



Cover legend: This confocal image from a postnatal day 26 mouse brain shows three cortical astrocytes labeled with GFAP (red) and membrane-targeted GFP (AAV5-gfaABC1D-lckGFP; cyan). Rosenberg et al. used this technique to analyze the morphology of individual astrocytes as they investigated the role of noradrenergic signaling in astrocyte maturation. See the manuscript by Rosenberg et al. (pages 8621–8636) for more information.

Cover image: Marci Rosenberg.

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8827 *Retraction:* The article “N-Cadherin Promotes Recruitment and Migration of Neural Progenitor Cells from the SVZ Neural Stem Cell Niche into Demyelinated Lesions,” by Michael Klingener, Manideep Chavali, Jagdeep Singh, Nadia McMillan, Alexandra Coomes, Peter J. Dempsey, Emily I. Chen, and Adan Aguirre, appeared on pages 9590–9606 of the July 16, 2014 issue. A retraction for this article appears on page 8827.

8828 **Acknowledgment of Reviewers**

8838 **Collaborating Reviewers**

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Articles

CELLULAR/MOLECULAR

Short- and Long-Term High-Fat Diet Exposure Differentially Alters Phasic and Tonic GABAergic Signaling onto Lateral Orbitofrontal Pyramidal Neurons

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The chronic consumption of caloric dense high-fat foods is a major contributor to increased body weight, obesity, and other chronic health conditions. The orbitofrontal cortex (OFC) is critical in guiding decisions about food intake and is altered with diet-induced obesity. Obese rodents have altered morphologic and synaptic electrophysiological properties in the lateral orbitofrontal cortex (lOFC). Yet the time course by which exposure to a high-fat diet (HFD) induces these changes is poorly understood. Here, male mice are exposed to either short-term (7 d) or long-term (90 d) HFD. Long-term HFD exposure increases body weight, and glucose signaling compared with short-term HFD or a standard control diet (SCD). Both short and long-term HFD exposure increased the excitability of lOFC pyramidal neurons. However, phasic and tonic GABAergic signaling was differentially altered depending on HFD exposure length, such that tonic GABAergic signaling was decreased with early exposure to the HFD and phasic signaling was changed with long-term diet exposure. Furthermore, alterations in the short-term diet exposure were transient, as removal of the diet restored electrophysiological characteristics similar to mice fed SCD, whereas long-term HFD electrophysiological changes were persistent and remained after HFD removal. Finally, we demonstrate that changes in reward devaluation occur early with diet exposure. Together, these results suggest that the duration of HFD exposure differentially alters lOFC function and provides mechanistic insights into the susceptibility of the OFC to impairments in outcome devaluation.

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Rescue of Normal Excitability in LGI1-Deficient Epileptic Neurons

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Leucine-rich glioma inactivated 1 (LGI1) is a glycoprotein secreted by neurons, the deletion of which leads to autosomal dominant lateral temporal lobe epilepsy. We previously showed that LGI1 deficiency in a mouse model (i.e., knock-out for LGI1 or KO-Lgi1) decreased Kv1.1 channel density at the axon initial segment (AIS) and at presynaptic terminals, thus enhancing both intrinsic excitability and glutamate release. However, it is not known whether normal excitability can be restored in epileptic neurons. Here, we show that the selective expression of LGI1 in KO-Lgi1 neurons from mice of both sexes, using single-cell electroporation, reduces intrinsic excitability and restores both the Kv1.1-mediated D-type current and Kv1.1 channels at the AIS. In addition, we show that the homeostatic-like shortening of the AIS length observed in KO-Lgi1 neurons is prevented in neurons electroporated with the Lgi1 gene. Furthermore, we reveal a spatial gradient of intrinsic excitability that is centered on the electroporated neuron. We conclude that expression of LGI1 restores normal excitability through functional Kv1 channels at the AIS.

