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SYNAPTIC PLASTICITY VERSUS STABILITY

INFORMATION UPTAKE, PROCESSING AND CODING

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ABSTRACTS

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ABSTRACTS

SPEAKERS

Deconstructing smell

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The sense of smell allows mammals to perceive a multitude of environmental chemicals as having a distinct odor. It also mediates the detection of pheromones and predator odors that elicit innate responses. We are interested in how the olfactory system detects different chemicals and how the nervous system translates those chemicals into diverse perceptions and behaviors. Using a combination of molecular, cellular, and genetic approaches, we have identified families of receptors that initially detect odorants and pheromones in peripheral sense organs, asked how those receptors encode the identities of different chemicals, and investigated how the signals they generate are routed and organized in the nervous system to yield distinct perceptions and instinctive responses. Our work also touches on other neural circuits that affect emotions and innate drives that modulate behavior.

Molecular motors, KIFs: Regulation of activity dependent trafficking, neuronal function, and development

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The intracellular transport is fundamental for neuronal morphogenesis, functioning and survival. To elucidate this mechanism we have identified and characterized kinesin superfamily proteins, KIFs, using molecular cell biology, molecular genetics, biophysics, and structural biology. KIFs transport various cargoes such as mitochondria (KIF1Balpha/KIF5s), synaptic vesicle precursor (KIF1A/KIF1Bbeta), NMDA type (KIF17) and AMPA type (KIF5s) glutamate receptors and mRNAs with a large protein complex (KIF5s) in neurons and other cells along microtubules. Concerning regulation of transport cells use adaptor proteins for recognition of cargos and phosphorylation and hydrolysis of G-proteins for loading and unloading cargoes. Molecular genetics unraveled that KIFs play significant roles not only on basic cellular functions by transporting various important cargoes, but also on fundamental phenomena in life such as memory and learning (KIF17/KIF1A), pain sensation (KIF1A) and development including brain wiring (KIF2A), activity dependent neuronal survival (KIF4), enteric neuronal development (KIF26A), determination of left-right asymmetry (KIF3) and suppression of tumorigenesis (KIF3). Furthermore, our recent studies uncovered deletion of KIFs causes certain diseases such as memory disturbance (KIF17), epilepsy (KIF5A), elevated anxiety (KIF13A), neuropathy (KIF1Bbeta), and hydrocephalus (KIF19A). In this conference I will focus on our recent studies on the mechanisms of activity- dependent intracellular transport, regulation of pain sensation and brain wiring.

The rodent olfactory bulb granule cell - an alliance of numerous inhibitory mini-neurons

Veronica Egger

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The vertebrate olfactory bulb processes olfactory stimuli within a two-stage network, the first located within the glomerular input layer and the second in the external plexiform layer below. These subnetworks are bridged via the principal mitral and tufted cells; both strongly draw on dendrodendritic interactions, with the axonless inhibitory granule cells being the main players in the second stage. Granule cells are directing their sole output towards the long lateral dendrites of mitral and tufted cells via reciprocal dendrodendritic synapses.

In spite or because of this apparently reduced anatomy, granule cells are capable of various modes of dendritic signalling, including local sodium spikes within their large dendrodendritic spines. To dissect the reciprocal microcircuit, we are using two-photon Ca2+ imaging and uncaging of glutamate in acute slices of juvenile rat olfactory bulbs in conjunction with whole cell recordings. I will discuss mechanisms underlying the local postsynaptic spine signals and how they might influence processing in mitral and tufted cells, backed by first evidence of local GABA release. We also have observed bidirectional long-term plasticity at the mitral to granule cell synapse that can be elicited via short bursts of glomerular activity - as might be triggered by whiffs of odors in an animal that navigates in the wild. Interestingly, long-term potentiation has not been reported at this synapse before. Simulations of our data imply that the sign of plasticity is a property of individual spines rather than of individual granule cells, thus independent action appears to be implemented within several aspects of processing. These findings broaden our view on the functionality of olfactory bulb granule cells and their role in synaptic processing.

How activity patterns shape hippocampal connectivity

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In response to specific patterns of correlated activity, chemical synapses can change their transmission characteristics. These changes, known as LTP and LTD, can last more than one hour and have been shown to occur during learning. To form stable long-term memories, however, analog changes in synaptic strength might only be the first step to a more radical rewiring of neuronal networks. Following the fate of individual Schaffer collateral synapses over several days allowed us to investigate the long-term consequences of LTP and LTD on synaptic stability. We found that LTP increased the survival rate of hippocampal synapses while LTD led to pruning of the depressed synapses and their immediate neighbors.

A potentiating event 24 hours after LTD completely rescued synaptic stability. Synaptic survival after LTD was strongly correlated with frequent glutamate release from the presynaptic terminal, but pharmacogenetic silencing of the presynaptic neuron did not lead to destabilization of the synapse. Thus, it takes uncorrelated activity, not just silence, to trigger removal of a synaptic connection. Furthermore, hippocampal synapses are able to decode the timing of pre- and postsynaptic activity with millisecond precision and adjust their strength according to the frequency of correlated events. Taken together, our data suggest that the hippocampal connectivity pattern at a given point in time can be interpreted as a record of (correlated) activity in this particular neuronal network.

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Mechanisms of $GABA_AR$ **targeting and clustering at inhibitory synapses**

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Synaptic inhibition plays a critical role in regulating the balance of excitation and inhibition in the brain and thus information processing. The strength of inhibition is determined to a large extent by the number of $GABA_AR$ receptors ($GABA_ARs$) at synaptic sites, which can be controlled by receptor stabilisation in the synaptic membrane. However, the machinery that regulates local signaling at inhibitory synapses and that stabilises synaptic receptor pools remains poorly understood. I will talk about our ongoing work to better understand the machinery important for targeting and stabilization of $GABA_ARs$ at synapses. I will focus on the role of local regulators of actin dynamics important for regulating inhibitory synapse strength and the role of small GTPase signaling pathways. I will also present our latest work on new transmembrane receptor-associated molecules important for driving the cell specific clustering of $GABA_ARs$ at inhibitory synapses in vitro and in vivo. Our identification of novel machineries important for regulating the synaptic targeting and clustering of $GABA_ARs$ opens up new avenues for understanding the construction and regulation of inhibitory synapses in the brain.

Molecular motors and associated proteins at neuronal synapses: Drivers of membrane trafficking underlying plasticity, learning and memory

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The delivery, removal, and recycling of synaptic neurotransmitter receptors involves post-Golgi transport through molecular motors along microtubules and actin filaments. In addition, at the cell surface, receptors exchange between synaptic and extrasynaptic positions via membrane diffusion and trapping. We have studied proteins that regulate the specificity of receptor trafficking, including cargo adapters and accessory transport factors.

For example, the multi-PDZ domain protein GRIP1 not only regulates the synaptic transport of AMPA receptors through the kinesin motor KIF5, but combines vesicular AMPA receptor transport with the delivery of N-Cadherin, also heading towards spine synapses. Furthermore, $GABA_AR$ 1-containing receptors bind to muskelin, which controls association with myosin VI or dynein motor complexes in subsequent steps of $GABA_AR$ endocytosis. The kinesin KIF21B mediates dual functions in regulating both cargo transport and microtubule dynamics. Recent data suggest that this motor participates in the submembrane recycling of synaptic receptors. Genetic knockout of KIF21B affects learning, memory indicating a critical role of this kinesin in higher order brain function.

Our data highlight specific trafficking factors as critical regulators in mediating the specificity of plasticity-related protein (PRP)-transport at neuronal synapses.

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Role of kinesin-3 molecular motors during synaptic plasticity in the hippocampus

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Synaptic plasticity mechanisms are widely studied as the cellular and molecular basis for learning and memory. A fundamental mechanism is the transport of AMPA-type glutamate receptors to and from the synapse in response to changes in neuronal activity. This continuous turnover of membrane proteins and

regulated transport is mediated, among others, by Rab GTPases that drive endosomal trafficking and carried out by molecular motors and cytoskeleton associated complexes.

In this work, we have investigated the role of microtubule-dependent motor proteins in the regulated transport of receptors during synaptic plasticity.

Using electrophysiological techniques in organotypic hippocampal slice cultures, in combination with dominant-negative approaches and shRNA-dependent knock-down, we have found that one member of the kinesin-3 family of motor proteins is required for long-term potentiation (LTP), but does not participate in the maintenance of synaptic transmission or in long-term depression (LTD). In addition, we have found that this kinesin-3 motor protein drives a subcellular redistribution of the dendritic endosomal machinery during LTP, as monitored by live fluorescence imaging of the Rab11-interacting protein FIP2. Using biochemical techniques, we are also characterizing the molecular components that couple AMPA receptor subunits to the motor protein complex.

Overall, these experiments are allowing us to establish specific kinesin molecular motors as key components of the activity-dependent endosomal transport of AMPA receptors during synaptic plasticity.

Transcription factors to define taste versus somatosensory neurons of the geniculate ganglion

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The geniculate ganglion is formed of chemosensory neurons innervating taste buds of anterior tongue and palate, and somatosensory neurons innervating the ear. Because neuronal diversity is defined by transcription factors (TFs), we sought to identify TFs that distinguish taste from somatosensory neurons in the geniculate ganglion of mice. First, we identified candidate TFs by differential expression in RNAseq of geniculate and trigeminal ganglia. Second, we tested up to 20 candidates to identify those expressed in discrete subsets of neurons. By single-neuron RT-PCR, mRNAs for Phox2b and Drg11 were detected respectively in 11 and 12 non-overlapping sets of neurons. Similarly, immunoreactivity for Phox2b and Drg11 was detected in separate populations of neurons, and accounted for all ganglion neurons. To assess if either of these two TFs is restricted to taste neurons, we co-stained for the taste afferent receptor, P2X2. Phox2b-immunoreactive nuclei were detected in 97% (of 138) of P2X2-immunoreactive neurons. Immunoreactivity for another TF, Brn3b, also did not overlap with Phox2b-expressing cells. Our results suggested that Phox2b may serve as a marker for taste neurons while Drg11 and Brn3b may be markers for somatosensory neurons in the ganglion. To test this, we anterograde-labeled chorda tympani (CT)

and greater superficial petrosal (GSP) taste nerves with fluorescent (Al488, TRITC) dextrans and subjected the ganglia to immunostaining. Drg11 was detected in only 1% (of 300) labeled taste neurons. Conversely, over 90% (of 83) GSP- and CT-labeled neurons included Phox2b-positive nuclei. Thus, Phox2b and Drg11 can serve as validated markers for taste and somatosensory neurons respectively. Recently, 5HT3A was shown to be expressed in a subset of geniculate ganglion neurons. To assess if this receptor is associated with one of the above groups, we immunostained ganglia from Htr3a-GFP mice. Only GFP-bright neurons were consistently positive for P2X2 and Phox2b; GFP-faint neurons were distributed in both the taste and somatosensory neuron populations. Thus, Htr3a-expressing neurons are likely a heterogeneous group of neurons with varying significance.

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A presynaptic mechanism for redistribution of synaptic weights in a recurrent circuit

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Recurrent excitatory networks face challenges in supporting synaptic plasticity for information storage yet maintaining overall stability. Avoidance of runaway firing despite potential positive feedback loops puts heavy demands on processes of homeostasis. Simulations of recurrent networks predict that cell-wide synaptic scaling would generate marked instabilities; stability can be achieved if individual synaptic weights are not yoked together by a single multiplicative factor, but are allowed greater autonomy (Buonomano). Indeed, clear distinctions have been noted in how recurrent and feedforward circuits respond to homeostatic challenges. We recorded from CA3 pyramidal neuron pairs in hippocampal slice cultures to characterize synaptic and circuit-level changes in recurrent synapses resulting from long-term inactivity (Mitra). Chronic tetrodotoxin treatment greatly reduced the percentage of connected CA3-CA3 neurons, but enhanced the strength of the remaining connections, an extreme form of heterogeneity. Presynaptic release probability (Pr) sharply increased, whereas quantal size was unaltered. Connectivity was decreased in activity-deprived circuits, not by reduction of spine or bouton density or aggregate dendrite length but by functional silencing of synapses. The silencing arose from enhanced Cdk5 activity and could be reverted by acute Cdk5 inhibition with roscovitine. The recurrent circuit adapted to chronic inactivity by reallocating presynaptic weights, strengthening certain connections while silencing others.

To study this heterogenous redistribution of synaptic weights, we used two-photon Ca2+ imaging to probe presynaptic Ca2+ transients (CaTs). Classically, an action potential (AP) traveling along a presynaptic axon is postulated to trigger Ca2+ entry into synaptic boutons without fail, leaving regulation of Pr entirely in the hands of downstream SNARE machinery. With a few exceptions, CaTs are thought to be 100% reliable.

