



Cover legend: This image shows a putative indirect-pathway striatal medium spiny neuron (cyan) labeled during in vivo juxtacellular recording in a mouse in which the fluorescent dye tomato (red) was expressed under the control of the D1 dopamine receptor promoter. For more information, see the article by Keifman, Coll et al. (Pages 8767–8779).
Cover Image: Barbara Yael Braz.

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Articles

CELLULAR/MOLECULAR

Shisa7-Dependent Regulation of GABA_A Receptor Single-Channel Gating Kinetics

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GABA_A receptors (GABA_ARs) mediate the majority of fast inhibitory transmission throughout the brain. Although it is widely known that pore-forming subunits critically determine receptor function, it is unclear whether their single-channel properties are modulated by GABA_A-associated transmembrane proteins. We previously identified Shisa7 as a GABA_AR auxiliary subunit that modulates the trafficking, pharmacology, and deactivation properties of these receptors. However, whether Shisa7 also regulates GABA_A single-channel properties has yet to be determined. Here, we performed single-channel recordings of $\alpha 2\beta 3\gamma 2L$ GABA_ARs cotransfected with Shisa7 in HEK293T cells and found that while Shisa7 does not change channel slope conductance, it reduced the frequency of receptor openings. Importantly, Shisa7 modulates GABA_AR gating by decreasing the duration and open probability within bursts. Through kinetic analysis of individual dwell time components, activation modeling, and macroscopic simulations, we demonstrate that Shisa7 accelerates GABA_AR deactivation by governing the time spent between close and open states during gating. Together, our data provide a mechanistic basis for how Shisa7 controls GABA_AR gating and reveal for the first time that GABA_AR single-channel properties can be modulated by an auxiliary subunit. These findings shed light on processes that shape the temporal dynamics of GABAergic transmission.

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DEVELOPMENT/PLASTICITY/REPAIR

Preserved Motility after Neonatal Dopaminergic Lesion Relates to Hyperexcitability of Direct Pathway Medium Spiny Neurons

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In Parkinson's disease patients and rodent models, dopaminergic neuron loss (DAN) results in severe motor disabilities. In contrast, general motility is preserved after early postnatal DAN loss in rodents. Here we used mice of both sexes to show that the preserved motility observed after early DAN loss depends on functional changes taking place in medium spiny neurons (MSN) of the dorsomedial striatum (DMS) that belong to the direct pathway (dMSN). Previous animal model studies showed that adult loss of dopaminergic input depresses dMSN response to cortical input, which likely contributes to Parkinson's disease motor impairments. However, the response of DMS-dMSN to their preferred medial PFC input is preserved after neonatal DAN loss as shown by *in vivo* studies. Moreover, their response to inputs from adjacent cortical areas is increased, resulting in reduced cortical inputs selectivity. Additional *ex vivo* studies show that membrane excitability increases in dMSN. Furthermore, chemogenetic inhibition of DMS-dMSN has a more marked inhibitory effect on general motility in lesioned mice than in their control littermates, indicating that expression of normal levels of locomotion and general motility depend on dMSN activity after early DAN loss. Contrastingly, DMS-dMSN inhibition did not ameliorate a characteristic phenotype of the DAN-lesioned animals in a marble burying task demanding higher behavioral control. Thus, increased dMSN excitability likely promoting changes in corticostriatal functional connectivity may contribute to the distinctive behavioral phenotype emerging after developmental DAN loss, with implications for our understanding of the age-dependent effects of forebrain dopamine depletion and neurodevelopment disorders.

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SYSTEMS/CIRCUITS

Single Nuclei Analyses Reveal Transcriptional Profiles and Marker Genes for Diverse Supraspinal Populations

