Transient activation of Npas1 neurons recreates ensemble bursting in the basal forebrain

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Abstract

Recent studies from our group have shown that reward-predicting stimuli robustly activate a special subset of basal forebrain (BF) neurons, which are referred to as BF bursting neurons. BF bursting neurons are important for behavior because their responses are strongly associated with improved performance and faster decision speeds toward the reward-predicting stimuli. A central feature of BF bursting neurons is their highly synchronized excitatory responses to reward-predicting stimuli, creating BF ensemble bursting responses. Such BF ensemble bursting responses are robust irrespective of sensory modality of the stimulus. These observations highlight the importance for understanding how the BF ensemble bursting is generated, which will allow us to recreate the BF ensemble bursting response and test its causal role in modulating behaviors. Here we show that transient optogenetic activations in a subset of Npas1 BF neurons recreated the ensemble bursting response and improved behavioral performance in an auditory detection task. Based on BF single cell transcriptomics, we first identified Npas1 as a novel candidate marker for BF bursting neurons, which labels a special subset of GABAergic BF neurons. Brief optogenetic activation of Npas1 neurons elicited a BF ensemble bursting response after a short delay (30-40 msec latency). This Npas1-induced BF ensemble bursting selectively involved all BF bursting neurons in both hemispheres even when the optogenetic stimulation was unilaterally delivered. Furthermore, The bursting response amplitude in individual BF bursting neurons induced by Npas1 optogenetic stimulation was positively correlated with their response amplitude to reward-predicting stimuli. These properties of Npas1-induced BF ensemble bursting resemble the endogenous BF ensemble bursting responses elicited by reward-predicting stimuli. At the behavioral level, optogenetic activation of Npas1 neurons increased correct response probabilities and decision speeds in an auditory detection task, while their optogenetic inhibition had the opposite effects. Finally, the Npas1-induced BF ensemble bursting was completely abolished under anesthesia, suggesting that the delayed ensemble bursting response likely involved other brain regions. These results begin to reveal the circuit mechanisms in the BF that transform an excitatory input targeting a subset of Npas1 neurons into an BF ensemble bursting response, and establish its causal role in improving behavioral performance.

Decoding the focus of cross-modal selective attention in single trials via neuronal activity in the basal forebrain

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Abstract

Animals and humans have the ability to selectively focus their attention on one sensory modality while ignoring other irrelevant ones. This form of attention, referred to as cross-modal selective attention, is poorly understood because of the covert nature of attentional shift, and therefore the focus of attended sensory modality cannot be easily determined at any given moment. This makes it difficult to study cross-modal selective attention at the behavioral level as well as its implementations at the neural circuit level. Here we address this issue at both behavioral and neural activity levels to pinpoint the focus of cross-modal selective attention in single trials. At the behavioral level, we developed a novel behavioral task for rats that provided a clear readout of animals' attention focus. In this new cross-modal oddball task, auditory and visual stimuli were presented simultaneously once every two seconds. In each trial block, oddball targets in one of the two sensory modalities were task-relevant and predicted reward in either the left (auditory) or the right (visual) reward port. Behavioral responses toward the same multi-sensory stimulus were robustly different depending on the relevant modality in that trial block, and the behavioral response patterns rapidly switched across trial blocks. At the neuronal level, we showed that the activity of a special subset of neurons in the basal forebrain (BF), referred to as BF bursting neurons, can be used to decode animals' attention focus. BF bursting neurons preferentially responded to the oddball target in the attended sensory modality, while ignoring the same stimulus when the modality was not the focus of attention. Shifts of attention between auditory and visual modalities were also associated with significant shifts in BF response latencies. Moreover, shifts in BF neuronal activity were rapid and tightly coupled with behavioral switching at the trial block transitions. Such coordinated behavioral and BF activity shifts were also observed during occasional spontaneous shifts of attention initiated by the animal. Together, these results establish a new approach to study cross-modal selective attention and their dynamic shifts with fine temporal resolution. These results also highlight the important role of BF bursting neurons in cross-modal selective attention, which likely exert their influences through amplifying information processing in the prefrontal cortex.

