



Cover legend: Coronal section of the olfactory epithelium showing the dorsal region stained against NQ01 (red), and absence of α -synuclein pathology by detecting pSer129- α -syn (green) in wild type mice. For more information, see the article by Martin-Lopez et al. (pages 1051–1071).

Cover image: Eduardo Martin-Lopez.

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Articles

CELLULAR/MOLECULAR

NCK1 Modulates Neuronal Actin Dynamics and Promotes Dendritic Spine, Synapse, and Memory Formation

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Memory formation and maintenance is a dynamic process involving the modulation of the actin cytoskeleton at synapses. Understanding the signaling pathways that contribute to actin modulation is important for our understanding of synapse formation and function, as well as learning and memory. Here, we focused on the importance of the actin regulator, noncatalytic region of tyrosine kinase adaptor protein 1 (NCK1), in hippocampal dependent behaviors and development. We report that male mice lacking NCK1 have impairments in both short-term and working memory, as well as spatial learning. Additionally, we report sex differences in memory impairment showing that female mice deficient in NCK1 fail at reversal learning in a spatial learning task. We find that NCK1 is expressed in postmitotic neurons but is dispensable for neuronal proliferation and migration in the developing hippocampus. Morphologically, NCK1 is not necessary for overall neuronal dendrite development. However, neurons lacking NCK1 have lower dendritic spine and synapse densities *in vitro* and *in vivo*. EM analysis reveal increased postsynaptic density (PSD) thickness in the hippocampal CA1 region of NCK1-deficient mice. Mechanistically, we find the turnover of actin-filaments in dendritic spines is accelerated in neurons that lack NCK1. Together, these findings suggest that NCK1 contributes to hippocampal-dependent memory by stabilizing actin dynamics and dendritic spine formation.

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Muscarinic Acetylcholine Receptors Modulate HCN Channel Properties in Vestibular Ganglion Neurons

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Efferent modulation of vestibular afferent excitability is linked to muscarinic signaling cascades that close low-voltage-gated potassium channels (i.e., KCNQ). Here, we show that muscarinic signaling cascades also depolarize the activation range of hyperpolarization-activated cyclic-nucleotide gated (HCN) channels. We compared the voltage activation range and kinetics of HCN channels and induced firing patterns before and after administering the muscarinic acetylcholine receptor (mAChR) agonist oxotremorine-M (Oxo-M) in dissociated vestibular ganglion neurons (VGNs) from rats of either sex using perforated whole-cell patch-clamp methods. Oxo-M depolarized HCN channels' half-activation voltage ($V_{1/2}$) and sped up the rate of activation near resting potential twofold. HCN channels in large-diameter and/or transient firing VGN (putative cell bodies of irregular firing neuron from central epithelial zones) had relatively depolarized $V_{1/2}$ in control solution and were less sensitive to mAChR activation than those found in small-diameter VGN with sustained firing patterns (putatively belonging to regular firing afferents). The impact of mAChR on HCN channels is not a direct consequence of closing KCNQ channels since pretreating the cells with Linopirdine, a KCNQ channel blocker, did not prevent HCN channel depolarization by Oxo-M. Efferent signaling promoted ion channel configurations that were favorable to highly regular spiking in some VGN, but not others. This is consistent with previous observations that low-voltage gated potassium currents in VGN are conducted by mAChR agonist-sensitive and -insensitive channels. Connecting efferent signaling to HCN channels is significant because of the channel's impact on spike-timing regularity and nonchemical transmission between Type I hair cells and vestibular afferents.