We found that repeated single AP (1AP) stimulation of CA3 pyramidal cell axons produced abundant CaT failures. These occurred intermittently and locally rather than distributed across an entire axonal branch, indicating that they were not accounted for by conduction failure. Manipulations of AP duration and external Ca2+/Mg2+ ratio altered the incidence of CaT failures and highlighted their slow regulation, likely by kinases and phosphatases. CaT failures changed in reaction to chronic activity blockade, providing underpinning for the heterogeneous reallocation of synaptic weights. While some boutons strengthened as seen by increases in both CaT amplitude and Psuccess, another subset of boutons became inert to 1AP stimulation, while staying responsive to a 10 Hz train. Remarkably, both effects of chronic TTX treatment were rescued by CDK5 block with roscovitine. Taken together, our findings uncover large all-or-none variations in axonal CaT dynamics and leave ample room for Pr regulation via Ca2+ channel modulation, upstream of fusion machinery. Such presynaptic mechanisms may enable re-allocation of synaptic weights in response to homeostatic challenges. Increasing dynamic range in this way offers potent advantages for information capacity, energy-efficiency and network stability.

Odorant receptors and neural circuits involved in innate behaviors in mice

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Molecular bases for odorant or pheromone-induced innate behaviors have begun to be revealed in mice. However, how individual odorant receptors (ORs) are involved in behavior to each odorant or pheromone has not been known. Using odorants that are recognized by a small number of ORs and induce preference or avoidance behavior, we show that ORs are functionally redundant at a peripheral odorant-binding level but each OR sends a signal to a neural circuit that possesses distinct valence, leading to a certain behavior. Further, the detailed neuronal circuits in the brain that process distinct signals to evoke appropriate behavioral responses are largely unknown. We have attempted to dissect neuronal circuits for a mouse sex pheromone ESP1 as a model, by using viral and genetic tools. We identified a specific type of projection neurons in the medial amygdala that convey the pheromone signals selectively to a downstream target in the hypothalamus. We also functionally identified a specific hypothalamus-midbrain pathway necessary for the behavior at a cellular resolution.

Flexible coding of taste quality in the human brain

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The taste system provides important information about the edibility and macronutrient content of a food via differentiation between taste qualities. Specific receptors on the tongue are activated by chemicals signifying a taste quality before the signal is conveyed to the brain. How this peripheral signal is used by the central nervous system to encode taste quality is largely unknown. Taste qualities have been shown to differ in behavioral response times in humans and rodents yet the relevance of these latency differences remains unclear. In human participants, we investigated spatio-temporal properties of taste quality representations in the cortex and whether these representations are used for perceptual decisions during different tasks. Time-resolved multivariate pattern analyses of head-surface electrophysiological brain responses evoked by tasting salty, sweet, sour, and bitter tasting solutions revealed that global neuronal response patterns allow to decode which tastant participants tasted on a given trial. Taste quality information was largely limited to the delta and theta frequency bands (<8 Hz) in line with recent findings from local field potentials in the rat. Moreover, taste quality decoding was successful as soon as the earliest taste evoked response was observed highlighting that quality is encoded early during taste processing. Quality-specific differences in decoding onset were more pronounced during fast-paced tasks and predictive for behavioral response latencies suggesting that neural response latencies reflect processing speed in a task-dependent.

Together, the findings suggest flexible neural gustatory response coding which is predictive for taste-related decision-making.

Imaging neural ensembles during learning

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We study plasticity within the motor cortex during motor learning. We previously showed that the relationship between the activity of motor cortex L2/3 neurons and movements can be fundamentally shaped with motor learning. The motor cortex can control movements through direct connections to motor circuitry within the spinal cord, but it is unknown whether these changes are ultimately funneled through stable corticospinal output activity or if the corticospinal output itself is plastic. We are investigating the consistency of the relationship between corticospinal neuron activity and movement through in vivo two-photon calcium imaging in mice across learning of a lever-press task. Furthermore,

we study how the cortex-wide macro-scale activity may reorganize during motor learning. We are investigating cortex-wide activity of the mouse brain using wide-field calcium imaging while the mouse learned a motor task over weeks. I will share the latest results from these investigations.

Controlling synapse variability and plasticity in single neurons

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Dendrite is a neuronal structure specialized for receiving and processing information through its many synapses. How incoming activity modifies synaptic strength distribution across the dendrite is fundamental to understanding brain function although much remains unclear. Using a combination of electrophysiology and imaging approaches in hippocampal networks, we have studied the relationship between neighboring synapses in single postsynaptic neurons. We provide evidence for a novel cellular mechanism that enhances the heterogeneity of presynaptic strengths of convergent connections received by the dendrite.

Threat detection by the mammalian olfactory system

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There is currently increased interest in the neural circuits underlying threat detection in vertebrates. The mammalian olfactory system has evolved multiple circuits and subsystems for the detection and avoidance of threatening stimuli such as predator odors, pathogen-associated molecules, and chemical cues reflecting spoiled food. Recent evidence has shown that the olfactory system comprises also specific detection and avoidance mechanisms for some environmental cues that reflect acute danger. This lecture will focus on a subset of sensory neurons in the mouse main olfactory system that express the soluble guanylate cyclase Gucy1b2 and the two cation channel Trpc2 and Cnga2: type B cells. We have recently reported the first sensory stimulus for type B cells, a reduced level of environmental oxygen. Low oxygen induces calcium influx in these neurons, and Gucy1b2 and Trpc2 are both required for these cellular responses. In vivo exposure of a mouse to low environmental oxygen causes Gucy1b2-dependent activation of postsynaptic olfactory bulb neurons in close vicinity to the glomeruli formed by axons of Gucy1b2-expressing sensory neurons. Low environmental oxygen also induces conditioned place aversion, for which Gucy1b2 and Trpc2 are required. We propose that this chemosensory function enables a mouse to assess rapidly the oxygen level in the external environment. This is the first report of an oxygen

sensor in the mammalian olfactory system and the first evidence for a physiological and biological function for the Trpc2 cation channel outside vomeronasal sensory neurons. Our results suggest a novel signaling paradigm in olfaction that is based on parallel TRP- and CNG channel networks within a given type of sensory neuron.

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Electrophysiological correlates of sniffing and smelling in human piriform cortex

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Odor-evoked oscillatory activity is pervasive throughout vertebrate and invertebrate nervous systems, implying that rhythmic activation patterns play a fundamental role in odor coding. However, while respiratory oscillations are a ubiquitous hallmark of olfactory system function in animals, there is scant evidence for such patterns in the human brain. By using intracranial EEG recording techniques to measure local field potentials from rare patients with medically resistant epilepsy, we have shown that electrical fluctuations in human piriform cortex (PC) are in phase with the natural cycle of breathing. This respiratory synchrony extends across both temporal and spatial scales, with higher-frequency oscillatory entrainment not only in PC, but also in amygdala and hippocampus, and is reliant on the movement of airflow through the nose. We have also found that odor stimulation elicits theta oscillations in human PC that are robust across trials, odors, and subjects. Classification analysis reveals that piriform theta activity conveys odor-specific content that can be decoded within 110 milliseconds of a sniff, suggesting a mechanism by which the human olfactory system can rapidly differentiate qualitative features of a smell. The identification of odor-induced theta – despite the fact that humans breathe an order of magnitude slower than theta – plausibly suggests that the theta frequency is a privileged frequency, conserved throughout the evolution of mammalian brains as an optimal rhythm for mediating information transfer and exchange among limbic networks.

Similarity matching: A new principle of neural computation

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Abundance of recently obtained datasets on brain structure (connectomics) and function (neuronal population activity) calls for a normative theory of neural computation. In the conventional, so-called, reconstruction approach to neural computation, population activity is thought to represent the stimulus.

Instead, we propose that the similarity of population activity matches the similarity of the stimuli under certain constraints. From this similarity matching principle, we derive online algorithms that can account for both structural and functional observations.

Regulation of microtubule minus-end dynamics by a complex of microcephaly-related proteins ASPM and katanin

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Microcephaly is a neurodevelopmental disorder characterized by small head and brain, and intellectual disability. ASPM (abnormal spindle-like microcephaly-associated) is the most common gene mutated in microcephaly patients, but the molecular mechanisms underlying ASPM activity are poorly understood. We found that ASPM forms a physiological complex with the microtubule-severing protein katanin, which is also known to be mutated in microcephaly patients. In vitro reconstitution experiments demonstrated that ASPM autonomously tracks growing microtubule minus ends and inhibits their growth, while katanin decorates and bends both ends of dynamic microtubules and enhances the minus-end blocking activity of ASPM. ASPM also binds along microtubules and recruits katanin, promoting efficient katanin-mediated severing of dynamic microtubules. The two proteins colocalize at the poles of mitotic spindles and regulate spindle flux and spindle positioning. We propose that ASPM-katanin complex controls microtubule disassembly at spindle poles, and that misregulation of this process can lead to microcephaly by perturbing cell division of neural progenitors.

Molecular, cellular and neural analyses of multiple sweet signaling pathways in the mouse periphery

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Previous studies in mice demonstrated that sweet (T1R2+T1R3), umami (T1R1+T1R3), bitter (T2Rs), salty (ENaCs) and sour (PKDs/ASICs etc) receptors are expressed in the different set of taste bud cells,

respectively. Such molecular evidence suggest that 5 fundamental taste qualities might be sensed by dedicated taste bud cells that relay quality information to gustatory nerve fibers. However, physiological responses of taste cells and gustatory nerve fibers might not be so simple. We found that there are at least two types of salty-, sweet- and umami-responsive taste cells and gustatory nerve fibers segregated by their susceptibilities to amiloride, an ENaCs inhibitor, and gurmarin, a T1R3 inhibitor. In addition, a significant portion of taste cells and gustatory nerve fibers respond to multiple taste qualities. Multiple sensitivity in taste cells may be caused by cell-cell communication, or expressing multiple taste receptors, or taste receptors that are sensitive to multiple taste qualities.

Recently, Dr. Morgolskee and his colleagues demonstrated that in addition to T1R2+T1R3, the primary sweet sensor for sugars and noncaloric sweeteners, glucose transporters (GLUTs, SGLTs), and the ATP-gated K^+ (KATP) channel were expressed in sweet-responsive cells forming a T1R-independent sweet sensing pathway detecting sugars. We also found that there exist sweet-responsive fibers whose responses to sugars, but not to noncaloric sweeteners, are enhanced by addition of Na ion and the mixture responses are inhibited by Phloridin, a SGLT inhibitor, and sweet-responsive cells whose responses to sweet compounds are inhibited by leptin via KATP channels. Furthermore, similar to sugar-sensing pathway in gut enteroendocrine cells, sweet responsive cells expressed a gut peptide hormone, GLP-1 and its receptors were expressed in gustatory neurons. GLP-1 was released immediately from taste bud cells in response to sweet compounds but not to other taste stimuli, suggesting that GLP-1 may be involved in normal sweet taste signal transmission together with ATP in mice. The results of the above experiments will be described and their implication for functional significance of multiple sweet sensing pathways will be discussed.

Associative learning and anticipatory signals in the gustatory system

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As animals navigate their environment, they associate various stimuli with the presence of food. These associations transform neutral stimuli into predictive cues. Research on how anticipatory cues are learned and shape behavior has largely focused on limbic areas. However, expectations triggered by anticipatory cues can also influence sensory processing. Yet, little is known on anticipatory activity in sensory areas.

Over the past years, my group has studied how stimuli predictive of taste change activity in the gustatory cortex (GC), modulate taste processing and affect behavior. Our research has relied on behavioral electrophysiology, manipulations of neural activity, and computational methods. We found that after learning cue-taste associations, neurons in GC change their firing activity in responses to non-gustatory

stimuli. Cue-responses emerge with learning and encode general expectations of gustatory stimulation, as well as expectations of specific gustatory outcomes. When the ability of different modalities to engage into cue-taste associations was tested, we observed that odors and tactile stimuli were learned more rapidly than sounds and lights. This result is consistent with the distribution of GC responses to stimuli of different modalities in naïve animals, which shows a bias toward odors and tactile stimuli.

Cue responses in GC show a rich phenomenology, but what is their function? We found that cue responses play a role in guiding consummatory behaviors and in speeding up taste coding. The effect of cue responses on coding was analyzed further, and I will show that it can be explained by expectation-induced changes in attractor dynamics of GC networks.

The significance of this work for current theories of GC function and computations of sensory cortices in general will be discussed.

Neural circuits mediating the locomotor state dependent firing of neurons in the hippocampal formation

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Hippocampal oscillations and neuronal activity rates have long been known to depend on locomotion. However, the circuit mechanisms by which locomotion-related activity translates into speed-correlated neuronal activity have remained obscure along with the underlying circuitry. I will present the results of our research on the function of circuits within the basal forebrain (the medial septal nucleus and the diagonal Band of Broca) that play a role in the initiation and velocity-modulation of locomotor behavior. We describe a glutamatergic medial septal circuit that, in addition to a direct modulation of locomotor activity itself, mediates the pre-motor initiation of theta oscillations and, via hippocampal disinhibition, underlies the locomotion speed dependence of hippocampal CA1 neuronal firing rates. Furthermore, I will provide evidence for a role of the same circuit in providing speed-correlated input to several cell-types in the layers 2/3 of medial entorhinal cortex. The glutamatergic speed signal is integrated most effectively by pyramidal cells but also excites stellate cells and interneurons. Thus, during locomotion the MSDB conveys speed information that can be used by hippocampal and MEC neurons for spatial representation of self-location.