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In Vivo Optical Interrogation of Neuronal Responses to Genetic, Cell Type-Specific Silencing

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We established a low background, Cre-dependent version of the inducible Tet-On system for fast, cell type-specific transgene expression *in vivo*. Coexpression of a constitutive, Cre-dependent fluorescent marker selectively allowed single-cell analyses before and after inducible, Tet-dependent transgene expression. Here, we used this method for precise, acute manipulation of neuronal activity in the living brain. The goal was to study neuronal network homeostasis at cellular resolution. Single induction of the potassium channel Kir2.1 produced cell type-specific silencing within hours that lasted for at least 3 d. Longitudinal *in vivo* imaging of spontaneous calcium transients and neuronal morphology demonstrated that prolonged silencing did not alter spine densities or synaptic input strength. Furthermore, selective induction of Kir2.1 in parvalbumin interneurons increased the activity of surrounding neurons in a distance-dependent manner. This high-resolution, inducible interference and interval imaging of individual cells (high I⁵, HighFive) method thus allows visualizing temporally precise, genetic perturbations of defined cells.

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β -Adrenergic Signaling Promotes Morphological Maturation of Astrocytes in Female Mice

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Astrocytes play essential roles in the developing nervous system, including supporting synapse function. These astrocyte support functions emerge coincident with brain maturation and may be tailored in a region-specific manner. For example, gray matter astrocytes have elaborate synapse-associated processes and are morphologically and molecularly distinct from white matter astrocytes. This raises the question of whether there are unique environmental cues that promote gray matter astrocyte identity and synaptogenic function. We previously identified adrenergic receptors as preferentially enriched in developing gray versus white matter astrocytes, suggesting that noradrenergic signaling could be a cue that promotes the functional maturation of gray matter astrocytes. We first characterized noradrenergic projections during postnatal brain development in mouse and human, finding that process density was higher in the gray matter and increased concurrently with astrocyte maturation. RNA sequencing revealed that astrocytes in both species expressed α - and β -adrenergic receptors. We found that stimulation of β -adrenergic receptors increased primary branching of rodent astrocytes *in vitro*. Conversely, astrocyte-conditional knockout of the β 1-adrenergic receptor reduced the size of gray matter astrocytes and led to dysregulated sensorimotor integration in female mice. These studies suggest that adrenergic signaling to developing astrocytes impacts their morphology and has implications for adult behavior, particularly in female animals. More broadly, they demonstrate a mechanism through which environmental cues impact astrocyte development. Given the key roles of norepinephrine in brain states, such as arousal, stress, and learning, these findings could prompt further inquiry into how developmental stressors impact astrocyte development and adult brain function.

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Changes in Cortical Microstructure of the Human Brain Resulting from Long-Term Motor Learning

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The mechanisms subserving motor skill acquisition and learning in the intact human brain are not fully understood. Previous studies in animals have demonstrated a causal relationship between motor learning and structural rearrangements of synaptic connections, raising the question of whether neurite-specific changes are also observable in humans. Here, we use advanced diffusion magnetic resonance imaging (MRI), sensitive to dendritic and axonal processes, to investigate neuroplasticity in response to long-term motor learning. We recruited healthy male and female human participants (age range 19–29) who learned a challenging dynamic balancing task (DBT) over four consecutive weeks. Diffusion MRI signals were fitted using Neurite Orientation Dispersion and Density Imaging (NODDI), a theory-driven biophysical model of diffusion, yielding measures of tissue volume, neurite density and the organizational complexity of neurites. While NODDI indices were unchanged and reliable during the control period, neurite orientation dispersion increased significantly during the learning period mainly in primary sensorimotor, prefrontal, premotor, supplementary, and cingulate motor areas. Importantly, reorganization of cortical microstructure during the learning phase predicted concurrent behavioral changes, whereas there was no relationship between microstructural changes during the control phase and learning. Changes in neurite complexity were independent of alterations in tissue density, cortical thickness, and intracortical myelin. Our results are in line with the notion that structural modulation of neurites is a key mechanism supporting complex motor learning in humans.