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DEVELOPMENT/PLASTICITY/REPAIR

A Unique Role for Protocadherin γ C3 in Promoting Dendrite Arborization through an Axin1-Dependent Mechanism

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The establishment of a functional cerebral cortex depends on the proper execution of multiple developmental steps, culminating in dendritic and axonal outgrowth and the formation and maturation of synaptic connections. Dysregulation of these processes can result in improper neuronal connectivity, including that associated with various neurodevelopmental disorders. The γ -Protocadherins (γ -Pcdhs), a family of 22 distinct cell adhesion molecules that share a C-terminal cytoplasmic domain, are involved in multiple aspects of neurodevelopment including neuronal survival, dendrite arborization, and synapse development. The extent to which individual γ -Pcdh family members play unique versus common roles remains unclear. We demonstrated previously that the γ -Pcdh-C3 isoform (γ C3), via its unique “variable” cytoplasmic domain (VCD), interacts in cultured cells with Axin1, a Wnt-pathway scaffold protein that regulates the differentiation and morphology of neurons. Here, we confirm that γ C3 and Axin1 interact in the cortex *in vivo* and show that both male and female mice specifically lacking γ C3 exhibit disrupted Axin1 localization to synaptic fractions, without obvious changes in dendritic spine density or morphology. However, both male and female γ C3 knock-out mice exhibit severely decreased dendritic complexity of cortical pyramidal neurons that is not observed in mouse lines lacking several other γ -Pcdh isoforms. Combining knock-out with rescue constructs in cultured cortical neurons pooled from both male and female mice, we show that γ C3 promotes dendritic arborization through an Axin1-dependent mechanism mediated through its VCD. Together, these data identify a novel mechanism through which γ C3 uniquely regulates the formation of cortical circuitry.

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SYSTEMS/CIRCUITS

Tilt in Place Microscopy: a Simple, Low-Cost Solution to Image Neural Responses to Body Rotations

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Animals use information about gravity and other destabilizing forces to balance and navigate through their environment. Measuring how brains respond to these forces requires considerable technical knowledge and/or financial resources. We present a simple alternative—Tilt In Place Microscopy (TIPM), a low-cost and noninvasive way to measure neural activity following rapid changes in body orientation. Here, we used TIPM to study vestibulospinal neurons in larval zebrafish during and immediately after roll tilts. Vestibulospinal neurons responded with reliable increases in activity that varied as a function of ipsilateral tilt amplitude. TIPM differentiated tonic (i.e., sustained tilt) from phasic responses, revealing coarse topography of stimulus sensitivity in the lateral vestibular nucleus. Neuronal variability across repeated sessions was minor relative to trial-to-trial variability, allowing us to use TIPM for longitudinal studies of the same neurons across two developmental time points. There, we observed global increases in response strength and systematic changes in the neural representation of stimulus direction. Our data extend classical characterization of the body tilt representation by vestibulospinal neurons and establish the utility of TIPM to study the neural basis of balance, especially in developing animals.

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Relating Pupil Diameter and Blinking to Cortical Activity and Hemodynamics across Arousal States

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Arousal state affects neural activity and vascular dynamics in the cortex, with sleep associated with large changes in the local field potential and increases in cortical blood flow. We investigated the relationship between pupil diameter and blink rate with neural activity and blood volume in the somatosensory cortex in male and female unanesthetized, head-fixed mice. We monitored these variables while the mice were awake, during periods of rapid eye movement (REM), and non-rapid eye movement (NREM) sleep. Pupil diameter was smaller during sleep than in the awake state. Changes in pupil diameter were coherent with both gamma-band power and blood volume in the somatosensory cortex, but the strength and sign of this relationship varied with arousal state. We observed a strong negative correlation between pupil diameter and both gamma-band power and blood volume during periods of awake rest and NREM sleep, although the correlations between pupil diameter and these signals became positive during periods of alertness, active whisking, and REM. Blinking was associated with increases in arousal and decreases in blood volume when the mouse was asleep. Bilateral coherence in gamma-band power and in blood volume dropped following awake blinking, indicating a reset of neural and vascular activity. Using only eye metrics (pupil diameter and eye motion), we could determine the arousal state of the mouse (‘Awake,’ ‘NREM,’ ‘REM’) with >90% accuracy with a 5 s resolution. There is a strong relationship between pupil diameter and hemodynamics signals in mice, reflecting the pronounced effects of arousal on cerebrovascular dynamics.