Effect of age on the epigenetics of learning and memory genes

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Aging is associated with the occurrence of numerous physiological modifications in various organs including the brain. With advancing age, neurons lose their capability to adapt to and recover from accumulating and potentially damaging alterations such as oxidative stress, DNA damage, mitochondrial impairment, and protein misfolding and aggregation. One of the most evident consequences of these biochemical changes are deficits in learning and memory. While these are, in general, minimally invalidating, the underlying biochemical alterations constitute an indispensable condition for the occurrence of pathological brain aging. To address this problematic we studied the epigenetic regulation of early memory genes in response to a low NMDA dose, as model for long term depression, a synaptic plasticity paradigm. In young animals, NMDA/LTD induces the transcription of Bdnf gene from promoters I, II, IV and VI possibly through the demethylation of Histone 3 at Lysine 27 (H3K27Me3) and by the phosphorylation at Serine 28 of H3K27Me3, leading to displacement of EZH2, the catalytic subunit of Polycomb Repressor Complex 2. In addition to de-repression, NMDA-LTD induces the dissociation of another transcriptionally repressive enzyme such as histone deacetylase 4 (HDAC4) while enhancing positive regulation via acetylation of histone H3K27 via pCREB/CBP. Logically, all these changes elicited by NMDA result in Bdnf transcription. Differently from the young animal situation, old animals present a significantly reduced Bdnf induction when exposed to NMDA-LTD, as a result of impaired HDAC4 dissociation and poor CBP recruitment and Histone H3K27 acetylation at Bdnf promoters. Mechanistically, the deficits in the old seem to be due to the loss of cholesterol at the neuronal plasma membrane, affecting the efficacy of NMDA activation of the CaMCa2 activation of CREB/CBP and HDAC chromatin displacement. These results unveil one of the mechanisms involved in the cognitive decline of the old.

PI3K-PTEN signaling for synaptic plasticity

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Synaptic connections in the brain are continuously remodeled in response to neuronal activity. This process, known as synaptic plasticity, is critical for the establishment of functional neuronal circuits during development and also for learning and memory in adulthood. Multiple signaling pathways and molecular mechanisms contribute to synaptic plasticity in different brain regions. During this presentation I will describe our latest results on phosphoinositide-dependent signaling and their role during long-term

potentiation and long-term depression in the hippocampus. Interestingly, these pathways appear to be off-balance in Alzheimer's disease, leading to cognitive dysfunction. We will consider this information for potential therapeutic avenues.

The GC-D/necklace olfactory subsystem and food-related social learning

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The main olfactory system contains a number of subsystems that can be differentiated by the stimuli to which they respond, the receptors and signaling molecules used to detect and transduce those stimuli, the regions of the main olfactory bulb (MOB) they innervate, and the behaviors they subserve. For example, olfactory sensory neurons (OSNs) expressing the unique olfactory receptor GC-D (guanylyl-cyclase D) and effector channel Cnga3 (cyclic nucleotide-gated channel A3) have been found to respond to a small group of semiochemicals implicated in social learning about food. These OSNs project to the caudal MOB, a poorly defined region that includes the "necklace glomeruli" (a target of GC-D+ OSNs) and that also receives input from other chemosensory neurons that utilize a cGMP-mediated transduction mechanism. In this presentation, I will discuss our ongoing studies of the anatomy, function and behavioral relevance of the GC-D/necklace olfactory subsystem, particularly in the context of other main olfactory subsystems.

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Molecular architecture of inhibitory synapses: Implications for plasticity and disorders

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Over the past three decades, purification and analysis of protein complexes at the excitatory postsynapse has led to fundamental insights in neurobiology. These insights include how receptor trafficking, synaptic adhesion, cytoskeletal remodeling, and protein phosphorylation contribute to the synaptic plasticity underlying learning and memory. Moreover, genetic perturbations of excitatory postsynaptic proteins are now known to contribute to developmental brain disorders and psychiatric conditions.

In contrast to the well-studied excitatory synapse, biochemical purification and analysis of the inhibitory postsynaptic specialization has remained largely intractable. Fast inhibitory synaptic inputs onto

excitatory neurons modify neuronal membrane potentials, spike timing, and the summation of postsynaptic excitatory potentials. Abnormalities of symmetric (inhibitory) synapses at excitatory neurons are linked to multiple developmental brain disorders (DBDs), including autism spectrum disorders (ASD), neonatal hyperekplexia, intellectual disability (ID), and epilepsy. Yet the molecular mechanisms that regulate the inhibitory postsynaptic structure (termed here iPSD) of excitatory neurons are poorly understood as the proteins at this site were, until recently, obscure. We performed a chemico-genetic proteomic study to resolve the molecular composition of the iPSD as it exists in vivo. We discovered a rich diversity of proteins enriched at the iPSD, including several novel proteins as well as proteins encoded by genes whose mutations are implicated in developmental brain disorders. These results and the analysis of their function at the iPSD will be discussed.

Deconstruction and reconstruction of olfactory computations

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We use the olfactory system of zebrafish as a model to understand neuronal computations involved in pattern classification. Exploiting the small size of the zebrafish brain, we measure neuronal activity patterns using multiphoton calcium imaging, manipulate neuronal activity using optogenetics, and reconstruct neuronal circuits using serial block face scanning electron microscopy (SBEM). We developed new methods for SBEM, densely reconstructed all 1047 neurons in the olfactory bulb of a zebrafish larva, and annotated most of their synapses. The results allowed us to classify neurons into morphological classes, to identify new rare cell types, and to analyze the topology of inter-glomerular projections. We found that the larval olfactory bulb contains a “core circuitry” that corresponds to the superficial interneuron network in the adult olfactory bulb and shows similarities to the insect antennal lobe. Long-range inter-glomerular projections were not random but organized by the identity of olfactory glomeruli. Although synapse annotation is still ongoing, preliminary results already provide evidence that the non-random organization of projections contributes to neuronal computations involved in the classification of odor representations. These results indicate that neuronal computations performed by a core circuitry of the olfactory bulb depend on specific patterns of inter-glomerular connectivity. More generally, these results provide proof-of-principle that “higher-order” circuit functions can depend on neuronal wiring diagrams, and that computational consequences of wiring diagrams can be analyzed by “functional connectomics” approaches.

Functional flexibility of the vertebrate bitter taste receptor family

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Bitter compounds occur frequently in nature and some of these substances represent powerful toxins or show other detrimental pharmacological effects. Therefore, the recognition of bitter substances prior to ingestion is important for the survival of species. Since the presence of toxic bitter substances changes between habitats and environmental conditions, the compounds that were required to be recognized fluctuated during evolution. To identify the relevant bitter chemicals, species rely on a family of G protein-coupled receptors, the taste 2 receptors (TAS2R). The number of putatively functional TAS2R genes deviates considerably among vertebrates ranging from 0 to ~80, a fact that has been associated with different nutritional habits. In addition to the sizes of TAS2R gene repertoires, the tuning breadths of the individual receptors exhibit vast differences ranging from “specialist receptors” with small ligand spectra to “generalist receptors” with wide ligand spectra, which again hints at the considerable evolutionary dynamics shaping bitter taste perception in vertebrates. Humans possess an average sized TAS2R gene repertoire consisting of ~25 differently tuned receptors. The frequent occurrence of TAS2R gene variants in humans further increases the number of functionally different receptors within the population. We have carefully characterized human TAS2Rs as well as a number of bitter taste receptors of other vertebrate species providing a solid fundament for comparisons and for the identification of signatures of evolutionary dynamics shaping these receptors. Our detailed structure-function analyses of several human TAS2Rs revealed insights into the architecture of ligand binding pockets and allows predictions about the conservation of agonist profiles in related bitter taste receptors of other species. Functional expression of human TAS2Rs also enabled the discovery of selective artificial and natural bitter taste receptor inhibitors, which exhibit an ambivalent mode of action by inhibiting some receptors, while activating others. In particular the occurrence of inhibitors in the same plants that synthesize bitter metabolites suggests that such compounds may have played an important role during bitter taste receptor evolution. The fact that bitter taste receptor expression is not limited to the oral cavity, but extends to numerous additional tissues indicates that non-gustatory processes might have contributed to shape TAS2R genes as well.

The presentation will summarize our recent findings with a focus on evolutionary aspects.

Neural coding and plasticity of representations in cell assemblies of the mammalian olfactory system

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Sensory information is translated into ensemble representations by various populations of projection neurons in brain circuits. The dynamics of ensemble representations formed by distinct channels of output neurons in diverse behavioral contexts remains largely unknown. We studied the two output neuron layers in the olfactory bulb (OB), mitral and tufted cells, using chronic two-photon calcium imaging in awake mice. Both output populations displayed similar odor response profiles. During passive sensory experience, both populations showed reorganization of ensemble odor representations yet stable pattern separation across days. Intriguingly, during active odor discrimination learning, mitral but not tufted cells exhibited improved pattern separation, although both populations showed reorganization of ensemble representations. An olfactory circuitry model suggests that cortical feedback on OB interneurons can trigger both forms of plasticity. In conclusion, we show that different OB output layers display unique context-dependent long-term ensemble plasticity, allowing parallel transfer of non-redundant sensory information to downstream centers.

Synaptic correlates of learning and memory

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Learning and memory depend on the hippocampus and are impaired in Alzheimer's disease (AD). Synapse loss represents a major hallmark of AD. However, whether the formation and elimination of synapses contribute to learning and memory and how this rewiring of the neuronal network is influenced by disease remains largely unexplored. Therefore, we investigated rewiring within a hippocampal microcircuit consisting of CA1 pyramidal neurons and oriens lacunosum moleculare (O-LM) interneurons. We aimed at identifying mechanisms contributing to rewiring of synapses under normal and disease conditions. We used two-photon in vivo imaging of CA1 pyramidal neurons and O-LM interneurons in APP/PS1dE9 mice to analyze pre- and post-synaptic morphology throughout disease progression and during learning and memory. We performed awake Calcium imaging of O-LM interneurons in head-fixed mice to analyze the

activity of O-LM interneurons during memory acquisition. We carried out mono-transsynaptic retrograde tracing experiments to analyze the connectivity of O-LM interneurons. Furthermore, we performed pharmacogenetic and pharmacological experiments to determine the mechanism of O-LM interneuron dysfunction in a mouse model of AD. We revealed structural plasticity deficits of O-LM interneuron synapses with disease progression and dependent on Abeta-pathology. Furthermore, we detected impaired synaptic rewiring upon memory acquisition under AD-like conditions on both CA1 pyramidal neurons and O-LM interneurons. We identified decreased cholinergic input from the medial septum onto O-LM interneurons as a mechanism for memory impairment in a mouse model of AD. Our data provide a new mechanism how cholinergic degeneration affects memory via dysfunction of O-LM interneurons.
This research has been funded by the DZNE, the German research foundation (KFO177, CRC1089), and Centres of Excellence in Neurodegeneration (CoEN).

Molecular and neural circuit mechanisms for experience-dependent behavioral switching in C. elegans

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How neural circuit dynamically changes the mode of information flow based on memory is a major question in neuroscience. We are addressing this question by using a small nervous system of the nematode C. elegans. Specifically, we concentrate our efforts on associative learning between salt (NaCl) and food. Worms apparently memorize the concentration of salt and approaches this concentration if the salt was associated with food, but avoids it if salt was associated with starvation.
Insulin/PI3-kinase pathway plays an essential role in the salt-starvation associative learning. Mutants of ins-1, one of the forty insulin genes in C. elegans, and those of daf-2, encoding an insulin/IGF receptor homologue, fails to avoid the salt concentration associated with starvation. We found that localization of the insulin receptor DAF-2c is a key to this type of learning: DAF-2c is transported from the cell body to the axonal region and acts there, probably to regulate presynaptic functions. By temporal segregation experiments, activity of the INS-1 insulin was found to be required mainly during the test rather than during conditioning. In this respect, localization of DAF-2c to the axon serves as a memory of starvation, and directs the salt avoidance behavior upon activation of the receptor by INS-1. How is the behavioral response reversed (between migration towards higher and lower salt) depending on the status of the nervous system? We have identified the roles of primary interneurons immediately downstream of the salt-sensing neurons. By optogenetic manipulation, we further determined that the major source of the behavioral switch was the change in the transmission between sensory neurons and interneurons, and the interneurons send motor signals to regulate the forward/turning behaviors. The Gq/PLC/nPKC

pathway robustly regulates the behavior by acting in the sensory neuron, and appears to be part of the concentration memory. Concerted actions of these molecular regulators shape the information flow in the neural circuit and thereby regulate the sensorimotor program of the animals.

Ligand-gated ion channels: From 3D structure to transmembrane signaling

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Neurotransmitter-gated ion channels of the Cys-loop receptor family mediate fast neurotransmission throughout the nervous system. The molecular processes of neurotransmitter binding, subsequent opening of the ion channel and ion permeation remain poorly understood. Here we present recent results of high-resolution X-ray crystallography, single particle imaging, and molecular modeling studies of a mammalian Cys-loop receptor, the mouse serotonin 5-HT_3 receptor. We revealed at atomic detail how neurotransmitter binding on the extracellular domain of the 5-HT_3 receptor induces sequential conformational transitions in the receptor opening a transmembrane ion channel: Agonist binding first induced distinct conformational fluctuations of particular side chains in the highly conserved ligand binding cage, followed by tilting-twisting movements of the extracellular domain which coupled to the transmembrane TM2 helices to open the hydrophobic gate and forming a continuous transmembrane water pathway. The structural transitions in the receptor's transmembrane part finally coupled to the intracellular region opening passages for ion release. The details of structural transitions of the 5-HT_3 receptor deliver important insights for understanding the activation mechanism of mammalian Cys-loop receptors.