Inhibitory Control of the Thalamic Reticular Nucleus by the Basal Forebrain

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Abstract

Thalamus is the central gatekeeper that controls the flow of information to the cerebral cortex. Activity in the thalamus, in turn, is controlled by a sheet of GABAergic neurons surrounding the thalamus, called the thalamic reticular nucleus (TRN). Because of its critical strategic position, the TRN has been implicated to play a key role in selective attention. Understanding how the TRN activity is controlled is therefore of great importance. A major input to the TRN comes from the basal forebrain (BF). However, the neurochemical identity and behavioral function of the BF-TRN projection has remained unclear. By combining cell-type specific viral tracing, slice physiology and in vivo multi-electrode recording across multiple brain regions in behaving rodents, here we describe a novel inhibitory control mechanism of the anterior TRN (aTRN) by BF Npr3 neurons. We first identified Npr3 as a novel marker for a subset of BF GABAergic neurons based on single cell RNA sequencing database. Anatomical characterization of BF Npr3 neurons' projection patterns revealed specific and dense innervations to the aTRN and the prefrontal cortex (PFC). Consistent with their GABAergic identity, optogenetic activations of BF Npr3 axon terminals in brain slices elicited strong inhibitory postsynaptic currents in aTRN neurons. To further determine the behavioral significance of this BF-aTRN projection, we simultaneously recorded neuronal activities of BF, aTRN and PFC in vivo. The activity of a subset of BF neurons, referred to as BF bursting neurons, was strongly coupled with local field potential (LFP) responses specifically in the aTRN in single trials, both in terms of amplitude and timing. Moreover, both the aTRN and BF bursting neurons responded to sensory stimuli that predicted reward, irrespective of their sensory modalities. Finally, aTRN and BF responses were both coupled with EEG responses in the PFC. Together, these results establish BF Npr3 neurons as a novel inhibitory control mechanism of the aTRN, which is engaged when animals attend to reward-predicting stimuli. This novel BF(Npr3)-TRN pathway may serve as an attention mechanism to enhance thalamocortical processing of reward-predicting stimuli through a disinhibition mechanism.

The subthreshold basis of spike synchrony between hippocampal parvalbumin interneurons

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Abstract

Inhibition is important for neural network functions. It can balance excitatory inputs and control the spiking outputs of downstream neurons. Furthermore, inhibition can even generate network oscillations critical for many cognitive functions. Inhibition in cortical areas is mediated by a small population of inhibitory interneurons. These neurons often coordinate the timing of their action potentials to produce precise inhibition of the network. One of the most striking examples of such coordination is the synchronous activity of parvalbumin (PV)-expressing interneurons, in which the action potentials of one neuron occur within just a few milliseconds from those of other cells. Such a precise synchrony is considered essential for the function of PV cells. However, how PV cells produce synchronous activity in vivo remains unclear. Several synaptic mechanisms have been proposed. For example, PV cells are coupled by gap junctions, which conduct action potentials into fast spikelets to facilitate synchrony. PV cells also share excitation from upstream excitatory neurons, which could drive their synchronous activity. Finally, PV cells are known to inhibit each other. This reciprocal inhibition has also been shown to transform irregular activity into synchronous network oscillations. To understand which of these mechanisms dominates the synchrony between PV cells in vivo, we simultaneously monitored membrane potentials in multiple PV cells using voltage imaging. This allows us to correlate the synchrony between pairs of PV cells with subthreshold signatures that provide information about the synaptic interaction between cells. We found that although a large fraction of the spikes in the PV cells occurred synchronously, there were also many spikes that occurred in isolation. Around these spikes, the membrane potentials of other PV cells showed slow depolarization. This ‘co-depolarization’ is not consistent with a dominant contribution of mutual inhibitory between PV cells. Furthermore, the slow kinetics of co-depolarization is also inconsistent with the dominant contribution of gap junctions, which produce a much faster ‘spikelet’ signal. Moreover, the amplitudes of these co-depolarizations correlate with the strength of synchrony between PV cells. Together, these results suggest that co-depolarization, possibly reflecting shared excitation, plays a dominant role in driving synchrony between PV cells in vivo.