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The mammalian brain contains numerous neurons distributed across forebrain, midbrain, and hindbrain that project axons to the lower spinal cord and work in concert to control movement and achieve homeostasis. Extensive work has mapped the anatomic location of supraspinal cell types and continues to establish specific physiological functions. The patterns of gene expression that typify and distinguish these disparate populations, however, are mostly unknown. Here, using adult mice of mixed sex, we combined retrograde labeling of supraspinal cell nuclei with fluorescence-activated nuclei sorting and

single-nuclei RNA sequencing analyses to transcriptionally profile neurons that project axons from the brain to lumbar spinal cord. We identified 14 transcriptionally distinct cell types and used a combination of established and newly identified marker genes to assign an anatomic location to each. To validate the putative marker genes, we visualized selected transcripts and confirmed selective expression within lumbar-projecting neurons in discrete supraspinal regions. Finally, we illustrate the potential utility of these data by examining the expression of transcription factors that distinguish different supraspinal cell types and by surveying the expression of receptors for growth and guidance cues that may be present in the spinal cord. Collectively, these data establish transcriptional differences between anatomically defined supraspinal populations, identify a new set of marker genes of use in future experiments, and provide insight into potential differences in cellular and physiological activity across the supraspinal connectome.

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Circadian Regulation of the Rod Contribution to Mesopic Vision in Mice

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At intermediate (mesopic) light levels, rods and cones are both active and can contribute to vision. This presents a challenge to the retina because the visual responses originating with rods and cones are distinct, yet their visual responses must be seamlessly combined. The current study aimed to establish how the circadian clock regulates rod and/or cone vision in these conditions, given the strong time-of-day change in the reliance on each photoreceptor. Visual responses were recorded in the retina and visual thalamus of anaesthetized male mice at distinct circadian time points, and the method of receptor silent substitution was used to selectively stimulate different photoreceptor types. With stimuli designed to only activate rods, responses in the mesopic range were highly rhythmic and peaked in amplitude in the subjective night. This rhythm was abolished following intravitreal injection of the gap junction blocker meclofenamic acid, consistent with a circadian variation in the strength of electrical coupling of photoreceptors. In contrast, responses to stimuli designed to only activate cones were arrhythmic within the mesopic to photopic range when adapted to the background irradiance. The outcome was that combined rod-plus-cone responses showed a stable contrast-response relationship across mesopic-photopic backgrounds in the circadian day, whereas at night, responses were significantly amplified at lower light levels. These data support the idea that the circadian clock is a key regulator of vision, in this case defining the relative amplitude of rod/cone vision across the mesopic transition according to time of day.

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Whole-Brain Propagation Delays in Multiple Sclerosis, a Combined Tractography-Magnetoencephalography Study

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Two structurally connected brain regions are more likely to interact, with the lengths of the structural bundles, their widths, myelination, and the topology of the structural connectome influencing the timing of the interactions. We introduce an *in vivo* approach for measuring functional delays across the whole brain in humans (of either sex) using magneto/electroencephalography (MEG/EEG) and integrating them with the structural bundles. The resulting topochronic map of the functional delays/velocities shows that larger bundles have faster velocities. We estimated the topochronic map in multiple sclerosis patients, who have damaged myelin sheaths, and controls, demonstrating greater delays in patients across the network and that structurally lesioned tracts were slowed down more than unaffected ones. We provide a novel framework for estimating functional transmission delays *in vivo* at the single-subject and single-tract level.

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BEHAVIORAL/COGNITIVE

Evidence of Serial Dependence from Decoding of Visual Evoked Potentials

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It is well known that recent sensory experience influences perception, recently demonstrated by a phenomenon termed “serial dependence.” However, its underlying neural mechanisms are poorly understood. We measured ERP responses to pairs of stimuli presented randomly to the

left or right hemifield. Seventeen male and female adults judged whether the upper or lower half of the grating had higher spatial frequency, independent of the horizontal position of the grating. This design allowed us to trace the memory signal modulating task performance and also the implicit memory signal associated with hemispheric position. Using classification techniques, we decoded the position of the current and previous stimuli and the response from voltage scalp distributions of the current trial. Classification of previous responses reached full significance only 700 ms after presentation of the current stimulus, consistent with retrieval of an activity-silent memory trace. Cross-condition classification accuracy of past responses (trained on current responses) correlated with the strength of serial dependence effects of individual participants. Overall, our data provide evidence for a silent memory signal that can be decoded from the EEG potential, which interacts with the neural processing of the current stimulus. This silent memory signal could be the physiological substrate subserving at least one type of serial dependence.