Dynamics and multi-modality in gustatory cortical function

Donald Katz

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Taste function, and its neural underpinning, is often described in quite simple terms, with each taste represented by a specific set of neurons (either unique or overlapping with those coding other tastes). Our data show that taste responses in gustatory cortex (GC) and elsewhere are in fact dynamic and flexible, reflecting processing that culminates in consumption-related decisions--decisions that change with experience and context. These results adjust our understanding of taste processing, and of the "job" of GC in particular. Further work adjusts this understanding still further, demonstrating that activity in GC plays a role in the dynamic processing of even odor stimuli.

GRIP1 and its interactants in dendritogenesis and synaptic plasticity

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A crucial element of neuronal networks and their homeostatic plasticity are the dendritic trees, where neurons receive and begin to integrate information. The transmission and integration of information is heavily influenced by the structure of the dendritic tree, whose morphogenesis and maintenance are therefore highly regulated.

Our research focuses on key proteins involved in these processes, namely the glutamate receptor interacting protein (GRIP) 1 and its molecular partners. We have previously shown GRIP1 requirement for dendritic development; we also identified and molecularly characterized an interaction between GRIP1 and 14-3-3 proteins, which is essential for the function of GRIP1 in dendritic cargo transport and in dendritogenesis (Geiger et al, 2014). Furthermore, we showed that GRIP1 bridges a complex including the Reelin receptor ApoER2, the signalling molecule ephrinB2 and the GluR2 subunit of AMPA receptors, the formation of which also depends on the phosphorylation of a single residue of ephrinB2, the serine -9. Neuronal activity and Reelin stimulation induces the formation of the complex and regulates AMPA receptor new insertion into the dendritic membrane, thereby affecting synaptic strength (Essmann et al, 2008; Pfennig et al, in revision). Interestingly, we have also discovered an interaction between ephrinB2 and VEGFR2 in neurons, required for proper dendritic and spine morphogenesis in the developing hippocampus (Harde et al, in preparation).

In this context, my project aims to better understand the molecular mechanisms behind the functions of GRIP1 and its signalling partners in dendritogenesis and synaptic plasticity. My current results confirm the requirement of the neuronal interaction between ephrinB2 and VEGFR2 for long-term potentiation (LTP) in the young hippocampus, as well as of the GRIP1/GluR2/ephrinB2/ApoER2 complex for LTP in the adult hippocampus.

The evolutionary transcriptomic landscape of mammalian olfaction

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The importance of sensing the molecular environment is reflected in the genetic investment in encoding olfactory receptors (ORs), which constitute the largest mammalian gene family. The OR gene repertoire is largely species-specific, and shaped by the nature and necessity of chemosensory information for survival in each species' niche. In addition to differences in the ORs, the morphology, size, neural projections and organization of chemosensory epithelia vary remarkably across mammals, suggesting differences in wider gene expression networks. By combining RNA-seq with FACS in a hierarchical fashion from whole olfactory mucosa (WOM) to single olfactory sensory neurons (OSNs), we have identified the complete transcriptional profile of mouse OSNs, and their heterogeneity at the single cell level. But 25 years after the discovery of the ORs, the interspecific molecular heterogeneity of the olfactory system still remains largely unknown. To study the evolutionary dynamics of gene expression in the olfactory system among species with different chemosensory niches, we performed RNA-seq of the WOM of six species of rodents, carnivores and primates (including humans). Our comparative transcriptome-wide analysis reveals a high degree of molecular conservation across 95 million years of mammalian evolution. We found that ORs are expressed across a large dynamic range in these six species. RNA abundances correlate well with the number of OSNs expressing an OR. Combining RNA-seq with a phylogeny-based method that classifies ORs into orthologous gene groups (OGGs), we found that phylogenetic conservation does not imply conservation in OR gene expression: we find numerous examples of highly-expressed ORs specific for a single species or order. . Our data further suggests that some highly expressed ORs are involved in the detection of food odorants. This experimental strategy has identified OR genes that may have been selected for different niches, and identified food odorants' detection as one of the possible driving evolutionary forces contributing to a better understanding of the evolution of olfaction.

Short-term and long-term effects of human olfactory learning

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The human olfactory system is highly adaptable to changes in the chemical environment. Olfactory training can induce reliable olfactory cortical plasticity and perceptual changes in humans. While typical (non-associative) perceptual learning requires repeated sensory exposure and extended training, perceptual learning via aversive or appetitive conditioning possesses an extraordinary advantage of achieving equal or even stronger perceptual learning with only a few exposures paired with an aversive or appetitive event. Perceptual learning via conditioning would maximize the benefit of emotional learning by enhancing detection of the cue and hence facilitate defensive response, or, by improving discrimination, minimize fear overgeneralization and prevent hyperactivity of the defense system. However, mechanism underlying human perceptual learning via conditioning is still unclear, so is its relation with the emotional aspect of conditioning. Furthermore, the ecological benefit of learning depends on its successful transformation into long-term memory, processes of which also remain poorly understood, especially in humans. In this talk, we will present findings from two olfactory aversive conditioning studies using functional magnetic resonance imaging (fMRI), delineating emotional learning and perceptual learning borne out of conditioning and their neural correlates. Immediately after conditioning, the emotional aspect of conditioning is evinced by changes in arousal (skin conductance response) and risk ratings in response to the conditioned odor (CS) and its related odors, while the perceptual aspect of conditioning is demonstrated by sharpened discrimination between the CS and its closely related odors. On the neural level, multivoxel pattern analyses (MVPA) of fMRI signals isolate changes in the amygdala and orbitofrontal cortex (OFC) that would mediate emotional learning via conditioning, and changes in the piriform cortex (posterior and to some extent, anterior). Regarding long-term effects of learning (measured 8 days after conditioning), the emotional effects, both in behavior and neural plasticity, remained strong, whereas the perceptual effects (behavioral or neural) became fairly weak. Notably, the posterior piriform cortex may participate in the long-term effects of emotional learning by biasing its neuronal population encoding towards the CS, potentially by retuning its response to the CS. Overall, the findings will provide new insights into the intricacies of olfactory learning and its time course.

Powering axons: Novel functions of oligodendrocytes in energy metabolism

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Myelinating glial cells are best known for speeding up axonal impuls propagation, which is essential for normal motor-sensory functions. We had discovered that oligodendrocytes are also required for the survival of axons, independent of myelin itself (Griffiths et al., Science 1998). In fact, two glial functions in myelination and axonal support can be genetically uncoupled in mouse mutants. In MBP-deficient shiverer mice, oligodendrocytes fail to myelinate, but engulf axons that remain functional. In PLP- or CNP-deficient mice, in contrast, oligodendrocytes myelinate but cannot support long-term axon function, causing their widespread degeneration and premature death. We later discovered one underlying mechanism, showing that oligodendroytes provide metabolic support (pyruvate/lactate) to axonal compertment for the generation of ATP (Fünfschilling et al., Nature 2012). This trophic function is especially important for white matter tracts, where myelin shields the axonal compertment from the extracellular milieu. Trying to understand how lactate supply is matched to underlying axonal energy needs, we further discovered that oligodendrocytes use NMDA receptors to detect axonal glutamate release as a proxy for average spiking activity and axonal energy needs. Activation of oligodendroglial NMDA receptors causes a rapid redistribution of GLUT1, leading to enhanced glucose import and lactate release (Saab et al., Neuron 2016). In mice lacking oligodendroglial NMDA receptors functional GLUT1 expression in oligodendrocytes is reduced, which perturbs axon function under metabolic stress. Loss of metabolic support by oligodendrocytes is likely a contributing factor for a range of myelin diseases, such as multiple sclerosis, but is also relevant for other neurodegenerative diseases, where long axons have been recognized as the bottle neck of neuronal integrity.

Quick and reliable estimation of taste sensitivity using adaptive methods

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Measurements of perceptual sensitivity are a fundamental aspect of all psychophysiological investigations. In fact, the entire field of psychophysics was founded with the intention to unravel the relationship between physical and perceived stimulus intensity. While in the non-chemical senses, numerous methods for sensitivity threshold estimation have been developed during the past century, these methods have not yet been transferred to the chemical senses, especially the sense of taste, for

several reasons. Firstly, stimulus delivery is rarely automated, which hampers repeated stimulation. Further, taste stimulation requires rather long inter-stimulus intervals (ISIs) of typically 20 to 30 s, which limits the number of trials per experimental session. Lastly, liquid tastants must be readily prepared before the experimental session; they cannot be created "on-line" during testing, as is the case e.g. with auditory and visual stimuli. Given these limitations, existing taste threshold estimation methods either suffer from low resolution due to few dilution steps and thus only allow an assessment of general taste function or they require multiple stimulations per trial, asking the participants e.g. to identify an odd stimulus in a series. As participants are required to memorize and later retrieve previous perceptions, the latter procedures impose a high cognitive and memory load, and are therefore unsuitable for participants with limited cognitive resources, such as clinical populations. We set out to adapt two algorithms commonly used in the non-chemical senses, QUEST and SIAM, for the simple, quick, and reliable estimation of taste thresholds. In both methods, participants are presented with only a single stimulus per trial, and have to respond whether the stimulus was perceived or not. The duration of both procedures was less than 10 minutes per taste quality. Both methods were found to be test-retest reliable, with higher reliability for QUEST. Further, thresholds estimated with both methods were highly correlated, indicating they were both measuring the same underlying perceptual and sensory properties. We therefore recommend these methods for taste sensitivity estimation in populations with limited attentional or memory capacities.

Muskelin regulates PrP^C vesicle and membrane turnover in the context of prion disease

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Cellular prion protein (PrP^C) is a neuronally enriched GPI-anchored plasma membrane protein involved in cell signaling and adhesion. It can convert to a pathogenic form, PrP-Scrapie (PrP^{Sc}), implicated in neurological disorders including Creutzfeldt-Jakob disease in humans. PrP^C shows rapid turnover following internalization, endosome trafficking and degradation through acidic lysosomes. Alternatively, PrP^C may be either recycled back to the cell surface or may be secreted to the extracellular space via exosomes. The regulation of PrP^C turnover is not fully understood, yet. However, since both, PrP^C membrane levels as well as exosome content are thought to impact conversion and spreading of the misfolded isoform

PrP^{Sc}, PrP^{C} turnover may critically influence prion disease progression.

The vesicle transport of PrP^{C} in axons depends on kinesin-1 and cytoplasmic dynein, however, regulatory mechanisms that specify and control PrP^{C} endosome trafficking still remain unknown. Muskelin associates with actin- and microtubule-based motor protein complexes and has been shown to mediate regulatory and cargo adapter function in the transport of $GABA_A$ receptors. Here, we identify muskelin as a critical regulator of PrP^{C} vesicle trafficking. Muskelin in association with cytoplasmic dynein binds to and undergoes cotransport with PrP^{C} at a subset of intracellular vesicles. Interference with dynein-based motility or muskelin-dynein binding perturbs retrograde PrP^{C} trafficking. Notably, gene knockout of muskelin immobilizes retrograde PrP^{C} transport and interferes with PrP^{C} lysosomal targeting and degradation. Muskelin knockout instead causes elevated levels of PrP^{C} at the plasma membrane and increased packaging of PrP^{C} into exosomes. Accordingly, prion disease onset is significantly accelerated following in vivo injection of pathogenic prion into muskelin-depleted mice, consistent with mis-localization of PrP^{C} to the plasma membrane and to exosomes. Our data identify muskelin as a critical regulator of PrP intracellular targeting versus intercellular spreading and highlight the contribution of PrP^{C} vesicle turnover to the pathology of prion disease.

The interplay between nanoscale receptor dynamics and synaptic function

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The spatio-temporal organization of neurotransmitter receptors in the postsynaptic membrane is a fundamental determinant of synaptic transmission and thus information processing by the brain. Ionotropic AMPA glutamate receptors (AMPAR) mediate fast excitatory synaptic transmission in the central nervous system. Using a combination of high resolution single molecule superresolution imaging techniques and video-microscopy, we have established that AMPARs are not stable in the synapse as thought initially, but undergo continuous entry and exit to and from the post-synaptic density through lateral diffusion and that AMPAR are highly concentrated inside synapses into a few clusters of around seventy nanometers. These results open the new possibility that glutamatergic synaptic transmission is controlled by the regulation at the nanometer scale of the position and composition of these highly concentrated nanodomains. We demonstrate that AMPAR conformation strongly impacts their mobility, and that AMPAR surface diffusion directly controls both short and long term synaptic plasticity.