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Dissociation of Centrally and Peripherally Induced Transcranial Magnetic Stimulation Effects in Nonhuman Primates

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Transcranial magnetic stimulation (TMS) is a noninvasive brain stimulation method that is rapidly growing in popularity for studying causal brain–behavior relationships. However, its dose-dependent centrally induced neural mechanisms and peripherally induced sensory costimulation effects remain debated. Understanding how TMS stimulation parameters affect brain responses is vital for the rational design of TMS protocols. Studying these mechanisms in humans is challenging because of the limited spatiotemporal resolution of available noninvasive neuroimaging methods. Here, we leverage invasive recordings of local field potentials in a male and a female nonhuman primate (rhesus macaque) to study TMS mesoscale responses. We demonstrate that early TMS-evoked potentials show a sigmoidal dose–response curve with stimulation intensity. We further show that stimulation responses are spatially specific. We use several control conditions to dissociate centrally induced neural responses from auditory and somatosensory coactivation. These results provide crucial evidence regarding TMS neural effects at the brain circuit level. Our findings are highly relevant for interpreting human TMS studies and biomarker developments for TMS target engagement in clinical applications.

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Reward Modulates Visual Responses in the Superficial Superior Colliculus of Mice

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The processing of sensory input is constantly adapting to behavioral demands and internal states. The drive to obtain reward, e.g., searching for water when thirsty, is a strong behavioral demand and associating the reward with its source, a certain environment or action, is paramount for survival. Here, we show that water reward increases subsequent visual activity in the superficial layers of the superior colliculus (SC), which receive direct input from the retina and belong to the earliest stages of visual processing. We trained mice of either sex to perform a visual decision task and recorded the activity of neurons in the SC using two-photon calcium imaging and high-density electrophysiological recordings. Responses to visual stimuli in around 20% of visually responsive neurons in the superficial SC were affected by reward delivered in the previous trial. Reward mostly increased visual responses independent from modulations due to pupil size changes. The modulation of visual responses by reward could not be explained by movements like licking. It was specific to responses to the following visual stimulus, independent of slow fluctuations in neural activity and independent of how often the stimulus was previously rewarded. Electrophysiological recordings confirmed these results and revealed that reward affected the early phase of the visual response around 80 ms after stimulus onset. Modulation of visual responses by reward, but not pupil size, significantly improved the performance of a population decoder to detect visual stimuli, indicating the relevance of reward modulation for the visual performance of the animal.

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Dissociating the Contributions of Frontal Eye Field Activity to Spatial Working Memory and Motor Preparation

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Neurons within dorsolateral prefrontal cortex (PFC) of primates are characterized by robust persistent spiking activity exhibited during the delay period of working memory tasks. This includes the frontal eye field (FEF) where nearly half of the neurons are active when spatial locations are held in working memory. Past evidence has established the FEF's contribution to the planning and triggering of saccadic eye movements as well as to the control of visual spatial attention. However, it remains unclear whether persistent delay activity reflects a similar dual role in movement planning and visuospatial working memory. We trained male monkeys to alternate between different forms of a spatial working memory task which could dissociate remembered stimulus locations from planned eye movements. We tested the effects of inactivation of FEF sites on behavioral performance in the different tasks. Consistent with previous studies, FEF inactivation impaired the execution of memory-guided saccades (MGSs), and impaired performance when remembered locations matched the planned eye movement. In contrast, memory performance was largely unaffected when the remembered location was dissociated from the correct eye movement response. Overall, the inactivation effects demonstrated clear deficits in eye movements, regardless of task type, but little or no evidence of a deficit in

spatial working memory. Thus, our results indicate that persistent delay activity in the FEF contributes primarily to the preparation of eye movements and not to spatial working memory.