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A Novel Mechanism for T1R-Independent Taste Responses to Concentrated Sugars

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Recent findings from our laboratory demonstrated that the rostral nucleus of the solitary tract (rNST) retains some responsiveness to sugars in double-knock-out mice lacking either the T1R1+T1R3 (KO1+3) or T1R2+T1R3 (KO2+3) taste receptor heterodimers. Here, we extended these findings in the parabrachial nucleus (PBN) of male and female KO1+3 mice using warm stimuli to optimize sugar responses and employing additional concentrations and pharmacological agents to probe mechanisms. PBN T1R-independent sugar responses, including those to concentrated glucose, were more evident than in rNST. Similar to the NST, there were no “sugar-best” neurons in KO1+3 mice. Nevertheless, 1000 mM glucose activated nearly 55% of PBN neurons, with responses usually occurring in neurons that also displayed acid and amiloride-insensitive NaCl responses. In wild-type (WT) mice, concentrated sugars activated the same electrolyte-sensitive neurons but also “sugar-best” cells. Regardless of genotype, phlorizin, an inhibitor of the sodium-glucose co-transporter (SGLT), a component of a hypothesized alternate glucose-sensing mechanism, did not diminish responses to 1000 mM glucose. The efficacy of concentrated sugars for driving neurons broadly responsive to electrolytes implied an origin from Type III taste bud cells. To test this, we used the carbonic anhydrase (CA) inhibitor dorzolamide (DRZ), previously shown to inhibit amiloride-insensitive sodium responses arising from Type III taste bud cells. Dorzolamide had no effect on sugar-elicited responses in WT sugar-best PBN neurons but strongly suppressed them in WT and KO1+3 electrolyte-generalist neurons. These findings suggest a novel T1R-independent mechanism for hyperosmotic sugars, involving a CA-dependent mechanism in Type III taste bud cells.

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BEHAVIORAL/COGNITIVE

D_{2/3} Agonist during Learning Potentiates Cued Risky Choice

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Impulse control and/or gambling disorders can be triggered by dopamine agonist therapies used to treat Parkinson's disease, but the cognitive and neurobiological mechanisms underlying these adverse effects are unknown. Recent data show that adding win-paired sound and light cues to the rat gambling task (rGT) potentiates risky decision-making and impulsivity via the dopamine system, and that changing dopaminergic tone has a greater influence on behavior while subjects are learning task contingencies. Dopamine agonist therapy may therefore be potentiating risk-taking by amplifying the behavioral impact of gambling-related cues on novel behavior. Here, we show that ropinirole treatment in male rats transiently increased motor impulsivity but robustly and progressively increased choice of the high-risk/high-reward options when administered during acquisition of the cued but not uncued rGT. Early in training, ropinirole increased win-stay behavior after large unlikely wins on the cued rGT, indicative of enhanced model-free learning, which mediated the drug's effect on later risk preference. *Ex vivo* cFos imaging showed that both chronic ropinirole and the addition of win-paired cues suppressed the activity of dopaminergic midbrain neurons. The ratio of midbrain:prefrontal cFos⁺ neurons was lower in animals with suboptimal choice patterns and tended to predict risk preference across all rats. Network analyses further suggested that ropinirole induced decoupling of the dopaminergic cells of the VTA and nucleus accumbens but only when win-paired cues were present. Frontostriatal activity uninformed by the endogenous dopaminergic teaching signal therefore appeared to perpetuate risky choice, and ropinirole exaggerated this disconnect in synergy with reward-paired cues.

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Luminance Contrast Shifts Dominance Balance between ON and OFF Pathways in Human Vision