Behavior-dependent competition between bottom-up and top-down inputs to olfactory cortex

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Sensory cortices process afferent input in the context of a wide variety of top-down, inter-cortical inputs. These top-down inputs provide information about expectation, recent history and multisensory inputs that modulate the processing of bottom-up sensory input. Importantly the balance between bottom-up and top-down inputs in driving sensory cortical neurons is state- and behavior-dependent. Such shifts can, for example, be important for sleep-dependent memory consolidation during periods of reduced responsiveness to ongoing sensory input. Here, I will describe the competition between bottom-up and top-down drivers of olfactory cortical neurons using direct assays of synaptic strength in identified pathways of behaving animals. The dynamic balance between these two drivers provides insight into the complexity of maintain perceptual stability, and can help explain apparently random shifts in perceptual acuity.

The puzzle of peripheral taste signals: Breaking the code

Stephen Roper, Miller School of Medicine, University of Miami, Miami, USA

Researchers have long been searching for how signals transmitted from taste buds to the brain are encoded. There are many sites within the peripheral end organs of taste where signal processing can occur, including synaptic interactions between taste bud cells. The transmitters ATP, ACh, CGRP, GABA, glutamate, 5-HT and norepinephrine have all been implicated in excitatory and inhibitory interactions in taste buds. How the resultant output--trains of impulses in sensory afferent fibers--encode sweet, sour, salty, bitter and umami tastes remains unclear. Some researches hold that each gustatory sensory afferent fiber is dedicated to one of the basic tastes. For instance, a sensory afferent might be a “sweet” or a “bitter” fiber. This notion of "labeled lines" is an extension and narrowing of a concept originating with Rene Descartes in 1680 and refined by Johannes Müller and Sir Charles Bell in the early 19th century. Decartes, and especially Müller and Bell hypothesized that signals reached the brain via independent and separate lines to evoke independent and separate perceptions. Current research, however, suggests that interacting neural circuits with multiple coding mechanisms underlie sensory perceptions. Particularly in taste, findings suggest that some form of combinatorial coding involving ensembles of neurons, or temporal coding of impulses in gustatory neurons encode taste. I will review and explore the enigmatic question of taste coding, particularly in the periphery, and the research that has been directed to answering these questions.

Interrogating sweet taste cells

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Knockout mice lacking the sweet taste receptor subunit Tas1r3 lose behavioral and nerve responses to non-caloric sweeteners but retain responses to glucose and other sugars. This suggests the presence of a Tas1r3-independent mechanism to detect the sweetness of sugars. We used PCR, in situ hybridization and immunohistochemistry to identify signal transduction elements selectively expressed in sweet-responsive taste cells that might mediate Tas1r3-independent responses to sugars. Glucose transporters (GLUTs), Na-dependent glucose co-transporter-1 (SGLT1) and ATP-gated K^+ channels (K_{ATP}) are all present in Tas1r3+ taste cells and may constitute a Tas1r3-independent means to detect caloric sugars. In addition, Tas1r3+ taste cells selectively express disaccharidase enzymes sucrase, maltase, trehalase and lactase. In both wildtype and Tas1r3 knockout mice disaccharidase inhibitors significantly reduced gustatory nerve responses to the disaccharides sucrose and maltose, but not to the monosaccharides glucose and fructose or the noncaloric sweeteners. It appears that these orally expressed enzymes act in concert with salivary amylase to generate free glucose from starch, sucrose, maltose, trehalose and lactose that can activate the Tas1r3-independent sugar detection pathway. To identify additional signalling components and regulatory factors selectively expressed in Tas1r3+ taste cells we used single taste cell RNA-Seq (deep sequencing) and bioinformatics to “data-mine” the Tas1r3+ taste cell “transcriptome” (i.e. all genes transcribed in Tas1r3+ taste cells). Gli3, a key transcriptional effector in the sonic hedgehog signalling pathway, was found to be selectively expressed in Tas1r3+ taste cells and Lgr-5+ taste stem cells, but not in type I or type III taste cells. Gli3 conditional knockout mice were more sensitive to sweet, umami and bitter compounds and had increased numbers of type II taste cells. Our results suggest that Gli3 is an important negative regulator of taste bud maintenance that enhances the number of type II taste cells, including those responsive to sweet.

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Novel insights on regulation of F-actin dynamics and stability in dendritic spines

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Actin filaments represent the major cytoskeletal components of dendritic spines and are involved in structural plasticity as well as protein and organelle transport. Synaptic activity and associated spinous Ca^{2+}-transients can trigger the induction of long-term potentiation (LTP), which requires dynamic changes in F-actin structure. However, molecular mechanisms for the spatio-temporal regulation of F-actin dynamics by Ca^{2+} effectors are still poorly understood. We show that the Ca^{2+}-sensor caldendrin is involved in the stabilization of synaptic F-actin, which is essential for the maintenance of LTP. Caldendrin gene knockout resulted in higher spinous actin turnover, as well as deficits in spine plasticity. Although EM imaging showed no differences in brain organization, morphology of hippocampal CA1 pyramidal neurons and dendritic spine density, STED nanoscopy revealed miss-arrangement in spinous actin filament distribution in caldendrin knock out mice, which could be responsible for synaptic plasticity phenotypes. The caldendrin C-terminus contains four EF-hand motifs and closely resembles calmodulin, whereas the N-terminus harbors a unique proline-rich sequence, which provides a distinctive interface for interaction partners, including PXXP motifs mediating the interactions with SH3 domain proteins. An SH3 domain array performed for for the caldendrin N-terminus indicated an interaction with the actin-binding protein cortactin. Using combinations of biochemical, biophysical and cellular methods we could uncover a mechanism of calcium-dependent binding and activation of cortactin by caldendrin. Caldendrin binding keeps cortactin in an active, F-actin-stabilizing conformation, which protects a minimal pool of branched, spinous F-actin against cofilin-induced severing and primes soluble cortactin for sequential binding to N-WASP:Arp2/3 complex. In conclusion, we propose the model that during activity-dependent stabilization of spines, synaptic calcium signals are directly transduced to the actin cytoskeleton via the caldendrin:cortactin:Arp2/3 complex

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Synaptic mechanisms of pattern completion

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The hippocampal CA3 region plays a key role in learning and memory. One of the hallmark properties of the network is its ability to retrieve full memories from incomplete or degraded sets of patterns, a phenomenon referred to as pattern completion or autoassociative recall. However, the underlying synaptic mechanisms remain largely unclear. To address this question, we combined subcellular patch-clamp recording, multi-cell recording in slices, and reality-based modeling. To test whether mossy fiber synapses were sufficiently strong to activate the network, we made paired recordings between mossy fiber boutons and postsynaptic CA3 pyramidal neurons. Mossy fiber synapses were below the spike threshold in the postsynaptic CA3 pyramidal cells, but could be switched from a subdetonation into a full detonation regime by posttetanic potentiation (Vyleta et al., 2016). To test whether the functional properties of CA3–CA3 synapses were consistent with their proposed role in pattern completion, we characterized the properties of synaptic plasticity. We found that spike timing-dependent plasticity (STDP) in CA3–CA3 synapses was unique, with a broad and temporally symmetric STDP induction curve that lacks a depression component (Mishra et al., 2016). Finally to test whether the functional connectivity of CA3–CA3 synapses was consistent with a major role in pattern completion, we performed simultaneous recordings from up to eight neurons. Octuple recording revealed that connectivity was sparse and spatially distributed. Moreover, disynaptic connectivity motifs (including reciprocal, convergence, divergence, and disynaptic chain motifs) were much more abundant than expected by chance in a random network (Guzman et al., 2016). To determine how these synaptic properties would affect pattern completion, we developed a real-size model of the hippocampal CA3 region. 330000 neurons were implemented, and connected by glutamatergic synapses with Hebbian synaptic plasticity. Interestingly, network models with sparse connectivity and an overabundance of connectivity motifs were able to effectively participate in pattern completion. Our results suggest that both macroconnectivity and microconnectivity of the biological network contribute to the performance of pattern completion in the CA3 cell network.

ABSTRACTS

POSTERS

Taste-induced 'olfiction': Taste-induced changes in odor perception

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Taste and smell are closely intertwined during food perception. While their sensory interaction has gained considerable attention during the past decade, the role of semantic congruence, i.e. how well taste and smell match, in odor-taste perception remains to be elucidated. In a series of experiments, we investigated the role congruence plays in the subjective experience of odors and tastes. To address this question, we presented food odorants (chicken, orange, and 3 mixtures of the 2) and tastants (savory–salty and sour–sweet) in pairs varying in congruence to human participants. In study 1, we asked whether odor-taste congruence is a dichotomous, i.e. cross-modal pairs are either matching or mismatching, or a rather gradual or even continuous experience. We found that participants could perceive distinct congruence levels, thereby favoring a gradual account of congruence perception. We further asked whether congruence influences the subjective experience (e.g., intensity, pleasantness, familiarity) of odor-taste stimuli and found that congruence increases pleasantness (Amsellem & Ohla, 2016). Because odors are notoriously ambiguous and susceptible to contextual information, we tested the hypotheses that taste influences odor perception, specifically odor identity in study 2 and 3. Here, participants were to evaluate the composition, i.e. the proportion of orange and chicken, within odor samples in the presence of a task-irrelevant taste of varying degrees of congruence. Odors were generally more intense and less pleasant in the presence of a taste. Odor composition shifted toward the odor that was most congruent with the taste, e.g. an orange-chicken odor was perceived as containing more orange and less chicken in the context of a sour-sweet taste, suggesting a taste-specific transfer of perceptual properties from taste to odor. To test whether taste-induced odor suppression or enhancement accounted for the observed change in odor composition, we measured the intensity associated to either odor object category on separate scales (study 3). The results revealed that tastes selectively enhance the intensity of congruent odor components; no suppression of incongruent odor components was observed. In summary, our findings show that semantic congruence of odor and taste increases hedonic perception and that odor components congruent with a taste are selective enhanced taste-specific transfer of perceptual properties from taste to odor, likely to reduce odor ambiguity. Overall, the results bear implications for the understanding of the mechanisms of the perseverance of habitual food choices: we like what we know.

Optogenetic induction of spike-timing-dependent plasticity at hippocampal synapses

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Synaptic plasticity, activity-dependent modification of the strength of synaptic transmission, is believed to be a key mechanism for the formation of new memories. It has been shown that synapses that are active milliseconds before a postsynaptic action potential are strengthened (Hebbian plasticity), while synapses that are active immediately after a postsynaptic action potential are weakened. Until now, this spike-timing-dependent plasticity (STDP) was induced and evaluated with whole-cell patch clamp recordings, limiting measurements of synaptic strength to 1 hour at best. To test the long-term stability of synaptic connections over multiple days, we aimed at establishing a method for inducing synaptic plasticity in a manner which does not disrupt the pre- or postsynaptic neurons, and a method to read-out changes in the strength of connections at distant time points. We induce timing-dependent plasticity by an all-optical method, stimulating neurons with channelrhodopsins that are activated by different wavelengths of light in pre- and postsynaptic cells. We expressed Channelrhodpsin-2 or CheRiff as near-UV-sensitive opsins and induced action potentials with 400 nm light. ChrimsonR was expressed in the other cell population and excited with 635 nm light for plasticity induction. We stimulated presynaptic neurons with single flashes of light and paired these with bursts of 3 light flashes at 50 Hz to cause action potentials in the postsynaptic neurons either after arrival of the presynaptically evoked EPSP (causal pairing) or prior to the EPSP (anti-causal pairing). Three days after pairing, postsynaptic CA1 neurons were patched and EPSCs evoked by stimulating the presynaptic neurons with light. Several CA1 neurons were patched in each slice and the EPSCs evoked by light activation of the CA3 neurons were recorded. EPSCs from at least 2 non-transfected (i.e. non-paired) CA1 neurons were averaged and used to normalize the EPSCs recorded from transfected (i.e. paired) CA1 neurons. We found that the normalized EPSCs recorded from causally-paired transfected CA1 neurons (delay 10 ms, 5 Hz presynaptic stimulation) were significantly larger than normalized EPSCs recorded from slices that were similarly handled but not stimulated with light, suggesting that causal pairing led to long-lasting potentiation of input synapses. When causal pairing was evoked at 0.1 Hz, however, no plasticity was induced, suggesting that STDP is frequency-dependent. Our all-optical method allows us to investigate the integration of timing information (causality) at individual synaptic connections and the stability of timing-induced changes in synaptic strength over days.

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Tau toxicity and neurodegeneration: Staging and pharmacological intervention in a cell model

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The pathological aggregation of Tau protein is strongly implicated in the pathogenesis of AD and other tauopathies but the mechanism of this process is still poorly understood. We have generated a conditional expression (Tet-on) cell model of Tau pathology based on N2a cells expressing the 4-repeat domain of Tau with the Ftdp-17 mutation deltaK280 (termed $Tau^{4RDdeltaK}$). The "pro-aggregant" deletion variant deltaK280 of Tau is highly amyloidogenic and forms fibrous aggregates in the cells within few days staining brightly with the reporter dye Thioflavin S. The aggregation of $Tau^{4RDdeltaK}$ protein in cells is toxic, contrary to wildtype or anti-aggregant variants of the protein. We studied the correlation between stages and intermediate species of Tau aggregation with parameters of cellular toxicity, using a combination of microscopic analysis, fluorescence-activated cell sorting (FACS) and biochemical analysis. The pathway of aggregation includes initial dimerization which leads to further oligomerization and higher aggregation and induces an increase of reactive oxygen species (Ros) and cytoplasmic Ca^{2+}. This correlates with early signs of apoptosis (days 1-2), rapid induction and continuous increase of Ros (days 1-4), finally leading to cell damage, membrane leakiness and cell death (days 3-4). Tau aggregation and cell toxicity can be suppressed by inhibitors which reduce the aggregation of Tau, and as a consequence the toxicity, as demonstrated by the parameters of cell viability, and cell death.