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Traumatic Stress-Induced Increases in Anxiety-like Behavior and Alcohol Self-Administration Are Mediated by Central Amygdala CRF1 Neurons That Project to the Lateral Hypothalamus

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Avoidance stress coping, defined as persistent internal and/or external avoidance of stress-related stimuli, is a key feature of anxiety- and stress-related disorders, and contributes to increases in alcohol misuse after stress exposure. Previous work using a rat model of predator odor stress avoidance identified corticotropin-releasing factor (CRF) signaling via CRF Type 1 receptors (CRF1) in the CeA, as well as CeA projections to the lateral hypothalamus (LH) as key mediators of conditioned avoidance of stress-paired contexts and/or increased alcohol drinking after stress. Here, we report that CRF1-expressing CeA cells that project to the LH are preferentially activated in male and female rats that show persistent avoidance of predator odor stress-paired contexts (termed Avider rats), and that chemogenetic inhibition of these cells rescues stress-induced increases in anxiety-like behavior and alcohol self-administration in male and female Avider rats. Using slice electrophysiology, we found that prior predator odor stress exposure blunts inhibitory synaptic transmission and increases synaptic drive in CRF1 CeA-LH cells. In addition, we found that CRF bath application reduces synaptic drive in CRF1 CeA-LH cells in Non-Avoiders only. Collectively, these data show that CRF1 CeA-LH cells contribute to stress-induced increases in anxiety-like behavior and alcohol self-administration in male and female Avider rats.

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Stimulus-Induced Theta-Band LFP Oscillations Format Neuronal Representations of Social Chemosignals in the Mouse Accessory Olfactory Bulb

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Social communication is crucial for the survival of many species. In most vertebrates, a dedicated chemosensory system, the vomeronasal system (VNS), evolved to process ethologically relevant chemosensory cues. The first central processing stage of the VNS is the accessory olfactory bulb (AOB), which sends information to downstream brain regions via AOB mitral cells (AMCs). Recent studies provided important insights about the functional properties of AMCs, but little is known about the principles that govern their coordinated activity. Here, we recorded local field potentials (LFPs) and single-unit activity in the AOB of adult male and female mice during presentation of natural stimuli. Our recordings reveal prominent LFP theta-band oscillatory episodes with a characteristic spatial pattern across the AOB. Throughout an experiment, the AOB network shows varying degrees of similarity to this pattern, in a manner that depends on the sensory stimulus. Analysis of LFP signal polarity and single-unit activity indicates that oscillatory episodes are generated locally within the AOB, likely representing a reciprocal interaction between AMCs and granule cells. Notably, spike times of many AMCs are constrained to the negative LFP oscillation phase in a manner that can drastically affect integration by downstream processing stages. Based on these observations, we propose that LFP oscillations may gate, bind, and organize outgoing signals from individual AOB neurons to downstream processing stages. Our findings suggest that, as in other neuronal systems and brain regions, population-level oscillations play a key role in organizing and enhancing transmission of socially relevant chemosensory information.

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BEHAVIORAL/COGNITIVE

Changes in Behavior and Neural Dynamics across Adolescent Development

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Adolescence is an important developmental period, during which substantial changes occur in brain function and behavior. Several aspects of executive function, including response inhibition, improve during this period. Correspondingly, structural imaging studies have documented consistent decreases in cortical and subcortical gray matter volume, and postmortem histologic studies have found substantial (~40%) decreases in excitatory synapses in prefrontal cortex. Recent computational modeling work suggests that the change in synaptic density underlie improvements in task performance. These models also predict changes in neural dynamics related to the depth of attractor basins, where deeper basins can underlie better task performance. In this study, we analyzed task-related neural dynamics in a large cohort of longitudinally followed subjects (male and female) spanning early to late adolescence. We found that age correlated positively with behavioral performance in the Eriksen Flanker task. Older subjects were also characterized by deeper attractor basins around task related evoked EEG potentials during specific cognitive operations. Thus, consistent with computational models examining the effects of excitatory synaptic pruning, older adolescents showed stronger attractor dynamics during task performance.

