronal ablation of AnkG has differential consequences on nodal stability. Early loss of AnkG creates immature nodes with abnormal morphology, which undergo accelerated destabilization within a month, resulting in rapid voltage-gated sodium (Na_v) channel and β IV spectrin loss with reduced effects on neurofascin 186. On the other hand, late ablation of AnkG from established nodal complexes leads to slow but progressive nodal destabilization over 10 months, primarily affecting β IV spectrin, followed by Na_v channels, with modest impact on neurofascin 186. We also show that ankyrin R and β I spectrin are not sufficient to prevent nodal disorganization after AnkG ablation. Additionally, nodal disorganization in both early and late AnkG mutants is accompanied by axonal pathology and neurological dysfunction. Together, our results suggest that AnkG plays an indispensable role in the maturation and long-term stabilization of the newly assembled nodal complex, and that loss of AnkG after nodal stabilization does not lead to rapid nodal disassembly but to loss of specific nodal components in a time-dependent manner.

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Acid-Sensing Ion Channels Activated by Evoked Released Protons Modulate Synaptic Transmission at the Mouse Calyx of Held Synapse

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Acid-sensing ion channels (ASICs) regulate synaptic activities and play important roles in neurodegenerative diseases. We found that these channels can be activated in neurons of the medial nucleus of the trapezoid body (MNTB) of the auditory system in the CNS. A drop in extracellular pH induces transient inward ASIC currents (I_{ASICs}) in postsynaptic MNTB neurons from wild-type mice. The inhibition of I_{ASICs} by psalmotoxin-1 (PcTx1) and the absence of these currents in knock-out mice for ASIC-1a subunit (ASIC1a^{-/-}) suggest that homomeric ASIC-1as are mediating these currents in MNTB neurons. Furthermore, we detect ASIC1a-dependent currents during synaptic transmission, suggesting an acidification of the synaptic cleft due to the corelease of neurotransmitter and H^+ from synaptic vesicles. These currents are capable of eliciting action potentials in the absence of glutamatergic currents. A significant characteristic of these homomeric ASIC-1as is their permeability to Ca^{2+} . Activation of ASIC-1a in MNTB neurons by exogenous H^+ induces an increase in intracellular Ca^{2+} . Furthermore, the activation of postsynaptic ASIC-1as during high-frequency stimulation (HFS) of the presynaptic nerve terminal leads to a PcTx1-sensitive increase in intracellular Ca^{2+} in MNTB neurons, which is independent of glutamate receptors and is absent in neurons from ASIC1a^{-/-} mice. During HFS, the lack of functional ASICs in synaptic transmission results in an enhanced short-term depression

of glutamatergic EPSCs. These results strongly support the hypothesis of protons as neurotransmitters and demonstrate that presynaptic released protons modulate synaptic transmission by activating ASIC-1as at the calyx of Held–MNTB synapse.
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Regulation of Synaptic Amyloid- β Generation through BACE1 Retrograde Transport in a Mouse Model of Alzheimer's Disease

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Amyloid- β (A β) peptides play a key role in synaptic damage and memory deficits in the early pathogenesis of Alzheimer's disease (AD). Abnormal accumulation of A β at nerve terminals leads to synaptic pathology and ultimately to neurodegeneration. β -site amyloid precursor protein (APP) cleaving enzyme 1 (BACE1) is the major neuronal β -secretase for A β generation. However, the mechanisms regulating BACE1 distribution in axons and β cleavage of APP at synapses remain largely unknown. Here, we reveal that dynein–Snapin-mediated retrograde transport regulates BACE1 trafficking in axons and APP processing at presynaptic terminals. BACE1 is predominantly accumulated within late endosomes at the synapses of AD-related mutant human APP (hAPP) transgenic (Tg) mice and patient brains. Defective retrograde transport by genetic ablation of *snapin* in mice recapitulates late endocytic retention of BACE1 and increased APP processing at presynaptic sites. Conversely, overexpressing Snapin facilitates BACE1 trafficking and reduces synaptic BACE1 accumulation by enhancing the removal of BACE1 from distal AD axons and presynaptic terminals. Moreover, elevated Snapin expression via stereotactic hippocampal injections of adeno-associated virus particles in mutant hAPP Tg mouse brains decreases synaptic A β levels and ameliorates synapse loss, thus rescuing cognitive impairments associated with hAPP mice. Altogether, our study provides new mechanistic insights into the complex regulation of BACE1 trafficking and presynaptic localization through Snapin-mediated dynein-driven retrograde axonal transport, thereby suggesting a potential approach of modulating A β levels and attenuating synaptic deficits in AD.
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ARPP-16 Is a Striatal-Enriched Inhibitor of Protein Phosphatase 2A Regulated by Microtubule-Associated Serine/Threonine Kinase 3 (Mast 3 Kinase)