γ-TuRC regulates neuronal migration during embryonic cortical

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Abstract

The γ-tubulin ring complex (γ-TuRC) is a multi-subunit protein complex composed of γ-tubulin and γ-tubulin complex proteins (GCPs). γ-TuRC promotes microtubule assembly by serving as a template that allows efficient nucleation and elongation of α/β-tubulins into microtubule filaments, thus playing a crucial role in various cellular processes including cell division, cell differentiation, cell polarization and cell migration. Recent studies revealed that mutations in the tubulin superfamily lead to cortical dysgenesis with a wide spectrum of neurodevelopmental defects, collectively termed tubulinopathies. In particular, mutations in the γ-TuRC core subunit γ-tubulin and its activator Cdk5Rap2 cause brain developmental disorders known as malformations of cortical development (MCD). However, it remains elusive how γ-TuRC regulates cerebral cortex formation during embryonic brain development. In this study, we set out to systematically dissect the roles of γ-TuRC in this process and illuminate the molecular mechanisms underlying clinical deficits using mouse model. Our preliminary data indicate that knockdown of individual γ-TuRC subunits by in utero electroporation severely delays neuronal migration in developing brain. In particular, GCP2-knockdown cells are stalled at the intermediate zone. Surprisingly, loss of GCP2 neither affects progenitor proliferation nor induces neuronal cell death. Rather interestingly, they fail to differentiate into the neuronal lineage. Furthermore, using live brain-slice imaging, we found that GCP2 knockdown compromises neuronal radial migration. These findings suggest that GCP2 is indispensable for establishing neuronal polarity that guides neuronal maturation and migration during cortical development.

The Role of ASIC Channels in the Response of N2a Cells to the Micropipette Guided Ultrasound Stimulation

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Abstract

Lines of compelling evidence have shown that low-intensity focused ultrasound has the capability of neuromodulation modality with exquisite spatial specificity and depth penetration. Although low-intensity focused ultrasound holds great promise as a novel approach to the potential clinical applications of neuron stimulation, the underlying mechanism at the cellular and molecular level remain unclear. In this study, we utilized a device of micropipette-guided ultrasound to dissect the involved channels in ultrasound-induced activation of somatosensory neurons and neuroblastoma N2a cells. The glass micropipette with an end-closed tip is a developed wave-guide device to transport the force of ultrasound. Ultrasound from the tip generates two forms of force: one is the acoustic pressure into cell solution with radiation force exerting on cells placed along its path, and the other is the streaming flow applying shear force on cells. These two force modalities could be fine-tuned by the input voltage and the duty factor. Our results demonstrated streaming force dominantly modulate intracellular calcium concentration. By pharmacological approaches through ASICs inhibitors and mechanosensitive channel blockers, ASIC1a has been identified as a vital mechanosensitive channel to mediate low-intensity ultrasound-induced activation of N2a and dorsal root ganglion cells. We also found the response to ultrasound is extracellular matrix dependent, suggesting the tethering model of mechanogating may be involved.

Genetically encoded tools applying in iPSC derived neurons and astrocytes for phenotypic/functional screening