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Human vision processes light and dark stimuli in visual scenes with separate ON and OFF neuronal pathways. In nature, stimuli lighter or darker than their local surround have different spatial properties and contrast distributions (Ratliff et al., 2010; Cooper and Norcia, 2015; Rahimi-Nasrabadi et al., 2021). Similarly, in human vision, we show that luminance contrast affects the perception of lights and darks differently. At high contrast, human subjects of both sexes locate dark stimuli faster and more accurately than light stimuli, which is consistent with a visual system dominated by the OFF pathway. However, at low contrast, they locate light stimuli faster and more accurately than dark stimuli, which is consistent with a visual system dominated by the ON pathway. Luminance contrast was strongly correlated with multiple ON/OFF dominance ratios estimated from light/dark ratios of performance errors, missed targets, or reaction times (RTs). All correlations could be demonstrated at multiple eccentricities of the central visual field with an ON-OFF perimetry test implemented in a head-mounted visual display. We conclude that high-contrast stimuli are processed faster and more accurately by OFF pathways than ON pathways. However, the OFF dominance shifts toward ON dominance when stimulus contrast decreases, as expected from the higher-contrast sensitivity of ON

cortical pathways (Kremkow et al., 2014; Rahimi-Nasrabadi et al., 2021). The results highlight the importance of contrast polarity in visual field measurements and predict a loss of low-contrast vision in humans with ON pathway deficits, as demonstrated in animal models (Sarnaik et al., 2014).
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Proactive Interhemispheric Disinhibition Supports Response Preparation during Selective Stopping

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Response inhibition is essential for terminating inappropriate actions. A substantial response delay may occur in the nonstopped effector when only part of a multieffector action is terminated. This stopping-interference effect has been attributed to nonselective response inhibition processes and can be reduced with proactive cuing. This study aimed to elucidate the role of interhemispheric primary motor cortex (M1–M1) influences during selective stopping with proactive cuing. We hypothesized that stopping-interference would be reduced as stopping certainty increased because of proactive recruitment of interhemispheric facilitation or inhibition when cued to respond or stop, respectively. Twenty-three healthy human participants of either sex performed a bimanual anticipatory response inhibition paradigm with cues signaling the likelihood of a stop-signal occurring. Dual-coil transcranial magnetic stimulation was used to determine corticomotor excitability (CME), interhemispheric inhibition (IHI), and interhemispheric facilitation (IHF) in the left hand at rest and during response preparation. Response times slowed and stopping-interference decreased with increased stopping certainty. Proactive response inhibition was marked by a reduced rate of rise and faster cancel time in electromyographical bursts during stopping. There was a nonselective release of IHI but not CME from rest to in-task response preparation, whereas IHF was not observed in either context. An effector-specific reduction in CME but no reinstatement of IHI was observed when the left hand was cued to stop. These findings indicate that stopping speed and selectivity are better with proactive cueing and that interhemispheric M1–M1 channels modulate inhibitory tone during response preparation to support going but not proactive response inhibition.

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Ameliorating Hemianopia with Multisensory Training

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Hemianopia (unilateral blindness), a common consequence of stroke and trauma to visual cortex, is a debilitating disorder for which there are few treatments. Research in an animal model has suggested that visual-auditory stimulation therapy, which exploits the multisensory architecture of the brain, may be effective in restoring visual sensitivity in hemianopia. It was tested in two male human patients who were hemianopic for at least 8 months following a stroke. The patients were repeatedly exposed to congruent visual-auditory stimuli within their blinded hemifield during 2 h sessions over several weeks. The results were dramatic. Both recovered the ability to detect and describe visual stimuli throughout their formerly blind field within a few weeks. They could also localize these stimuli, identify some of their features, and perceive multiple visual stimuli simultaneously in both fields. These results indicate that the multisensory therapy is a rapid and effective method for restoring visual function in hemianopia.

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Deeper Than You Think: Partisanship-Dependent Brain Responses in Early Sensory and Motor Brain Regions

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Recent political polarization has illustrated how individuals with opposing political views often experience ongoing events in markedly different ways. In this study, we explored the neural mechanisms underpinning this phenomenon. We conducted fMRI scanning of 34 right- and left-wing participants (45% females) watching political videos (e.g., campaign ads and political speeches) just before the elections in Israel. As expected, we observed significant differences between left- and right-wing participants in their interpretation of the videos' content. Furthermore, neuroimaging results revealed partisanship-dependent differences in activation and synchronization in higher-order regions. Surprisingly, such differences were also revealed in early sensory, motor, and somatosensory regions. We found that the political content synchronized the responses of primary visual and auditory cortices in a partisanship-dependent manner. Moreover, right-wing (and not left-wing) individuals' sensorimotor cortex was involved in processing right-wing (and not left-wing) political content. These differences were pronounced to the extent that we could predict political orientation from the early brain-response alone. Importantly, no such differences were found with respect to neutral content. Therefore, these results uncover more fundamental neural mechanisms underlying processes of political polarization.