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ARPP-16 (cAMP-regulated phospho-protein of molecular weight 16 kDa) is one of several small acid-soluble proteins highly expressed in medium spiny neurons of striatum that are phosphorylated in response to dopamine acting via D1 receptor/protein kinase A (PKA) signaling. We show here that ARPP-16 is also phosphorylated *in vitro* and *in vivo* by microtubule-associated serine/threonine kinase 3 (MAST3 kinase), an enzyme of previously unknown function that is enriched in striatum. We find that ARPP-16 interacts directly with the scaffolding A subunit of the serine/threonine protein phosphatase, PP2A, and that phosphorylation of ARPP-16 at Ser46 by MAST3 kinase converts the protein into a selective inhibitor of B55 α - and B56 δ -containing heterotrimeric forms of PP2A. Ser46 of ARPP-16 is phosphorylated to a high basal stoichiometry in striatum, suggestive of basal inhibition of PP2A in striatal neurons. In support of this hypothesis, conditional knock-out of ARPP-16 in *CaMKII α ::cre/floxed ARPP-16/19* mice results in dephosphorylation of a subset of PP2A substrates including phospho-Thr75-DARPP-32, phospho-T308-Akt, and phospho-T202/Y204-ERK. Conditional knock-out of ARPP-16/19 is associated with increased motivation measured on a progressive ratio schedule of food reinforcement, yet an attenuated locomotor response to acute cocaine. Our previous studies have shown that ARPP-16 is phosphorylated at Ser88 by PKA. Activation of PKA in striatal slices leads to phosphorylation of Ser88, and this is accompanied by marked dephosphorylation of Ser46. Together, these studies suggest that phospho-Ser46-ARPP-16 acts to basally control PP2A in striatal medium spiny neurons but that dopamine acting via PKA inactivates ARPP-16 leading to selective potentiation of PP2A signaling.
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Cell-Specific PKM Isoforms Contribute to the Maintenance of Different Forms of Persistent Long-Term Synaptic Plasticity

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Multiple kinase activations contribute to long-term synaptic plasticity, a cellular mechanism mediating long-term memory. The sensorimotor synapse of *Aplysia* expresses different forms of long-term facilitation (LTF)—nonassociative and associative LTF—that require the timely activation of kinases, including protein kinase C (PKC). It is not known which PKC isoforms in the sensory neuron or motor neuron L7 are required to sustain each form of LTF. We show that different PKMs, the constitutively active isoforms of PKCs generated by calpain cleavage, in the sensory neuron and L7 are required to maintain each form of LTF. Different PKMs or calpain isoforms were blocked by overexpressing specific dominant-negative constructs in either presynaptic or postsynaptic neurons. Blocking either PKM Apl I in L7, or PKM Apl II or PKM Apl III in

the sensory neuron 2 d after 5-hydroxytryptamine (5-HT) treatment reversed persistent nonassociative LTF. In contrast, blocking either PKM Apl II or PKM Apl III in L7, or PKM Apl II in the sensory neuron 2 d after paired stimuli reversed persistent associative LTF. Blocking either classical calpain or atypical small optic lobe (SOL) calpain 2 d after 5-HT treatment or paired stimuli did not disrupt the maintenance of persistent LTF. Soon after 5-HT treatment or paired stimuli, however, blocking classical calpain inhibited the expression of persistent associative LTF, while blocking SOL calpain inhibited the expression of persistent nonassociative LTF. Our data suggest that different stimuli activate different calpains that generate specific sets of PKMs in each neuron whose constitutive activities sustain long-term synaptic plasticity.