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Accentuated Paralimbic and Reduced Mesolimbic $D_{2/3}$ -Impulsivity Associations in Parkinson's Disease

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Impulsivity is a behavioral trait that is elevated in many neuropsychiatric disorders. Parkinson's disease (PD) patients can exhibit a specific pattern of reward-seeking impulsive-compulsive behaviors (ICBs), as well as more subtle changes to generalized trait impulsivity. Prior studies in healthy controls (HCs) suggest that trait impulsivity is regulated by $D_{2/3}$ autoreceptors in mesocorticolimbic circuits. While altered $D_{2/3}$ binding is noted in ICB⁺ PD patients, there is limited prior assessment of the trait impulsivity– $D_{2/3}$ relationship in PD, and no prior direct comparison with patterns in HCs. We examined 54 PD (36 M; 18 F) and 31 sex- and age-matched HC (21 M; 10 F) subjects using [¹⁸F]fallypride, a high-affinity $D_{2/3}$ receptor ligand, to measure striatal and extrastriatal $D_{2/3}$ nondisplaceable binding potential (BP_{ND}). Subcortical and cortical assessment exclusively used ROI or exploratory-voxelwise methods, respectively. All completed the Barratt Impulsiveness Scale, a measure of trait impulsivity. Subcortical ROI analyses indicated a negative relationship between trait impulsivity and $D_{2/3}$ BP_{ND} in the ventral striatum and amygdala of HCs but not in PD. By contrast, voxelwise methods demonstrated a positive trait impulsivity– $D_{2/3}$ BP_{ND} correlation in ventral frontal olfactocentric-paralimbic cortex of subjects with PD but not HCs. Subscale analysis also highlighted different aspects of impulsivity, with significant interactions between group and motor impulsivity in the ventral striatum, and attentional impulsivity in the amygdala and frontal paralimbic cortex. These results suggest that dopamine functioning in distinct regions of the mesocorticolimbic circuit influence aspects of impulsivity, with the relative importance of regional dopamine functions shifting in the neuropharmacological context of PD.

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Stabilizing Immature Dendritic Spines in the Auditory Cortex: A Key Mechanism for mTORC1-Mediated Enhancement of Long-Term Fear Memories

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Mammalian target of rapamycin (mTOR) pathway has emerged as a key molecular mechanism underlying memory processes. Although mTOR inhibition is known to block memory processes, it remains elusive whether and how an enhancement of mTOR signaling may improve memory processes. Here we found in male mice that the administration of VO-OHpic, an inhibitor of the phosphatase and tensin homolog (PTEN) that negatively modulates AKT-mTOR pathway, enhanced auditory fear memory for days and weeks, while it left short-term memory unchanged. Memory enhancement was associated with a long-lasting increase in immature-type dendritic spines of pyramidal neurons into the auditory cortex. The persistence of spine remodeling over time arose by the interplay between PTEN inhibition and memory processes, as VO-OHpic induced only a transient immature spine growth in the somatosensory cortex, a region not involved in long-term auditory memory. Both the potentiation of fear memories and increase in immature spines were hampered by rapamycin, a selective inhibitor of mTORC1. These data revealed that memory can be potentiated over time by the administration of a selective PTEN inhibitor. In addition to disclosing new information on the cellular mechanisms underlying long-term memory maintenance, our study provides new insights on the molecular processes that aid enhancing memories over time.

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Menopause Status and Within-Group Differences in Chronological Age Affect the Functional Neural Correlates of Spatial Context Memory in Middle-Aged Females