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GRIP1 and its interactants in dendritogenesis and synaptic plasticity

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A crucial element of neuronal networks and their homeostatic plasticity are the dendritic trees, where neurons receive and begin to integrate information. The transmission and integration of information

is heavily influenced by the structure of the dendritic tree, whose morphogenesis and maintenance are therefore highly regulated.

Our research focuses on key proteins involved in these processes, namely the glutamate receptor interacting protein (GRIP) 1 and its molecular partners. We have previously shown GRIP1 requirement for dendritic development; we also identified and molecularly characterized an interaction between GRIP1 and 14-3-3 proteins, which is essential for the function of GRIP1 in dendritic cargo transport and in dendritogenesis (Geiger et al, 2014). Furthermore, we showed that GRIP1 bridges a complex including the Reelin receptor ApoER2, the signalling molecule ephrinB2 and the GluR2 subunit of AMPA receptors, the formation of which also depends on the phosphorylation of a single residue of ephrinB2, the serine -9. Neuronal activity and Reelin stimulation induces the formation of the complex and regulates AMPA receptor new insertion into the dendritic membrane, thereby affecting synaptic strength (Essmann et al, 2008; Pfennig et al, in revision). Interestingly, we have also discovered an interaction between ephrinB2 and VEGFR2 in neurons, required for proper dendritic and spine morphogenesis in the developing hippocampus (Harde et al, in preparation).

In this context, my project aims to better understand the molecular mechanisms behind the functions of GRIP1 and its signalling partners in dendritogenesis and synaptic plasticity. My current results confirm the requirement of the neuronal interaction between ephrinB2 and VEGFR2 for long-term potentiation (LTP) in the young hippocampus, as well as of the GRIP1/GluR2/ephrinB2/ApoER2 complex for LTP in the adult hippocampus.

The generalists and the specialists - insights from an expanded screening of human bitter taste receptor agonists

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Humans have only about 25 identified bitter taste receptors (TAS2Rs) but perceive a vast number of structurally varied substances as bitter-tasting. Recent findings revealed that many of the receptors can detect multiple bitter chemicals and, at the same time, a number of substances activate several TAS2Rs. It has been proposed that it is the broad activation range that enables the detection of thousands of bitter substances by so few sensors. However, there are still open questions. Not all receptors have been deorphaned: for TAS2R19, -42, -45 and -60 no agonist has been identified yet.

Moreover, several receptors have been shown to have a very broad receptive range and it would be interesting to know whether they recognize even more structurally different agonists. With a few exceptions, the ligand spectrum of individual receptors shows no obvious “bitter structures” or common chemical motifs. Testing more bitter substances and discovering new TAS2R agonists would greatly facilitate further elucidation of the mechanisms of TAS2R activation and ligand interaction. To address these issues, a joint analysis of previously published and novel screening of a bitter compound library against all 25 human TAS2Rs has been performed. The set of chemicals has been thus significantly expanded in comparison to earlier studies, which allows an even more thorough investigation of bitter taste receptor characteristics with respect to ligand recognition and specificity. The results show that, firstly, despite testing a wider set of substances, the 4 TAS2Rs without identified agonists still remain orphan, which suggests highly specialized agonist selectivity or alternatively, possible limitations of the experimental approach. Secondly, we found more additional agonists for receptors categorized as broadly tuned than for narrowly tuned receptors suggesting that tuning width is indeed a receptor intrinsic feature and not a consequence of compound library bias. A comparison of the agonist sets for individual receptors has been performed to find possible common features in their structure.

Periodic actin rings shape the neck of dendritic spines

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Dendritic spines are a specialized type of excitatory synapses on principal neuons of the forebrain. Their morphology, comprising a spine head connected to the dendritic branch via a thin neck, is well suited to provide biochemical and electrical compartmentalization during signal transmission. Spine shape is defined and tightly controlled by the organization of the actin cytoskeleton. Alterations in synaptic strength correlate with changes in the morphological appearance of the spine head and neck. Therefore, it is important to gain a better understanding of the nanoscale organization of the actin cytoskeleton in dendritic spines. The periodic organization of the actin/spectrin lattice was recently discovered in axons and a small fraction of dendrites using super-resolution microscopy. Here, we use the small probe phalloidin- Atto647N to label F-actin in mature hippocampal primary neurons and in living hippocampal slices. STED nanoscopy reveals that in contrast to beta-II spectrin antibody labelling, phalloidin-Atto647N stains periodic actin structures in all dendrites and the neck of nearly all dendritic

spines, including filopodia-like spines. These findings alter the current view on F-actin organization in dendritic spines and may provide new avenues for understanding the structural changes in the spine neck during induction of synaptic plasticity and active organelle transport or tethering.

Novel insights on regulation of F-actin dynamics and stability in dendritic spines

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Actin filaments represent the major cytoskeletal components of dendritic spines and are involved in structural plasticity as well as protein and organelle transport. Synaptic activity and associated spinous Ca^{2+}-transients can trigger the induction of long-term potentiation (LTP), which requires dynamic changes in F-actin structure. However, molecular mechanisms for the spatio-temporal regulation of F-actin dynamics by Ca^{2+} effectors are still poorly understood. We show that the Ca^{2+}-sensor caldendrin is involved in the stabilization of synaptic F-actin, which is essential for the maintenance of LTP. Caldendrin gene knockout resulted in higher spinous actin turnover, as well as deficits in spine plasticity. Although EM imaging showed no differences in brain organization, morphology of hippocampal CA1 pyramidal neurons and dendritic spine density, STED nanoscopy revealed miss-arrangement in spinous actin filament distribution in caldendrin knock out mice, which could be responsible for synaptic plasticity phenotypes. The caldendrin C-terminus contains four EF-hand motifs and closely resembles calmodulin, whereas the N-terminus harbors a unique proline-rich sequence, which provides a distinctive interface for interaction partners, including PXXP motifs mediating the interactions with SH3 domain proteins. An SH3 domain array performed for for the caldendrin N-terminus indicated an interaction with the actin-binding protein cortactin. Using combinations of biochemical, biophysical and cellular methods we could uncover a mechanism of calcium-dependent binding and activation of cortactin by caldendrin. Caldendrin binding keeps cortactin in an active, F-actin-stabilizing conformation, which protects a minimal pool of branched, spinous F-actin against cofilin-induced severing and primes soluble cortactin for sequential binding to N-WASP:Arp2/3 complex. In conclusion, we propose the model that during activity-dependent stabilization of spines,

synaptic calcium signals are directly transduced to the actin cytoskeleton via the caldendrin:cortactin:Arp2/3 complex.

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eIF2D/Ligatin coordinates synaptic function in vivo by modulating translation of specific mRNAs

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Translational control enables rapid, spatially-restricted modulation of gene expression, but its contribution to modulation of synapse composition and function in vivo remains largely unexplored. We have taken a reverse genetic approach to this problem, focusing on candidates to be selective regulators of translation in the nervous system. We selected one candidate, the non-canonical translation factor eIF2D/Ligatin, based on two criteria: (1) experiments with cultured neurons raised the possibility that eIF2D might function in the neuronal signaling, (2) work in cell-free systems showed that eIF2D has biochemical activities that would enable translational regulation of specific mRNAs via non-canonical mechanisms. However, no previous study has examined eIF2D function in vivo in a multicellular organism. To study eIF2D functions in vivo, we generated knockout flies and found that they are viable and fertile, but show locomotion defects. eIF2D is sufficient on either side of the larval neuromuscular junction (NMJ) to promote normal locomotion. NMJ synaptic morphology appeared largely normal in eIF2D-KO larvae, but electrophysiology data revealed reduced baseline transmission and pre-synaptic homeostasis defects. Taken together, these results imply that eIF2D functions both pre- and post-synaptically to promote efficient trans-synaptic communication at the NMJ and normal motor system function. To identify mRNAs regulated by eIF2D at the translational level in vivo, we combined genome-wide RNA-Seq with poly-ribosome profiling (“Poly-Seq”) from temporally staged eIF2D-KO larvae and WT control animals. This revealed strong effects on translation of specific mRNA classes. Prominent among these were mRNAs coding for factors implicated in synaptic processes and locomotion, including both pre- and post-synaptic components. Importantly, we observed specific changes in the molecular composition of NMJ synapses in eIF2D-KO larvae that could be largely explained by altered regulation observed by Poly-Seq. Thus, our results define a crucial in vivo role for

eIF2D within the motor system to promote synaptic function via coordinating synthesis of specific synaptic proteins.

Respiratory acidosis induces neuronal migration defects in the neocortex and hippocampus

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Diseases of the nervous system may result from genetic factors or from brain damage during development. Especially during late stages of gestation, hypoxia leading to acidosis may cause severe developmental defects. Generally, two forms of acidosis can be differentiated, metabolic and respiratory acidosis. Maternal acidosis may eventually affect the normal development of the fetus, but detailed studies are missing so far. In order to study the impact of acidosis on fetal brain development, we induced respiratory acidosis in pregnant mice by exposing them to 80 % carbon dioxide at E 17.5. This was followed by immunostaining of neuronal layers of the cerebral cortex and hippocampus in new-born mice using layer-specific markers. Under normal conditions, cortical neurons born in the ventricular zone migrate radially towards the marginal zone. In the hippocampus, new-born granule cells migrate from the hilus to the granule cell layer. The results of our experiments show that carbon dioxide exposure induced accumulation of late-born neurons in the deep layers of the cerebral cortex and loss of asymmetric polarity of migrating granule cells destined to the granule cell layer in the dentate gyrus. Cofilin is an actin-depolymerizing protein, and phosphorylation of cofilin induces its deactivation. Western blot analysis indicated that maternal acidosis caused an increased phosphorylation of cofilin in migrating neurons of the cerebral cortex and hippocampus. Our results provide evidence that maternal acidosis may induce migration defects of neurons in the cerebral cortex and hippocampus by promoting abnormal cofilin phosphorylation, which results in cytoskeletal stabilization and neuronal arrest.

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Optogenetic manipulation of cyclic nucleotides and hippocampal synaptic plasticity

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The cyclic nucleotides, cAMP and cGMP are ubiquitously expressed in eukaryotic cells. In neurons, cAMP in particular has been implicated as a key second messenger mediating activity-dependent synaptic plasticity. Various pre- and post-synaptic pathways have been invoked depending on the synapse being studied. Most studies have used forskolin stimulation of endogenous adenylyl cyclases combined with inhibition of phosphodiesterases to induce synaptic potentiation. While effective at inducing synaptic potentiation, such tools affect all cells in the preparation. We have taken advantage of recent developments in optogenetic tools to study the effects of selectively raising the cyclic nucleotides cAMP and cGMP in only the presynaptic or postsynaptic compartments of hippocampal Schaffer collateral synapses. Surprisingly, stimulation of bPAC (Beggiatoa photoactivated adenylyl cyclase) with blue/UV light in the postsynaptic CA1 neurons did not alter excitatory postsynaptic potentials (EPSCs) or alter the threshold for synaptic plasticity. Likewise, EPSCs recorded in CA1 neurons in response to action potentials evoked in presynaptic CA3 neurons co-expressing bPAC and ChrimsonR were not affected by raising cAMP with blue/UV light. The endogenous adenylyl cyclases that are thought to be responsible for the synaptic plasticity-inducing rises in neuronal cAMP are membrane associated and it has been postulated that the cAMP is largely confined to and mediates its actions within a microdomain adjacent to the plasma membrane. As bPAC is a soluble adenylyl cyclase, activating it will increase cAMP throughout the cytoplasm, possibly accounting for the lack of effect on synaptic transmission when compared with activating endogenous adenylyl cyclases. Rhodopsin guanylyl cyclase (RhGC) from Blastocladiella emersonii (beRhGC) has recently been described (Avelar et al., 2014, Curr. Biol.; Scheib et al., 2015, Sci. Signalling; Gao et al., 2015, Nat. Commun.). As there are also suggestions that cGMP may be important for setting synaptic strength, we have expressed RhGC in CA1 neurons to see if raising cGMP close to the plasma membrane would affect EPSCs. Green light applied to CA1 neurons expressing beRhGC with and without concomitant block of phosphodiesterases also had no effect on EPSCs, suggesting that increasing postsynaptic cGMP is also insufficient to increase synaptic transmission. In conclusion, increases in only presynaptic or only postsynaptic cAMP appear to be insufficient for increasing the strength of synaptic transmission and additional mechanisms must be involved.