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DEVELOPMENT/PLASTICITY/REPAIR

Diencephalic Size Is Restricted by a Novel Interplay Between GCN5 Acetyltransferase Activity and Retinoic Acid Signaling

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Diencephalic defects underlie an array of neurological diseases. Previous studies have suggested that retinoic acid (RA) signaling is involved in diencephalic development at late stages of embryonic development, but its roles and mechanisms of action during early neural development are still unclear. Here we demonstrate that mice lacking enzymatic activity of the acetyltransferase GCN5 (*Gcn5^{hat/hat}*), which were previously characterized with respect to their exencephalic phenotype, exhibit significant diencephalic expansion, decreased diencephalic RA signaling, and increased diencephalic WNT and SHH signaling. Using a variety of molecular biology techniques in both cultured neuroepithelial cells treated with a GCN5 inhibitor and forebrain tissue from (*Gcn5^{hat/hat}*) embryos, we demonstrate that GCN5, RAR α/γ , and the poorly characterized protein TACC1 form a complex in the nucleus that binds specific retinoic acid response elements in the absence of RA. Furthermore, RA triggers GCN5-mediated acetylation of TACC1, which results in dissociation of TACC1 from retinoic acid response elements and leads to transcriptional activation of RA target genes. Intriguingly, RA signaling defects caused by *in vitro* inhibition of GCN5 can be rescued through RA-dependent mechanisms that require RAR β . Last, we demonstrate that the diencephalic expansion and transcriptional defects seen in (*Gcn5^{hat/hat}*) mutants can be rescued with gestational RA supplementation, supporting a direct link between GCN5, TACC1, and RA signaling in the developing diencephalon. Together, our studies identify a novel, nonhistone substrate for GCN5 whose modification regulates a previously undescribed, tissue-specific mechanism of RA signaling that is required to restrict diencephalic size during early forebrain development.

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SYSTEMS/CIRCUITS

Organization of the Anterior Limb of the Internal Capsule in the Rat

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Dysfunction of the orbitofrontal (OFC) and anterior cingulate (ACC) cortices has been linked with several psychiatric disorders, including obsessive-compulsive disorder, major depressive disorder, posttraumatic stress disorder, and addiction. These conditions are also associated with abnormalities in the anterior limb of the internal capsule, the white matter (WM) bundle carrying ascending and descending fibers from the OFC and ACC. Furthermore, deep-brain stimulation (DBS) for psychiatric disorders targets these fibers. Experiments in rats provide essential information on the mechanisms of normal and abnormal brain anatomy, including WM composition and perturbations. However, whereas descending prefrontal cortex (PFC) fibers in primates form a well defined and topographic anterior limb of the internal capsule, the specific locations and organization of these fibers in rats is unknown. We address this gap by analyzing descending fibers from injections of an anterograde tracer in the rat ACC and OFC. Our results show that the descending PFC fibers in the rat form WM fascicles embedded within the striatum. These bundles are arranged topographically and contain projections, not only to the striatum, but also to the thalamus and brainstem. They can therefore be viewed as the rat homolog of the primate anterior limb of the internal capsule. Furthermore, mapping these projections allows us to identify the fibers likely to be affected by experimental manipulations of the striatum and the anterior limb of the internal capsule. These results are therefore essential for translating abnormalities of human WM and effects of DBS to rodent models.

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Nerve-Specific Input Modulation to Spinal Neurons during a Motor Task in the Monkey

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If not properly regulated, the large amount of reafferent sensory signals generated by our own movement could destabilize the CNS. We investigated how input from peripheral nerves to spinal cord is modulated during behavior. We chronically stimulated the deep radial nerve (DR; proprioceptive, wrist extensors), the median nerve (M; mixed, wrist flexors and palmar skin) and the superficial radial nerve (SR; cutaneous, hand dorsum) while four monkeys performed a delayed wrist flexion–extension task. Spinal neurons putatively receiving direct sensory input were defined based on their evoked response latency following nerve stimulation. We compared the influence of behavior on the evoked response (responsiveness to a specific peripheral input) and firing rate of 128 neuron–nerve pairs based on their source nerve. Firing rate increased during movement regardless of source nerve, whereas evoked response modulation was strikingly nerve-dependent. In SR ($n = 47$) and M ($n = 27$) neurons (cutaneous or mixed input), the evoked response was suppressed during wrist flexion and extension. In contrast, in DR neurons ($n = 54$, pure proprioceptive input), the evoked response was facilitated exclusively during movements corresponding to the contraction of DR spindle-bearing muscles (i.e., wrist extension). Furthermore, modulations of firing rate and evoked response were uncorrelated in SR and M neurons, whereas they tended to be positively comodulated in DR neurons. Our results suggest that proprioceptive and cutaneous inputs to the spinal cord are modulated differently during voluntary movements, suggesting a refined gating mechanism of sensory signals according to behavior.