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How Does Literacy Affect Speech Processing? Not by Enhancing Cortical Responses to Speech, But by Promoting Connectivity of Acoustic-Phonetic and Graphomotor Cortices

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Previous research suggests that literacy, specifically learning alphabetic letter-to-phoneme mappings, modifies online speech processing and enhances brain responses, as indexed by the BOLD, to speech in auditory areas associated with phonological processing (Dehaene et al., 2010). However, alphabets are not the only orthographic systems in use in the world, and hundreds of millions of individuals speak languages that are not written using alphabets. In order to make claims that literacy per se has broad and general consequences for brain responses to speech, one must seek confirmatory evidence from nonalphabetic literacy. To this end, we conducted a longitudinal fMRI study in India probing the effect of literacy in Devanagari, an abugida, on functional connectivity and cerebral responses to speech in 91 variously literate Hindi-speaking male and female human participants. Twenty-two completely illiterate participants underwent 6 months of reading and writing training. Devanagari literacy increases functional connectivity between acoustic-phonetic and graphomotor brain areas, but we find no evidence that literacy changes brain responses to speech, either in cross-sectional or longitudinal analyses. These findings show that a dramatic reconfiguration of the neurofunctional substrates of online speech processing may not be a universal result of learning to read, and suggest that the influence of writing on speech processing should also be investigated.

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Distinct Roles of Dopamine Receptor Subtypes in the Nucleus Accumbens during Itch Signal Processing

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Ventral tegmental area (VTA) dopaminergic neurons, which are well known for their central roles in reward and motivation-related behaviors, have been shown to participate in itch processing via their projection to the nucleus accumbens (NAc). However, the functional roles of different dopamine receptor subtypes in subregions of the NAc during itch processing remain unknown. With pharmacological approaches, we found that the blockade of dopamine D1 receptors (D1R), but not dopamine D2 receptors (D2R), in the lateral shell (LaSh) of the NAc impaired pruritogen-induced scratching behavior in male mice. In contrast, pharmacological activation of D2R in both the LaSh and medial shell (MeSh) of the NAc attenuated the scratching behavior induced by pruritogens. Consistently, we found that dopamine release, as detected by a dopamine sensor, was elevated in the LaSh rather than the MeSh of the NAc at the onset of scratching behavior. Furthermore, the elevation of dopamine release in the LaSh of the NAc persisted even though itch-relieving behavior was blocked, suggesting that the dopamine signal in the NAc LaSh represents a motivational component of itch processing. Our study revealed different dynamics of dopamine release that target neurons expressing two dopamine receptors subtypes within different subregions of the NAc, and emphasized that D1R in the LaSh of the NAc is important in itch signal processing.

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Updating Contextual Sensory Expectations for Adaptive Behavior

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The brain has the extraordinary capacity to construct predictive models of the environment by internalizing statistical regularities in the sensory inputs. The resulting sensory expectations shape how we perceive and react to the world; at the neural level, this relates to decreased neural responses to expected than unexpected stimuli (“expectation suppression”). Crucially, expectations may need revision as context changes. However, existing research has often neglected this issue. Further, it is unclear whether contextual revisions apply selectively to expectations relevant to the task at hand, hence serving adaptive behavior. The present fMRI study examined how contextual visual expectations spread throughout the cortical hierarchy as we update our beliefs. We created a volatile environment: two alternating contexts contained different sequences of object images, thereby producing context-dependent expectations that needed revision when the context changed. Human participants of both sexes attended a training session before scanning to learn the contextual sequences. The fMRI experiment then tested for the emergence of contextual expectation suppression in two separate tasks, respectively, with task-relevant and task-irrelevant expectations. Effects of contextual expectation emerged progressively across the cortical hierarchy as participants attuned themselves to the context: expectation suppression appeared first in the insula, inferior frontal gyrus, and posterior parietal cortex, followed by the ventral visual stream, up to early visual cortex. This applied selectively to task-relevant expectations. Together, the present results suggest that an insular and frontoparietal executive control network may guide the flexible deployment of contextual sensory expectations for adaptive behavior in our complex and dynamic world.