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Abstract

Neurodegenerative disease or neurodegeneration caused by cognitive disturbance, progressive loss of functional neurons affects cognition, function, and behavior. Age-related dementia Alzheimer's Disease (AD) is among the most popular neurodegenerative disease that affect millions of people worldwide. It is an urgent need to identify effective drugs for prevention and treatment. However, majority of failure clinical trials for AD drug development is due to the lack of suitable models. Availability of primary mature neurons, on the other hand, is limited and insufficient, thus hinders application of human primary cell-based disease modelling in the study of AD. Disease-based human induced pluripotent stem cells (hiPSCs) provides a great hope for being used as "Clinical Trial on a Dish" Model for high throughput drug screening and testing. LumiSTAR has established "Clinical Trial on a Dish"-based iPSC technology generated either from blood samples of AD patients or through genetic editing by Crispr/Cas9. Using AD based iPSC model as an example, we demonstrated that AD iPSC -derived cortical neurons and -derived astrocytes recapture human disease phenotypes based on morphological analysis, ROS level, calcium activity and accumulation of Aβ42/Aβ40 ratio. Moreover, we can observe impaired mitochondrial morphology and dynamic in AD astrocytes when compared with healthy control. Finally, multi-parametric assessments using combinations of spectral and calcium affinity indicator variants (mNG-GECO, mtLAR-GECO, er-LAREX-GECO or Orai1-K-GECO) are restricted to different cellular compartments are also demonstrated in the cells.

The efficient induction of human retinal ganglion-like cells provides a platform for studying optic neuropathies

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Abstract

Retinal ganglion cells (RGCs) are essential for vision perception. In mammals, RGCs and their optic nerve axons undergo neurodegeneration and loss when glaucoma and other optic neuropathies are present; this can result in irreversible vision loss. Here we developed a rapid protocol for directly inducing RGC differentiation from human induced pluripotent stem cells (iPSCs) by the overexpression of ATOH7, BRN3B and SOX4. The hiPSC-derived RGC-like cells (iRGCs) show robust expression of various RGC-specific markers, such as BRN3A, EBF1, ISL1 and RBPMS. A functional assessment was also carried out and this demonstrated that these iRGCs display stimulus-induced neuronal activity, as well as spontaneous neuronal activity. Ethambutol (EMB), an effective first-line antituberculosis agent, is known to cause serious visual impairment and irreversible vision loss due to the RGC degeneration in a significant number of treated patients. Using our iRGCs, EMB was found to induce significant dose-dependent and time-dependent increases in cell death and neurite degeneration. Western blot analysis revealed that the expression levels of p62 and LC3-II were upregulated, and further investigations revealed that EMB caused a blockade of lysosome-autophagosome fusion; this indicates that impairment of autophagic flux is one of the adverse effects of that EMB has on iRGCs. In addition, EMB was found to elevate intracellular reactive oxygen species (ROS) levels increasing apoptotic cell death. This could be partially rescued by the co-treatment with the ROS scavenger NAC. Taken together, our findings suggest that this iRGC model, which achieves both high yield and high purity, is suitable for investigating optic neuropathies, as well as being useful when searching for potential drugs for therapeutic treatment and/or disease prevention.

Toward a novel strategy for optogenetic control of synaptic transmission

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Abstract

Optogenetics is an evolutionary technology for precise control of biological functions. With genetic and optical manipulations, we can modulate the neuron of interest with high spatial and temporal resolution. To date, optical control of neurotransmission, the fundamental process of neuronal communications, has mainly been achieved through light-sensitive neurotransmitter receptors. However, this approach may have constrained applicability because it heavily relies on the use of knock-in animals that carry the genetically-modified receptors. Here we explore a novel strategy to enable optogenetic control of native GABAA receptors, the major mediator of inhibitory transmission in the nervous system. We engineer a series of “Loading Dock” (LD) proteins for recruiting photoswitchable tethered ligands (PTLs) onto the neuronal surface, thereby enabling optical control of local GABAA receptors. By incorporating a specialized intracellular motif, we are able to enrich the LD protein at the inhibitory synapses. Moreover, we strategically tune the LD’s binding affinity to the postsynaptic scaffold, allowing it to enrich at inhibitory synapses without causing apparent electrophysiological perturbations. As synaptic and extrasynaptic GABAA receptors mediate distinct forms of neuronal inhibition (phasic and tonic, respectively), this approach may allow specific manipulations of endogenous phasic inhibition. To employ the tools in vivo, we generate bicistronic adeno-associated viruses (AAVs) that encode the LD genes with a fluorescent expression marker. We deliver the AAVs via neonatal injection and observe the punctate distribution of the LDs in the mouse neocortex, hippocampus, and cerebellum. In-depth characterizations are currently underway to verify the LD’s synaptic localization in vivo. Concurrently, we are developing LD-reactive photoswitchable antagonists for GABAA receptors. We expect that the LD-PTL toolkits will allow neuroscientists to control native GABAergic activities with high versatility and precision.