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Reductions in the ability to encode and retrieve past experiences in rich spatial contextual detail (episodic memory) are apparent by midlife—a time when most females experience spontaneous menopause. Yet, little is known about how menopause status affects episodic memory-related brain activity at encoding and retrieval in middle-aged premenopausal and postmenopausal females, and whether any observed group differences in brain activity and memory performance correlate with chronological age within group. We conducted an event-related task fMRI study of episodic memory for spatial context to address this knowledge gap. Multivariate behavioral partial least squares was used to investigate how chronological age and retrieval accuracy correlated with brain activity in 31 premenopausal females (age range, 39.55–53.30 years; mean age, 44.28 years; SD age, 3.12 years) and 41 postmenopausal females (age range, 46.70–65.14 years; mean age, 57.56 years; SD age, 3.93 years). We found that postmenopausal status, and advanced age within postmenopause, was associated with lower spatial context memory. The fMRI analysis showed that only in postmenopausal females, advanced age was correlated with decreased activity in occipitotemporal, parahippocampal, and inferior parietal cortices during encoding and retrieval, and poorer spatial context memory performance. In contrast, only premenopausal females exhibited an overlap in encoding and retrieval activity in angular gyrus, midline cortical regions, and prefrontal cortex, which correlated with better spatial context retrieval accuracy. These results highlight how menopause status and chronological age, nested within menopause group, affect episodic memory and its neural correlates at midlife.

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Prefrontal Cortex Codes Representations of Target Identity and Feature Uncertainty

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Many objects in the real world have features that vary over time, creating uncertainty in how they will look in the future. This uncertainty makes statistical knowledge about the likelihood of features critical to attention demanding processes such as visual search. However, little is known about how the uncertainty of visual features is integrated into predictions about search targets in the brain. In the current study, we test the idea that regions prefrontal cortex code statistical knowledge about search targets before the onset of search. Across 20 human participants (13 female; 7 male), we observe target identity in the multivariate pattern and uncertainty in the overall activation of dorsolateral prefrontal cortex (DLPFC) and inferior frontal junction (IFJ) in advance of the search display. This indicates that the target identity (mean) and uncertainty (variance) of the target distribution are coded independently within the same regions. Furthermore, once the search display appears the univariate IFJ signal scaled with the distance of the actual target from the expected mean, but more so when expected variability was low. These results inform neural theories of attention by showing how the prefrontal cortex represents both the identity and expected variability of features in service of top-down attentional control.

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An Accumulating Neural Signal Underlying Binocular Rivalry Dynamics

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During binocular rivalry, conflicting images are presented one to each eye and perception alternates stochastically between them. Despite stable percepts between alternations, modeling suggests that neural signals representing the two images change gradually, and that the duration of stable percepts are determined by the time required for these signals to reach a threshold that triggers an alternation. However, direct physiological evidence for such signals has been lacking. Here, we identify a neural signal in the human visual cortex that shows these predicted properties. We measured steady-state visual evoked potentials (SSVEPs) in 84 human participants (62 females, 22 males) who were presented with orthogonal gratings, one to each eye, flickering at different frequencies. Participants indicated their percept while EEG data were collected. The time courses of the SSVEP amplitudes at the two frequencies were then compared across different percept durations, within participants. For all durations, the amplitude of signals corresponding to the suppressed stimulus increased and the amplitude corresponding to the dominant stimulus decreased throughout the percept. Critically, longer percepts were characterized by more gradual increases in the suppressed signal and more gradual decreases of the dominant signal. Changes in signals were similar and rapid at the end of all percepts, presumably reflecting perceptual transitions. These features of the SSVEP time courses are well predicted by a model in which perceptual

transitions are produced by the accumulation of noisy signals. Identification of this signal underlying binocular rivalry should allow strong tests of neural models of rivalry, bistable perception, and neural suppression.

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Feature-Specific Saliency Maps in Human Cortex

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Priority map theory is a leading framework for understanding how various aspects of stimulus displays and task demands guide visual attention. Per this theory, the visual system computes a priority map, which is a representation of visual space indexing the relative importance, or priority, of locations in the environment. Priority is computed based on both saliency, defined based on image-computable properties; and relevance, defined by an individual's current goals, and is used to direct attention to the highest-priority locations for further processing. Computational theories suggest that priority maps identify salient locations based on individual feature dimensions (e.g., color, motion), which are integrated into an aggregate priority map. While widely accepted, a core assumption of this framework, the existence of independent feature dimension maps in visual cortex, remains untested. Here, we tested the hypothesis that retinotopic regions selective for specific feature dimensions (color or motion) in human cortex act as neural feature dimension maps, indexing salient locations based on their preferred feature. We used fMRI activation patterns to reconstruct spatial maps while male and female human participants viewed stimuli with salient regions defined by relative color or motion direction. Activation in reconstructed spatial maps was localized to the salient stimulus position in the display. Moreover, the strength of the stimulus representation was strongest in the ROI selective for the saliency-defining feature. Together, these results suggest that feature-selective extrastriate visual regions highlight salient locations based on local feature contrast within their preferred feature dimensions, supporting their role as neural feature dimension maps.