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Synchronous Infra-Slow Bursting in the Mouse Accessory Olfactory Bulb Emerge from Interplay between Intrinsic Neuronal Dynamics and Network Connectivity

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Rhythmic neuronal activity of multiple frequency bands has been described in many brain areas and attributed to numerous brain functions. Among these, little is known about the mechanism and role of infra-slow oscillations, which have been demonstrated recently in the mouse accessory olfactory bulb (AOB). Along with prolonged responses to stimuli and distinct network connectivity, they inexplicably affect the AOB processing of social relevant stimuli. Here, we show that assemblies of AOB mitral cells are synchronized by lateral interactions through chemical and electrical synapses. Using a network model, we demonstrate that the synchronous oscillations in these assemblies emerge from interplay between intrinsic membrane properties and network connectivity. As a consequence, the AOB network topology, in which each mitral cell receives input from multiple glomeruli, enables integration of chemosensory stimuli over extended time scales by interglomerular synchrony of infra-slow bursting. These results provide a possible functional significance for the distinct AOB physiology and topology. Beyond the AOB, this study presents a general model for synchronous infra-slow bursting in neuronal networks.

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Ventrolateral Striatal Medium Spiny Neurons Positively Regulate Food-Incentive, Goal-Directed Behavior Independently of D1 and D2 Selectivity

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The ventral striatum is involved in motivated behavior. Akin to the dorsal striatum, the ventral striatum contains two parallel pathways: the striatomesencephalic pathway consisting of dopamine receptor Type 1-expressing medium spiny neurons (D1-MSNs) and the striatopallidal pathway consisting of D2-MSNs. These two genetically identified pathways are thought to encode opposing functions in motivated behavior. It has also been reported that D1/D2 genetic selectivity is not attributed to the anatomical discrimination of two pathways. We wanted to determine whether D1- and D2-MSNs in the ventral striatum functioned in an opposing manner as previous observations claimed, and whether D1/D2 selectivity corresponded to a functional segregation in motivated behavior of mice. To address this question, we focused on the lateral portion of ventral striatum as a region implicated in food-incentive, goal-directed behavior, and recorded D1 or D2-MSN activity by using a gene-encoded ratio-metric Ca^{2+} indicator and by constructing a fiberphotometry system, and manipulated their activities via optogenetic inhibition during ongoing behaviors. We observed concurrent event-related compound Ca^{2+} elevations in ventrolateral D1- and D2-MSNs, especially at trial start cue-related and first lever press-related times. D1 or D2 selective optogenetic inhibition just after the trial start cue resulted in a reduction of goal-directed behavior, indicating a shared coding of motivated behavior by both populations at this time. Only D1-selective inhibition just after the first lever press resulted in the reduction of behavior, indicating D1-MSN-specific coding at that specific time. Our data did not support opposing encoding by both populations in food-incentive, goal-directed behavior.

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Evidence for an Evolutionarily Conserved Memory Coding Scheme in the Mammalian Hippocampus

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Decades of research identify the hippocampal formation as central to memory storage and recall. Events are stored via distributed population codes, the parameters of which (e.g., sparsity and overlap) determine both storage capacity and fidelity. However, it remains unclear whether the parameters governing information storage are similar between species. Because episodic memories are rooted in the space in which they are experienced, the hippocampal response to navigation is often used as a proxy to study memory. Critically, recent studies in rodents that mimic the conditions typical of navigation studies in humans and nonhuman primates (i.e., virtual reality) show that reduced sensory input alters hippocampal representations of space. The goal of this study was to quantify this effect and determine whether there are commonalities in information storage across species. Using functional molecular imaging, we observe that navigation in virtual environments elicits activity in fewer CA1 neurons relative to real-world conditions. Conversely, comparable neuronal activity is observed in hippocampus region CA3 and the dentate gyrus under both conditions. Surprisingly, we also find evidence that the absolute number of neurons used to represent an experience is relatively stable between nonhuman primates and rodents. We propose that this convergence reflects an optimal ensemble size for episodic memories.