ExBrainable: An Open-Source GUI for EEG Decoding and Model Interpretation Based on Explainable Neural Networks

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Abstract

Recently, convolutional neural networks (CNN) are used to decode various types of electroencephalographic (EEG) sig- nals and have achieved improvement in the decoding accuracy. Yet, what CNN models learn from the EEG data remains unclear due to the lack of interpretability of models. In response to the need to explainable modeling tools for EEG data analysis, we introduce an open, compact, and easy- to-use tool for investigators in brain/neuroscience research to leverage the cutting-edge computational algorithms and functions for CNN-based EEG decoding and model interpretation. We have developed a graphic user interface (GUI), ExBrainable, dedicated to modeling, decoding, and visualization of electroencephalography (EEG) data based on explainable neural network models. Available functions include model training, evaluation, and parameter visualization. Demonstration on motor-imagery EEG data exhibits the spatial and temporal representations of EEG patterns associated with existing knowledge of neuroscience. As a growing open-source platform, ExBrainable offers fast, simplified, and user-friendly analysis of EEG data using cutting-edge computational approaches for brain/neuroscience research.

Nonlinear Dendritic Activity Drives Hippocampal Place-Field Forming Plasticity as A Function of Synaptic Input Dynamics And State

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Abstract

To achieve goals, it is a challenge for the animal's neural circuits to encode spatial and non-spatial features of the environments. Place cells in the hippocampus acquire these properties through experience. However, the mechanisms and algorithms of synaptic plasticity rules underlying place-field formation remain a fundamental problem. In light of in-vivo electrophysiology during mouse navigation behavior, we systematically investigated the properties of plasticity induction driven by dendritic calcium (Ca2+) plateau potentials. In acute hippocampal CA1 slices, an associative long-term potentiation (LTP) can be triggered by Ca2+ plateaus 1–2 seconds away from the to-be-potentiated synapses—recapturing the hallmark characteristics of the plasticity that rapidly produces place fields in vivo. Here, using patch-clamp recording in vitro, we found that presynaptic input frequency, existing synaptic weight, and temporal relationship of the presynaptic and postsynaptic activations jointly determined the magnitude and polarity of such behavioral timescale plasticity in CA1 pyramidal neurons. Interestingly, this is consistent with a latest theoretical prediction made by fitting in-vivo electrophysiological data to a hypothetical model. We posit that these mechanisms play an essential role in determining the transfer of spatial information to the CA1 in response to physiological dynamics of the upstream area. We attempt to analyze this possibility, in relation to changing rewards, using modeling techniques.

Investigation of the heterogeneity of calcium activity in the motor cortical and the striatal astrocytes

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Abstract

Astrocytic calcium signaling regulates the neuronal activity and various physiological functions. Aberrant astrocytic calcium signaling reduces motor function and is highly associated with movement disorders, such as Huntington's disease. This suggests that astrocytic calcium signaling plays a crucial role in the motor circuits. However, a comprehensive study of the properties of the astrocytic calcium activity in the motor circuit is still missing. Whether the astrocytic calcium activity exhibits regional heterogeneity, especially in the different layers of the primary motor cortex (M1) and the striatum, remains elusive. Here we monitored the astrocytic morphology and calcium activity in the layer 1, 2/3, 5, and 6 of the M1 (L1, L2/3, L5, and L6) and the striatum in acute brain slices of transgenic mice (Aldh1l1-CreERT2::lck-GCaMP6f or Aldh1l1-CreERT2::Salsa6f), in which the astrocytes express membrane-tethered GCaMP6f or GCaMP6f/tdTomato fusion proteins in an inducible manner. We used state-of-the-art software, Astrocyte Quantification and Analysis (AQuA), to conduct calcium event-based analysis and found that astrocytes show heterogeneity in both their morphology and calcium activity. The L1 astrocytes are comparatively smaller in their territory size but exhibit significantly higher calcium event frequency density than other regions. This is correlated with a higher immunostaining level of glial fibrillary acidic protein (GFAP), a marker for reactive astrocytes, in the L1. On the other hand, the L2/3 and the L5 astrocytes occupy a larger territory, and their processes often surround the neuronal somas. Furthermore, consistent with our previous findings, the calcium events are highly confined in fine local processes in all observed astrocytes. The L1, L2/3, and L5 astrocytic calcium events have a higher probability of spreading to the whole cell, whereas events in L6 and striatal astrocytes are restricted in propagation. In summary, our work provides a complete picture of the astrocytic morphology and calcium activity in the M1 and the striatum. This region-specific heterogeneity in astrocytic calcium activity might correlate directly to their diverse morphology, differential interaction with neuronal counterparts, and physiological functions.