Activity-dependent compensatory endocytosis is controled by N-cadherin at central synapses

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The synaptic adhesion molecule N-cadherin has been described to play an essential postsynaptic role in long-term potentiation and spine stabilization at mammalian central synapses. In addition, N-cadherin has also been found to influence presynaptic function. However, the specific role of N-cadherin in presynaptic vesicle exo- and endocytosis remains to be elucidated.

To study the influence of N-cadherin on both vesicle exo- and endocytosis in one experiment, we performed synaptophysin-pHluorin (SypHy) fluorescence imaging of individual release sites during extracellular stimulation. Upon overexpression of N-cadherin in cultured mouse cortical neurons, vesicle exocytosis was enhanced similar to overexpression of another synaptic adhesion molecule, Neuroligin1. Most interestingly, overexpression of N-cadherin also strongly accelerated vesicle endocytosis, while overexpression of Neuroligin1 did not. Conditional knockout of N-cadherin in individual cultured neurons by Cre expression only weakly changed vesicle endocytosis induced by low release activity. However, upon strong vesicle release, endocytosis was strongly defective in N-cadherin-deficient neurons.

To begin to investigate the molecular mechanisms underlying the activity dependence of the regulation of endocytosis by N-cadherin, we studied the alterations of the synaptic localisation of N-cadherin upon strong synaptic activation. We performed super-resolution structured illumination microscopy (SIM) imaging of immunocytochemically stained N-cadherin clusters and quantitatively analysed their spatial relation to pre- (vGlut1) and postsynaptic (PSD95) sites. We observed that strong vesicle release led to a recruitment of N-cadherin to the peri-active zone of synapses largely devoid of N-cadherin prior to stimulation.

In summary, we hypothesize that N-cadherin has an essential inductive role in compensatory endocytosis at mammalian central synapses.

Synaptic degeneration in animal models of Tau pathology: Toxicity with or without aggregation

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Abnormal changes of Tau protein (such as aggregation) are common features of several neurodegenerative diseases such as Alzheimer, Frontotemporal Dementia, and other Tauopathies that cause the gradual decay of neurons, preceded by impairments of presynaptic and postsynaptic functions. Tau protein is a natively unfolded protein capable of interacting mainly with axonal microtubules but also with multiple other cell components (proteins, nucleic acids, vesicles), suggesting the potential of distinct pathways of toxicity. Moreover, disease-related mutations are distributed over several domains of Tau which can elicit different types of adverse cellular responses and would require different types of treatment approaches. To address this issue we have developed regulatable transgenic mice and C. elegans models expressing Tau with mutations in different domains, affecting aggregation or other functions of Tau, analyzed their cellular, physiological, and behavioral consequences, and tested treatment strategies.

The results show that the effects of certain Tau mutations in the repeat domain are clearly related to their aggregation propensity (e.g. ΔK280, P301L). Their effects on cellular and physiological functions can be rescued by switching off the toxic Tau protein, or ameliorated by Tau aggregation inhibitors. Unexpectedly, they can also be ameliorated by treatments which do not target Tau aggregation as such but rather its consequence, a reduced neuronal energy metabolism. This can be seen by a decreased level of ATP, impairment of paired-pulse facilitation and LTP, reduced network activity, and cognitive decline. Using rolofylline, an antagonist of the neuronal adenosine A1 receptors improves neuronal activity and rescues behavioral deficits in spite of ongoing Tau aggregation (Dennissen et al., PNAS 2016). By contrast, some mutations in other domains (e.g. Tau-A152T) do not cause toxicity via aggregation but via other signalling pathways leading to pronounced inflammation and excitotoxicity (Decker et al., EMBO Rep 2016; Pir et al., Mol. Neurodeg. 2016). We conclude that Tau mutations can induce toxicity in transgenic animal models via different pathways which must be addressed by distinct therapeutic approaches.

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Single synapses on mossy cells control the hippocampal network depending on their histories

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The dentate gyrus relays information flow from the entorhinal cortex to the hippocampus proper. Individual dentate granule cells (GC) projecting via the mossy fibers (MF) to hippocampal CA3 and to mossy cells (MC) receive segregated input from entorhinal axons. MCs in turn modulate GC activity directly and indirectly by the innervation of distant GCs and hilar interneurons, thereby forming a divergent feed-back loop between GCs. If indeed GCs contribute individually to microcircuits, one would expect that individual MF synapses are encountered in individual states of synaptic transmission at a given time point. However, this is difficult to assess experimentally. In order to analyze the structure and function of single MF synapses, we combined single-bouton stimulation and two-photon imaging of spines postsynaptic to the stimulated mossy fiber bouton. We labeled MCs in organotypic entorhino-hippocampal slice cultures in the whole-cell patch clamp configuration using dye-filled pipettes. Alexa 594 was used to visualize the morphology of spines, whereas fluo-4FF served to report calcium transients in single spines. Alexa 488 released from a second pipette transiently stained the extracellular space and allowed for targeted cell-attached patching of unlabeled boutons presynaptic to labeled identified spines. Stimulation of the bouton evoked very heterogeneous excitatory synaptic responses pointing to a varying contribution of different glutamate receptors of MF synapses - even when two MF synapses on the same MC were studied. Synaptic responses ranged from subthreshold to suprathreshold excitatory postsynaptic potentials resulting in AP firing of the MC (direct detonator synapses), thereby recruiting all cells postsynaptic to the MC to a functional microcircuit. We identified three synaptic states, with respect to detonation defined as all-subthreshold, all-suprathreshold, and mixed sub- and suprathreshold responses. Induction of plasticity at single MF synapses with an identical associative protocol modified these synaptic states depending on the initially encountered state, suggesting that the encountered synaptic state reflects the individual history of activity at a synapse. These results suggest that MF synapses on MCs provide metastable network switches that contribute individually to computation in the hippocampus depending on their previous activity.

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Imaging glutamate release at individual Schaffer collateral synapses

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Information transmission at chemical synapses is most likely a quantal process based on the release of transmitter-filled vesicles from the presynaptic terminal. This process can be analyzed in detail by comparing the amplitude distribution of stimulation-evoked postsynaptic potentials to spontaneous release events using binomial statistics. This method works well at the neuromuscular synapse, but is of limited use in the central nervous system, where each neuron receives thousands of synapses at different electrotonic distances from the soma. Optical methods based on fluorescent calcium indicators have been used to isolate the response of individual synapses on dendritic spines in intact brain tissue. However, the non-linear relations between glutamate concentration, receptor activation and spine calcium concentration complicate quantal analysis of calcium signals. Here we introduce direct optical measurements of glutamate concentration in the synaptic cleft based on the genetically encoded glutamate sensor iGluSnFR, using a fast scanning two-photon microscope. All Schaffer collateral synapses we sampled showed a large dynamic range and were capable of multivesicular release in high calcium saline. In physiological calcium concentration, however, these synapses had a high failure rate and typically released only one vesicle. The amplitude distributions from individual synapses were well fit by a quantal model if photon shot noise was taken into account. Furthermore, localizing the fusion site on the surface of the presynaptic bouton with an accuracy that exceeds the resolution limit of the two-photon microscope, we show that release was confined to a single active zone which did not expand during multivesicular release.

Makorin ring zinc-finger protein 1 (MKRN1), a novel PABP-interacting protein, stimulates translation in nerve cells

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The poly(A)-binding protein (PABP), a key component of different ribonucleoprotein complexes (RNPs), plays a crucial role in the control of mRNA translation rates, stability and subcellular targeting.

To better understand the molecular action of PABP in regulating mRNA fate in nerve cells we employed yeast-two-hybrid techniques. Thus, we identified RING-zinc-finger protein Makorin-1 (MKRN1-short) as a PABP-interacting protein. MKRN1-short, a bona fide RNA-binding protein, contains distinct arrays of C3H zinc-finger (ZF) motifs, a ZF structure with unusual Cys/His spacing, and an incomplete RING domain. MKRN1-short interacts with PABP in an RNA-independent manner. It is the major MKRN1 isoform in rat brain and co-localizes with PABP in granule-like structures along dendrites. Moreover, in primary rat neurons MKRN1-short associates with dendritically localized mRNAs. In stressed eukaryotic cells MKRN1-short accumulates in so-called stress granules, which requires the PAM2 domain of MKRN1-short. When tethered to a reporter mRNA, MKRN1-short significantly enhances reporter protein synthesis in primary neurons, a stimulatory function that depends on the first zinc finger and the PAM2 motif. LARP1, a 5' TOP mRNA (translation modifying /regulating) and PABP binding protein, was identified as interaction partner of MKRN1-short and could contribute to the stimulating effect. Finally, after induction of synaptic plasticity via electrical stimulation of the performant path in vivo, MKRN1-short specifically accumulates in the activated dendritic lamina, the middle molecular layer of the hippocampal dentate gyrus. Collectively, these data indicate that in mammalian neurons MKRN1-short interacts with PABP and LARP1 to locally control the translation of dendritic mRNAs at synapses.

Neurobeachin/KIF21B interactions regulate NMDA receptor endocytic recycling and participate in social behavior

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Different genetic polymorphisms of synaptic genes, including the neurobeachin gene, contribute to autism spectrum disorder (ASD) in humans. Neurobeachin regulates neurotransmitter receptor trafficking to synapses and its depletion affects synaptic transmission, spine formation and social and cognitive behavior. Here we identify neurobeachin as a mobile vesicular factor that transiently enters active spine synapses. Neurobeachin is located to tubular vesicles that extend from Rab4-positive recycling endosomes associated with the microtubule motor proteins KIF21B and dynein. Live imaging reveals co-transport of neurobeachin with recycling endosomes or EHD3, an early-endosome-to-Golgi transport marker. Consistent with human GRIN2B gene mutations associated with autism,

neurobeachin binds to GluN2B and neurobeachin knockout causes abnormal surface membrane recycling of GluN2B-containing NMDA receptors. Finally, KIF21B knockout mice exhibit deficits in social preference and social recognition. Our data suggest neurobeachin/KIF21B interactions as critical regulators of synaptic recycling.

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Role of kinesin-3 molecular motors during synaptic plasticity in the hippocampus

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Synaptic plasticity mechanisms are widely studied as the cellular and molecular basis for learning and memory. A fundamental mechanism is the transport of AMPA-type glutamate receptors to and from the synapse in response to changes in neuronal activity. This continuous turnover of membrane proteins and regulated transport is mediated, among others, by Rab GTPases that drive endosomal trafficking and carried out by molecular motors and cytoskeleton associated complexes.

In this work, we have investigated the role of microtubule-dependent motor proteins in the regulated transport of receptors during synaptic plasticity.

Using electrophysiological techniques in organotypic hippocampal slice cultures, in combination with dominant-negative approaches and shRNA-dependent knock-down, we have found that one member of the kinesin-3 family of motor proteins is required for long-term potentiation (LTP), but does not participate in the maintenance of synaptic transmission or in long-term depression (LTD). In addition, we have found that this kinesin-3 motor protein drives a subcellular redistribution of the dendritic endosomal machinery during LTP, as monitored by live fluorescence imaging of the Rab11-interacting protein FIP2. Using biochemical techniques, we are also characterizing the molecular components that couple AMPA receptor subunits to the motor protein complex.

Overall, these experiments are allowing us to establish specific kinesin molecular motors as key components of the activity-dependent endosomal transport of AMPA receptors during synaptic plasticity.

Functional analysis of SHANK3 mutations associated with autism spectrum disorders

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SHANK/ProSAP proteins are essential for synapse formation, development, and function. Mutations in the family of SHANK genes are associated with autism spectrum disorders and other neurodevelopmental disorders. Solving the three dimensional structure of an N-terminal fragment of SHANK3 showed that the SHANK/ProSAP N-terminal (SPN) domain forms a large intramolecular interface with the ankyrin repeat region (ARR). In addition, the SPN domain is a novel binding motif for active G-proteins of the Ras family, which is disrupted by the autism-associated mutations R12C and L68P. Here we performed a mass spectrometry analysis to identify new interaction partners of the N-terminal part of SHANK3. To define the relevance of the interaction of SHANK3 with small G-proteins of Ras family for synaptic function, we used EGF stimulation to activate Ras, and 8-CPT treatment to activate Rap, and analyzed the effects of Ras and Rap activation on the SHANK3 interactions with both new and previously known interaction partners. The results show that some of the SHANK3 interaction partners are highly affected by stimulation of Ras or Rap activated pathways.

Muskelin regulates PrP^C vesicle and membrane turnover in the context of prion disease

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Cellular prion protein (PrP^C) is a neuronally enriched GPI-anchored plasma membrane protein involved in cell signaling and adhesion. It can convert to a pathogenic form, PrP-Scrapie (PrP^{Sc}), implicated in neurological disorders including Creutzfeldt-Jakob disease in humans. PrP^C shows rapid turnover following internalization, endosome trafficking and degradation through acidic lysosomes. Alternatively, PrP^C may be either recycled back to the cell surface or may be secreted to the extracellular space via exosomes. The regulation of PrP^C turnover is not fully understood, yet. However, since both, PrP^C membrane levels as well as exosome content are thought to impact conversion and spreading of the misfolded isoform PrP^{Sc}, PrP^C turnover may critically influence prion disease progression.