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BEHAVIORAL/COGNITIVE

Structural and Functional Cortical Connectivity Mediating Cross Education of Motor Function

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Cross-education (CE) is the process whereby training with one limb leads to subsequent improvement in performance by the opposite untrained limb. We used multimodal neuroimaging in humans to investigate the mediating neural mechanisms by relating quantitative estimates of functional and structural cortical connectivity to individual levels of interlimb transfer. Resting-state (rs)-fMRI and diffusion weighted imaging (DWI) scans were undertaken before unilateral ballistic wrist flexion training. The rs-fMRI sequence was repeated immediately afterward. The increase in performance of the untrained limb was 83.6% of that observed for the trained limb and significantly greater than that of a control group who undertook no training. Functional connectivity in the resting motor network between right and left supplementary motor areas (SMA) was elevated after training. These changes were not, however, correlated with individual levels of transfer. Analysis of the DWI data using constrained spherical deconvolution-based tractography indicated that fractional anisotropy and apparent fiber density in tracts connecting bilateral SMA were negatively correlated with and predictive of transfer. The findings suggest that interhemispheric interactions between bilateral SMA play an instrumental role in CE and that the structural integrity of the connecting white matter pathways influences the level of transfer.

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Neural Predictors of Decisions to Cognitively Control Emotion

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Deciding to control emotional responses is a fundamental means of responding to environmental challenges, but little is known about the neural mechanisms that predict the outcome of such decisions. We used fMRI to test whether human brain responses during initial viewing of negative images could be used to predict decisions to regulate affective responses to those images. Our results revealed the following: (1) decisions to regulate were more frequent in individuals exhibiting higher average levels of activity within the amygdala and regions of PFC known a priori to be involved in the cognitive control of emotion and (2) within-person expression of a distributed brain pattern associated with regulating emotion predicted choosing to regulate responses to particular stimuli beyond the predictive value of stimulus intensity or self-reports of emotion. These results demonstrate the behavioral relevance of variability in brain responses to aversive stimuli and provide a model that leverages this variability to predict behavior.

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Temperature Manipulation in Songbird Brain Implicates the Premotor Nucleus HVC in Birdsong Syntax

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Variable motor sequences of animals are often structured and can be described by probabilistic transition rules between action elements. Examples include the songs of many songbird species such as the Bengalese finch, which consist of stereotypical syllables sequenced according to probabilistic rules (song syntax). The neural mechanisms behind such rules are poorly understood. Here, we investigate where the song syntax is encoded in the brain of the Bengalese finch by rapidly and reversibly manipulating the temperature in the song production pathway. Cooling the premotor nucleus HVC (proper name) slows down the song tempo, consistent with the idea that HVC controls moment-to-moment timings of acoustic features in the syllables. More importantly, cooling HVC alters the transition probabilities between syllables. Cooling HVC reduces the number of repetitions of long-repeated syllables and increases the randomness of syllable sequences. In contrast, cooling the downstream motor area RA (robust nucleus of the arcopallium), which is critical for singing, does not affect the song syntax. Unilateral cooling of HVC shows that control of syllables is mostly lateralized to the left HVC, whereas transition probabilities between the syllables can be affected by cooling HVC in either hemisphere to varying degrees. These results show that HVC is a key site for encoding song syntax in the Bengalese finch. HVC is thus involved both in encoding timings within syllables and in sequencing probabilistic transitions between syllables. Our finding suggests that probabilistic selections and fine-grained timings of action elements can be integrated within the same neural circuits.

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Identity-Specific Reward Representations in Orbitofrontal Cortex Are Modulated by Selective Devaluation

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Goal-directed behavior is sensitive to the current value of expected outcomes. This requires independent representations of specific rewards, which have been linked to orbitofrontal cortex (OFC) function. However, the mechanisms by which the human brain updates specific goals on the fly, and translates those updates into choices, have remained unknown. Here we implemented selective devaluation of appetizing food odors in combination with pattern-based neuroimaging and a decision-making task. We found that in a hungry state, participants chose to smell high-intensity versions of two value-matched food odor rewards. After eating a meal corresponding to one of the two odors, participants switched choices toward the low intensity of the sated odor but continued to choose the high intensity of the nonsated odor. This sensory-specific behavioral effect was mirrored by pattern-based changes in fMRI signal in lateral posterior OFC, where specific reward identity representations were altered after the meal for the sated food odor but retained for the nonsated counterpart. In addition, changes in functional connectivity between the OFC and general value coding in ventromedial prefrontal cortex (vmPFC) predicted individual differences in satiety-related choice behavior. These findings demonstrate how flexible representations of specific rewards in the OFC are updated by devaluation, and how functional connections to vmPFC reflect the current value of outcomes and guide goal-directed behavior.