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Age-Related Learning and Working Memory Impairment in the Common Marmoset

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Aging is the greatest risk factor for the development of neurodegenerative diseases, yet we still do not understand how the aging process leads to pathologic vulnerability. The research community has relied heavily on mouse models, but the considerable anatomic, physiological, and cognitive differences between mice and humans limit their translational relevance. Ultimately, these barriers necessitate the development of novel aging models. As a nonhuman primate (NHP), the common marmoset (*Callithrix jacchus*) shares many features in common with humans and yet has a significantly shorter lifespan (10 years) than other primates, making it ideally suited to longitudinal studies of aging. Our objective was to evaluate the marmoset as a model of age-related cognitive impairment. To do this, we used the Delayed Recognition Span Task (DRST) to characterize age-related changes in working memory capacity in a cohort of sixteen marmosets, of both sexes, varying in age from young adult to geriatric. These monkeys performed thousands of trials over periods of time ranging up to 50% of their adult lifespan. To our knowledge, this represents the most thorough cognitive profiling of any marmoset aging study conducted to date. By analyzing individual learning curves, we found that aged animals exhibited delayed onset of learning, slowed learning rate after onset, and decreased asymptotic working memory performance. These findings are not accounted for by age-related impairments in motor speed and motivation. This work firmly establishes the marmoset as a model of age-related cognitive impairment.

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NEUROBIOLOGY OF DISEASE

The SYNGAP1 3'UTR Variant in ALS Patients Causes Aberrant SYNGAP1 Splicing and Dendritic Spine Loss by Recruiting HNRNPK

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Fused in sarcoma (FUS) is a pathogenic RNA-binding protein in amyotrophic lateral sclerosis (ALS). We previously reported that FUS stabilizes Synaptic Ras-GTPase activating protein 1 (*Syngap1*) mRNA at its 3' untranslated region (UTR) and maintains spine maturation. To elucidate the pathologic roles of this mechanism in ALS patients, we identified the *SYNGAP1* 3'UTR variant rs149438267 in seven (four males and three females) out of 807 ALS patients at the FUS binding site from a multicenter cohort in Japan. Human-induced pluripotent stem cell (hiPSC)-derived motor neurons with the *SYNGAP1* variant showed aberrant splicing, increased isoform $\alpha 1$ levels, and decreased isoform γ levels, which caused dendritic spine loss. Moreover, the *SYNGAP1* variant excessively recruited FUS and heterogeneous nuclear ribonucleoprotein K (HNRNPK), and antisense oligonucleotides (ASOs) blocking HNRNPK altered aberrant splicing and ameliorated dendritic spine loss. These data suggest that excessive recruitment of RNA-binding proteins, especially HNRNPK, as well as changes in *SYNGAP1* isoforms, are crucial for spine formation in motor neurons.

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Modulation of Hippocampal Network Oscillation by PICK1-Dependent Cell Surface Expression of mGlu3 Receptors

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Metabotropic glutamate receptor Type 3 (mGlu3) controls the sleep/wake architecture, which plays a role in the glutamatergic pathophysiology of schizophrenia. Interestingly, mGlu3 receptor expression is decreased in the brain of schizophrenic patients. However, little is known about the molecular mechanisms regulating mGlu3 receptors at the cell membrane. Subcellular receptor localization is strongly dependent on protein–protein interactions. Here we show that mGlu3 interacts with PICK1 and that this scaffolding protein is important for mGlu3 surface expression and function in hippocampal primary cultures. Disruption of their interaction via an mGlu3 C-terminal mimicking peptide or an inhibitor of the PDZ domain of PICK1 altered the functional expression of mGlu3 receptors in neurons. We next investigated the impact of disrupting the mGlu3–PICK1 interaction on hippocampal theta oscillations *in vitro* and *in vivo* in WT male mice. We found a decreased frequency of theta oscillations in organotypic hippocampal slices, similar to what was previously observed in mGlu3 KO mice. In addition, hippocampal theta power was reduced during rapid eye movement sleep, non-rapid eye movement (NREM) sleep, and wake states after intraventricular administration of the mGlu3 C-terminal mimicking peptide. Targeting the mGlu3–PICK1 complex could thus be relevant to the pathophysiology of schizophrenia.

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