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NEUROBIOLOGY OF DISEASE

Predicting Atrophy of the Cochlear Stria Vascularis from the Shape of the Threshold Audiogram

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Several lines of evidence have suggested that steeply sloping audiometric losses are caused by hair cell degeneration, while flat audiometric losses are caused by stria atrophy, but this concept has never been rigorously tested in human specimens. Here, we systematically compare audiograms and cochlear histopathology in 160 human cases from the archival collection of celloidin-embedded temporal bones at the Massachusetts Eye and Ear. The dataset included 106 cases from a prior study of normal-aging ears, and an additional 54 cases selected by combing the database for flat audiograms. Audiogram shapes were classified algorithmically into five groups according to the relation between flatness (i.e., SD of hearing levels across all frequencies) and low-frequency pure-tone average (i.e., mean at 0.25, 0.5, and 1.0 kHz). Outer and inner hair cell losses, neural degeneration, and stria atrophy were all quantified as a function of cochlear location in each case. Results showed that stria atrophy was worse in the apical than the basal half of the cochlea and was worse in females than in males. The degree of stria atrophy was uncorrelated with audiogram flatness. Apical atrophy was correlated with low-frequency thresholds and basal atrophy with high-frequency thresholds, and the former correlation was higher. However, a multivariable regression with all histopathological measures as predictors and audiometric thresholds as the outcome showed that stria atrophy was a significant predictor of threshold shift only in the low-frequency region, and, even there, the contribution of outer hair cell damage was larger.

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Nascent A β 42 Fibrillization in Synaptic Endosomes Precedes Plaque Formation in a Mouse Model of Alzheimer's-like β -Amyloidosis

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Accumulation of amyloid- β peptide (A β) aggregates in synapses may contribute to the profound synaptic loss characteristic of Alzheimer's disease (AD). The origin of synaptic A β aggregates remains elusive, but loss of endosomal proteostasis may trigger their formation. In this study, we identified the synaptic compartments where A β accumulates, and performed a longitudinal analysis of synaptosomes isolated from brains of TgCRND8 APP transgenic mice of either sex. To evaluate the specific contribution of A β -degrading protease endothelin-converting enzyme (ECE-1) to synaptic/endosomal A β homeostasis, we analyzed the effect of partial *Ece1* KO in brain and complete *ECE1* KO in SH-SY5Y cells. Global inhibition of ECE family members was used to further

assess their role in preventing synaptic A β accumulation. Results showed that, before extracellular amyloid deposition, synapses were burdened with detergent-soluble A β monomers, oligomers, and fibrils. Levels of all soluble A β species declined thereafter, as A β 42 turned progressively insoluble and accumulated in A β -producing synaptic endosomal vesicles with characteristics of multivesicular bodies. Accordingly, fibrillar A β was detected in brain exosomes. ECE-1-deficient mice had significantly increased endogenous synaptosomal A β 42 levels, and protease inhibitor experiments showed that, in TgCRND8 mice, synaptic A β 42 became nearly resistant to degradation by ECE-related proteases. Our study supports that A β accumulating in synapses is produced locally, within endosomes, and does not require the presence of amyloid plaques. ECE-1 is a determinant factor controlling the accumulation and fibrillization of nascent A β in endosomes and, in TgCRND8 mice, A β overproduction causes rapid loss of A β 42 solubility that curtails ECE-mediated degradation.

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