Common Topological Properties and Self-similarity Shared by Neurons with Diverse Morphology in Drosophila melanogaster

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Abstract

Neuronal morphology directly influences the arrangement of synaptic inputs, outputs, intrinsic electrical properties, and, consequently, the computation performed by a neuron. Because of the extreme diversity of fruit fly's neuronal morphology, it is unclear whether the neurons share any morphological similarity with implies common computational characteristics. Thus, we aim to identify the structural patterns that are shared across diversified neurons and discover the existence of a universal building block of neurons. We analyze neuronal skeleton data from FlyCircuit and FlyEM databases using metrics including topological networks, branch lengths, and branch angles. To study the local bifurcating structures, we used the Balance Ratio to calculate the local symmetrical property within a neuron. We classified neurons with their structural levels evaluated by the Strahler Order System, which represents the symmetrical property and complexity in a whole neuron picture. This classification is found related to other neuronal properties including branch lengths, branching distribution, and fractals characteristics. This result reveals a crucial and interesting observation: even widely complex and diverse neurons share topological features which further imply a widely adapted neuronal computational principle. Finally, we aim to bridge the gap between our understanding of the neuronal structures and their computational abilities by studying how the fundamental features of a neuron's branching structure influence its ability to process diverse patterns of synaptic inputs. Our analysis suggests that the topological features of neurons in Drosophila represent balance between spatial and temporal signal processing.

Construction of forebrain projectome in adult zebrafish

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Abstract

Zebrafish has a nervous system that contains up to 10^7 neurons, an order of magnitude less than that in mice, and is an ideal system to study the neuronal projections, i.e. the projectome, throughout the brain. Previous studies focused on zebrafish larvae, which is small and transparent but exhibits limited cognitive functions. On the other hand, adult zebrafish has a fully developed brain which supports various cognitive functions such as associative learning and social behaviors. Here we developed a protocol for mapping the projections of sparsely labeled, cell type-specific neurons in adult zebrafish forebrain. We focused our investigation on glutamatergic and GABAergic neurons and injected plasmids encoding UAS: tdTomato-CAAX in the following transgenic lines: Tg[vglut1:gal4], Tg[vglut2a:gal4], and Tg[gad1b:gal4], all in the background of UAS:GFP. After removing a small piece of the skull at desired locations, plasmids were injected into the brain and electroporation was performed. By controlling the volume and concentration of plasmid injection, a sparse labeling of less than 30 neurons per animal can be achieved. 5 days after the injection, brain clearing was performed using a CUBIC protocol optimized for zebrafish. Then the entire forebrain was imaged using a confocal microscope to reveal the morphology of individual neurons expressing tdTomato. The neuronal projections were traced using a semi-automatic software to extract the 3-dimentional coordinates of the neurites. To combine data from different animals, we performed linear registrations on the contour of the brains and used the transformation matrix to pool the projectome data from different animals into a reference brain. Using this protocol, we aim to perform a comprehensive mapping of cell-typed specific neuronal projections throughout the forebrain in adult zebrafish. This structural investigation lays the basis for functional analysis of the forebrain in a small vertebrate model of cognitive functions.