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NMDA Receptor Activation-Dependent Antidepressant-Relevant Behavioral and Synaptic Actions of Ketamine

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Ketamine is a well-characterized NMDA receptor (NMDAR) antagonist, although the relevance of this pharmacology to its rapid (within hours of administration) antidepressant actions, which depend on mechanisms convergent with strengthening of excitatory synapses, is unclear. Activation of synaptic NMDARs is necessary for the induction of canonical long-term potentiation (LTP) leading to a sustained expression of increased synaptic strength. We tested the hypothesis that induction of rapid antidepressant effects requires NMDAR activation, by using behavioral pharmacology, western blot quantification of hippocampal synaptoneurosomal protein levels, and *ex vivo* hippocampal slice electrophysiology in male mice. We found that ketamine exerts an inverted U-shaped dose-response in antidepressant-sensitive behavioral tests, suggesting that an excessive NMDAR inhibition can prevent ketamine's antidepressant effects. Ketamine's actions to induce antidepressant-like behavioral effects, up-regulation of hippocampal AMPAR subunits GluA1 and GluA2, as well as metaplasticity measured *ex vivo* using electrically-stimulated LTP, were abolished by pretreatment with other non-antidepressant NMDAR antagonists, including MK-801 and CPP. Similarly, the antidepressant-like actions of other putative rapid-acting antidepressant drugs (2R,6R)-hydroxynorketamine (ketamine metabolite), MRK-016 (GABA_A $\alpha 5$ negative allosteric modulator), and LY341495 (mGlu_{2/3} receptor antagonist) were blocked by NMDAR inhibition. Ketamine acted synergistically with an NMDAR positive allosteric modulator to exert antidepressant-like behavioral effects and activation of the NMDAR subunit GluN2A was necessary and sufficient for such relevant effects. We conclude rapid-acting antidepressant compounds share a common downstream NMDAR-activation dependent effector mechanism, despite variation in initial pharmacological targets. Promoting NMDAR signaling or other approaches that enhance NMDAR-dependent LTP-like synaptic potentiation may be an effective antidepressant strategy.

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α -Synuclein Pathology and Reduced Neurogenesis in the Olfactory System Affect Olfaction in a Mouse Model of Parkinson's Disease

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Parkinson's disease (PD) is characterized by multiple symptoms including olfactory dysfunction, whose underlying mechanisms remain unclear. Here, we explored pathologic changes in the olfactory pathway of transgenic (Tg) mice of both sexes expressing the human A30P mutant α -synuclein (α -syn; α -syn-Tg mice) at 6–7 and 12–14 months of age, representing early and late-stages of motor progression, respectively. α -Syn-Tg mice at late stages exhibited olfactory behavioral deficits, which correlated with severe α -syn pathology in projection neurons (PNs) of the olfactory pathway. In parallel, olfactory bulb (OB) neurogenesis in α -syn-Tg mice was reduced in the OB granule cells at six to seven months and OB periglomerular cells at 12–14 months, respectively, both of which could contribute to olfactory dysfunction. Proteomic analyses showed a disruption in endocytic and exocytic pathways in the OB during the early stages which appeared exacerbated at the synaptic terminals when the mice developed olfactory deficits at 12–14 months. Our data suggest that (1) the α -syn-Tg mice recapitulate the olfactory functional deficits seen in PD; (2) olfactory structures exhibit spatiotemporal disparities for vulnerability to α -syn pathology; (3) α -syn pathology is restricted to projection neurons in the olfactory pathway; (4) neurogenesis in adult α -syn-Tg mice is reduced in the OB; and (5) synaptic endocytosis and exocytosis defects in the OB may further explain olfactory deficits.

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