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Motor Learning Enhances Use-Dependent Plasticity

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Motor behaviors are shaped not only by current sensory signals but also by the history of recent experiences. For instance, repeated movements toward a particular target bias the subsequent movements toward that target direction. This process, called use-dependent plasticity (UDP), is considered a basic and goal-independent way of forming motor memories. Most studies consider movement history as the critical component that leads to UDP (Classen et al., 1998; Verstynen and Sabes, 2011). However, the effects of learning (i.e., improved performance) on UDP during movement repetition have not been investigated. Here, we used transcranial magnetic stimulation in two experiments to assess plasticity changes occurring in the primary motor cortex after individuals repeated reinforced and nonreinforced actions. The first experiment assessed whether learning a skill task modulates UDP. We found that a group that successfully learned the skill task showed greater UDP than a group that did not accumulate learning, but made comparable repeated actions. The second experiment aimed to understand the role of reinforcement learning in UDP while controlling for reward magnitude and action kinematics. We found that providing subjects with a binary reward without visual feedback of the cursor led to increased UDP effects. Subjects in the group that received comparable reward not associated with their actions maintained the previously induced UDP. Our findings illustrate how reinforcing consistent actions strengthens use-dependent memories and provide insight into operant mechanisms that modulate plastic changes in the motor cortex.

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Individual Differences in Resting Corticospinal Excitability Are Correlated with Reaction Time and GABA Content in Motor Cortex

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Individuals differ in the intrinsic excitability of their corticospinal pathways and, perhaps more generally, their entire nervous system. At present, we have little understanding of the mechanisms underlying these differences and how variation in intrinsic excitability relates to behavior. Here, we examined the relationship between individual differences in intrinsic corticospinal excitability, local cortical GABA levels, and reaction time (RT) in a group of 20 healthy human adults. We measured corticospinal excitability at rest with transcranial magnetic stimulation, local concentrations of basal GABA with magnetic resonance spectroscopy, and RT with a behavioral task. All measurements were repeated in two separate sessions, and tests of reliability confirmed the presence of stable individual differences. There was a negative correlation between corticospinal excitability and RT, such that larger motor-evoked potentials (MEPs) measured at rest were associated with faster RTs. Interestingly, larger MEPs were associated with higher levels of GABA in M1, but not in three other cortical regions. Together, these results suggest that individuals with more excitable corticospinal pathways are faster to initiate planned responses and have higher levels of GABA within M1, possibly to compensate for a more excitable motor system.

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Mouth and Voice: A Relationship between Visual and Auditory Preference in the Human Superior Temporal Sulcus

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Cortex in and around the human posterior superior temporal sulcus (pSTS) is known to be critical for speech perception. The pSTS responds to both the visual modality (especially biological motion) and the auditory modality (especially human voices). Using fMRI in single subjects with no spatial smoothing, we show that visual and auditory selectivity are linked. Regions of the pSTS were identified that preferred visually presented moving mouths (presented in isolation or as part of a whole face) or moving eyes. Mouth-preferring regions responded strongly to voices and showed a significant preference for vocal compared with nonvocal sounds. In contrast, eye-preferring regions did not respond to either vocal or nonvocal sounds. The converse was also true: regions of the pSTS that showed a significant response to speech or preferred vocal to nonvocal sounds responded more strongly to visually presented mouths than eyes. These findings can be explained by environmental statistics. In natural environments, humans see visual mouth movements at the same time as they hear voices, while there is no auditory accompaniment to visual eye movements. The strength of a voxel's preference for visual mouth movements was strongly correlated with the magnitude of its auditory speech response and its preference for vocal sounds, suggesting that visual and auditory speech features are coded together in small populations of neurons within the pSTS.

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Resting-State Network Topology Differentiates Task Signals across the Adult Life Span

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Brain network connectivity differs across individuals. For example, older adults exhibit less segregated resting-state subnetworks relative to younger adults (Chan et al., 2014). It has been hypothesized that individual differences in network connectivity impact the recruitment of brain areas during task execution. While recent studies have described the spatial overlap between resting-state functional correlation (RSFC) subnetworks and task-evoked activity, it is unclear whether individual variations in the connectivity pattern of a brain area (topology) relates to its activity during task execution. We report data from 238 cognitively normal participants (humans), sampled across the adult life span (20–89 years), to reveal that RSFC-based network organization systematically relates to the recruitment of brain areas across two functionally distinct tasks (visual and semantic). The functional activity of brain areas (network nodes) were characterized according to their patterns of RSFC: nodes with relatively greater connections to nodes in their own functional system (“non-connector” nodes) exhibited greater activity than nodes with relatively greater connections to nodes in other systems (“connector” nodes). This “activation selectivity” was specific to those brain systems that were central to each of the tasks. Increasing age was accompanied by less differentiated network topology and a corresponding reduction in activation selectivity (or differentiation) across relevant network nodes. The results provide evidence that connectional topology of brain areas quantified at rest relates to the functional activity of those areas during task. Based on these findings, we propose a novel network-based theory for previous reports of the “dedifferentiation” in brain activity observed in aging.

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Are There Multiple Kinds of Episodic Memory? An fMRI Investigation Comparing Autobiographical and Recognition Memory Tasks

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What brain regions underlie retrieval from episodic memory? The bulk of research addressing this question with fMRI has relied upon recognition memory for materials encoded within the laboratory. Another, less dominant tradition has used autobiographical methods, whereby people recall events from their lifetime, often after being cued with words or pictures. The current study addresses how the neural substrates of successful memory retrieval differed as a function of the targeted memory when the experimental parameters were held constant in the two conditions (except for instructions). Human participants studied a set of scenes and then took two types of memory test while undergoing fMRI scanning. In one condition (the picture memory test), participants reported for each scene (32 studied, 64 nonstudied) whether it was recollected from the prior study episode. In a second condition (the life memory test), participants reported for each scene (32 studied, 64 nonstudied) whether it reminded them of a specific event from their preexperimental lifetime. An examination of successful retrieval (yes responses) for recently studied scenes for the two test types revealed pronounced differences; that is, autobiographical retrieval instantiated with the life memory test preferentially activated the default mode network, whereas hits in the picture memory test preferentially engaged the parietal memory network as well as portions of the frontoparietal control network. When experimental cueing parameters are held constant, the neural underpinnings of successful memory retrieval differ when remembering life events and recently learned events.

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NEUROBIOLOGY OF DISEASE

Histone Deacetylase Inhibitors Protect Against Pyruvate Dehydrogenase Dysfunction in Huntington's Disease

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Transcriptional deregulation and changes in mitochondrial bioenergetics, including pyruvate dehydrogenase (PDH) dysfunction, have been described in Huntington's disease (HD). We showed previously that the histone deacetylase inhibitors (HDACIs) trichostatin A and sodium butyrate (SB) ameliorate mitochondrial function in cells expressing mutant huntingtin. In this work, we investigated the effect of HDACIs on the regulation of PDH activity in striatal cells derived from HD knock-in mice and YAC128 mice. Mutant cells exhibited decreased PDH activity and increased PDH E1 α phosphorylation/inactivation, accompanied by enhanced protein levels of PDH kinases 1 and 3 (PDK1 and PDK3). Exposure to dichloroacetate, an inhibitor of PDKs, increased mitochondrial respiration and decreased production of reactive oxygen species in mutant cells, emphasizing PDH as an interesting therapeutic target in HD. Treatment with SB and sodium phenylbutyrate, another HDACI, recovered cell viability and overall mitochondrial metabolism in mutant cells. Exposure to SB also suppressed hypoxia-inducible factor-1 (HIF-1 α) stabilization and decreased the transcription of the two most abundant PDK isoforms, PDK2 and PDK3, culminating in increased PDH activation in mutant cells. Concordantly, PDK3 knockdown improved mitochondrial function, emphasizing the role of PDK3 inactivation on the positive effects achieved by SB treatment. YAC128 mouse brain presented higher mRNA levels of PDK1–3 and PDH phosphorylation and decreased energy levels that were significantly ameliorated after SB treatment. Furthermore, enhanced motor learning and coordination were observed in SB-treated YAC128 mice. These results suggest that HDACIs, particularly SB, promote the activity of PDH in the HD brain, helping to counteract HD-related deficits in mitochondrial bioenergetics and motor function.

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