The vesicle transport of PrP^C in axons depends on kinesin-1 and cytoplasmic dynein, however, regulatory mechanisms that specify and control PrP^C endosome trafficking still remain unknown. Muskelin associates with actin- and microtubule-based motor protein complexes and has been shown to mediate regulatory and cargo adapter function in the transport of $GABA_A$ receptors.

Here, we identify muskelin as a critical regulator of PrP^C vesicle trafficking. Muskelin in association with cytoplasmic dynein binds to and undergoes cotransport with PrP^C at a subset of intracellular vesicles. Interference with dynein-based motility or muskelin-dynein binding perturbs retrograde PrP^C trafficking. Notably, gene knockout of muskelin immobilizes retrograde PrP^C transport and interferes with PrP^C lysosomal targeting and degradation. Muskelin knockout instead causes elevated levels of PrP^C at the plasma membrane and increased packaging of PrP^C into exosomes. Accordingly, prion disease onset is significantly accelerated following in vivo injection of pathogenic prion into muskelin-depleted mice, consistent with mis-localization of PrP^C to the plasma membrane and to exosomes. Our data identify muskelin as a critical regulator of PrP intracellular targeting versus intercellular spreading and highlight the contribution of PrP^C vesicle turnover to the pathology of prion disease.

Novel exploration of discrete positional or directional spatial cues induces IEG mRNA expression in distinct hippocampal subregions

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Hippocampal synaptic plasticity is tightly linked to the encoding and consolidation of spatial and context-dependent memory. In rodents it has been shown, long-term depression (LTD) is associated with learning about spatial content, whereas long-term potentiation is linked to learning about changes in global space (Manahan-Vaughan & Braunewell, 1999; Kemp & Manahan-Vaughan, 2004; Kemp & Manahan-Vaughan, 2007). It has been reported that LTD in the CA1 region is induced by encoding of spatial content, whereas LTD in the dentate gyrus is induced by directional landmarks encoding (Kemp & Manahan-Vaughan, 2008).

In the present study, we conducted cellular compartment analysis of immediate early gene activity by using fluorescence in situ hybridization to investigate how the hippocampal subregions of rats respond to spatial learning by analyzing the effect of exploration of discrete spatial content and directional landmarks.

We detected an increase in the expression of immediate early gene (IEG) mRNA in the CA1 region after

exploration of spatial content. The novel exploration of directional landmarks led to an increase in IEG mRNA in the dentate gyrus. These results suggest different encoding of spatial information in the CA1 region and dentate gyrus and support the parallel map theory (Jabobs & Schenk, 2003)

Quick and reliable estimation of taste sensitivity using adaptive methods

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Measurements of perceptual sensitivity are a fundamental aspect of all psychophysiological investigations. In fact, the entire field of psychophysics was founded with the intention to unravel the relationship between physical and perceived stimulus intensity. While in the non-chemical senses, numerous methods for sensitivity threshold estimation have been developed during the past century, these methods have not yet been transferred to the chemical senses, especially the sense of taste, for several reasons. Firstly, stimulus delivery is rarely automated, which hampers repeated stimulation. Further, taste stimulation requires rather long inter-stimulus intervals (ISIs) of typically 20 to 30 s, which limits the number of trials per experimental session. Lastly, liquid tastants must be readily prepared before the experimental session; they cannot be created “on-line” during testing, as is the case e.g. with auditory and visual stimuli. Given these limitations, existing taste threshold estimation methods either suffer from low resolution due to few dilution steps and thus only allow an assessment of general taste function or they require multiple stimulations per trial, asking the participants e.g. to identify an odd stimulus in a series. As participants are required to memorize and later retrieve previous perceptions, the latter procedures impose a high cognitive and memory load, and are therefore unsuitable for participants with limited cognitive resources, such as clinical populations. We set out to adapt two algorithms commonly used in the non-chemical senses, QUEST and SIAM, for the simple, quick, and reliable estimation of taste thresholds. In both methods, participants are presented with only a single stimulus per trial, and have to respond whether the stimulus was perceived or not. The duration of both procedures was less than 10 minutes per taste quality. Both methods were found to be test-retest reliable, with higher reliability for QUEST. Further, thresholds estimated with both methods were highly correlated, indicating they were both measuring the same underlying perceptual and sensory properties. We therefore recommend these methods for taste sensitivity estimation in populations with limited attentional or memory capacities.

Respiratory entrainment of prefrontal circuits

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Decades of research have identified neural oscillations as a mechanistic substrate for the formation of cell assemblies and the coordination of information transfer between remote brain regions. During exploratory behavior, the hippocampus and the prefrontal cortex are organized by theta oscillations, known to support memory encoding and retrieval, while during sleep the same structures are dominated by slow oscillations that underlie the consolidation of recent experiences. Recently, a novel internally generated brain state characterized by prefrontal 4Hz oscillation was identified as a physiological signature of fear memory in mice. This oscillation synchronizes prefrontal-amygdala circuits and entrains neuronal activity to dynamically regulate the development of neuronal ensembles facilitating the encoding and expression of fear memory. However, the source of this oscillation remains unknown.

Here, we focused our attention to respiration, a persistent rhythmic input to the brain. We report respiratory entrainment of the prefrontal cortex and hippocampus, two structures critically involved in memory consolidation and retrieval. Using a combination of extracellular recordings, calcium imaging, photometry, pharmacological and optogenetic manipulations in mice, we demonstrate a causal role of re-afferent respiratory inputs in synchronizing neuronal activity between prefrontal cortex and hippocampus in different behavioral states. Importantly, respiration entrains prefrontal cortex not only during fear behavior but in a variety of behavioral scenarios in the awake and sleep state. The frequency changes as a function of the behavioral state and this oscillation coexists with theta and slow oscillations, contributing to the formation and expression of neuronal ensembles.

Breathing is the most fundamental and ubiquitous rhythmic activity in life. Our results highlight the breathing rhythm as a novel oscillatory mechanism mediating inter-region synchronization of limbic memory circuits.

Characterization of CaSR-expressing taste cells in the mouse posterior tongue

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The sense of taste provides valuable information about nutritional quality of food. Human and mice can sense five basic tastes, sweet, bitter, sour, salty and umami. Receptors for each of the basic tastes are thought to be expressed in taste bud cells. It is well established that sweet and bitter tastes are elicited by the activation of T1R2+T1R3 and T2Rs, respectively. The major receptor for umami is considered T1R1+T1R3 and it demonstrated that mGluR1 and mGluR4 also contribute to umami taste. Additionally it is suggested that 'taste of fat' might be elicited by free fatty acid receptor. We previously demonstrated that the orally administered agonists/modulators of calcium-sensing receptor (CaSR) act on orosensory perception senses. For instance, in human sensory studies, γ-glutamyl valyl glycine (γEVG) enhances the intensities of umami, sweet and salty tastes also modify the continuity, mouth-fullness and thickness in a CaSR-dependent manner. These phenomena are called 'kokumi'. Importantly, the kokumi substances do not elicit any taste itself. To elucidate the molecular mechanisms of kokumi, we characterized CaSR-expressing taste cells and detected that various taste receptor molecules are coexpressed with CaSR. Double labeled experiments were performed using in situ hybridization and/or immunohistochemistry in mouse vallate papillae. Collectively, our data show that CaSR was expressed in several different types of taste cells. We found that CaSR was expressed in type II and type III taste cells. Interestingly, CaSR-expressing cells form different subset of T1R3-expressing umami or sweet taste cells. CaSR-expressing cells that do not express T1R3 co-expressed other taste receptors. Our results suggest the possibility that CaSR may contribute to multiple functions of taste cells and that kokumi substances might affect taste perception through a coordinated complex system of individual taste cells which express CaSR.

Functional relevance of the trans-Golgi associated protein PIST in the central nervous system

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PDZ-domain containing proteins play different roles in the subcellular sorting of membrane proteins. PIST (protein interacting specifically with tc10) is mainly located at the trans-golgi-network of cells. In neurons, PIST is also present in Golgi outposts in dendrites, which are important sorting points for membrane proteins. PIST interacts with a variety of neurotransmitter receptors such as NMDAR subunits, Stargazin and cell adhesion proteins such as neuroligin 1 (Nlg1). Suggested roles of PIST concern the anterograde as well as the retrograde pathway of membrane proteins, such as the transport to specialized regions at the plasma membrane, lysosomal degradation or recycling. For most interaction partners, we and others observed a retardation of interacting membrane proteins at the trans-golgi-network upon PIST overexpression, leading to a decreased protein amount at the cell surface. Many of PIST interacting partners are enriched at the postsynaptic density (PSD). We investigated whether depletion of PIST leads to an altered protein amount in the PSD, with consequences for neuronal function. By preparing the PSD fraction from wildtype and homozygous PIST knock out mice, we observed changes in the protein amount of some interaction partners. In addition, we performed cell surface biotinylation experiments on primary cultured cortical neurons and hippocampal slices and immunocytochemical stainings on primary cultured hippocampal neurons. To investigate the consequences of a changed protein amount at the PSD we analyzed signaling pathway activity in primary cultured cortical neurons and in acute hippocampal slices following chemical induction of LTP and LTD.

Finally, PIST ko mice were analyzed in several well established behavioral tests. There was no difference between wt and heterozygous mice in most of the parameters analyzed. However, in the Morris water maze test we observed a significant reduction in the long-term spatial memory of heterozygous PIST KO-mice compared to WT-mice.

Time matters: Tracking organelle-organelle interactions in living cells

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Secretory trafficking is essential for many neuronal processes including development, homeostasis, synaptic maintenance and synaptic plasticity. Membrane proteins and lipids are processed through the ER, the Golgi complex and endosomal system on their way to the plasma membrane. At the plasma membrane proteins can be targeted for recycling via endosomes or degradation by lysosomes. During secretory trafficking, coordinated movement or local anchoring of two or more organelles could ensure a proper passage of proteins from one compartment to the other. Correlated movement or pausing observed by imaging organelles labeled with different fluorescent markers. The time of colocalization between moving or stationary organelles is a key parameter for analyzing their degree of interaction during secretory processes. Therefore, it is important to have an algorithm allowing non-biased analysis of organelle-organelle colocalization time. Currently available tracking programs lack the ability to analyses colocalization time during movement. Here we developed the NI LabVIEW based program, which allows customization of all tracking steps, starting from improvement of signal-to-noise ratio, particle detection to calculation of various statistics (e. g. path velocities of all particles). We tested the performance of this algorithm in neuronal and non-neuronal cells and compared with a classical kymograph as well as spectral correlation analysis.

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Photopharmacological control of bipolar cells restores visual function in blind mice

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Vision is probably the most fundamental sense in humans and its loss can be devastating. Degenerative diseases that affect the outer retina, such as retinitis pigmentosa (RP) or age-related macular degeneration (AMD), result in visual impairment and blindness. These diseases are characterized by the slow degeneration of rod and cone photoreceptors, however, leaving the rest of the retinal circuitry relatively intact. Photopharmacological control of neuronal activity with synthetic photoswitches is a promising new approach for restoring visual function in patients suffering from degenerative retinal diseases. Azobenzene photoswitches such as AAQ and DENAQ have been shown to restore retinal ganglion cell light responses in mouse models of retinal degeneration. We now describe DAD, a third-generation photoswitch that restores retinal ganglion cell light responses to blue or white light and quickly relaxes to its inactive form in the dark. DAD is not permanently charged, enabling the photoswitch to rapidly and effectively cross biological barriers and photosensitize retinal neurons. Intravitreal injection of DAD restores light-driven behavior to blind mice. Unlike DENAQ, DAD acts upstream of retinal ganglion cells, primarily conferring light sensitivity to bipolar cells. DAD is capable of generating ON and OFF visual responses in the blind retina by utilizing intrinsic retinal circuitry, which may be advantageous for restoring visual function.

Spastin regulates microtubule dynamics and is required for normal motor and cognitive functions

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The distribution of membrane proteins to specific subcellular domains poses particular challenges to the protein trafficking machinery of nerve cells. Most transmembrane proteins are transported over long distances from the soma into axons and dendrites. This intracellular transport is driven in an ATP-dependent manner by kinesin and dynein motor proteins along microtubules.

Microtubules are polymeric cytoskeletal structures with variable lengths. They can grow or shrink resulting in a dynamic cellular network. Neurons contain both stable and dynamic pools of microtubules that can be regulated by microtubule severing proteins. Spastin, a member of AAA ATPase family, encoded by SPG4 gene, is one of the severing proteins expressed in neurons. Microtubule function can be modulated by microtubule associated proteins and different post-translational modifications of tubulin subunits. Notably, tubulin polyglutamylation promotes microtubule severing through spastin. Here, we used a new mouse model lacking spastin to analyze the role of microtubule severing proteins regarding motor protein-dependent transport of glutamate receptors. In hippocampal spastin knockout neurons, we observed increased microtubule stability and altered microtubule dynamics. In addition, the transport of glutamate receptors was diminished. Accordingly, glutamate receptor levels at the cell surface were significantly reduced. The behavioral characterization showed an impaired motor performance and learning/memory deficits in spastin knockout mice. Our data suggest that microtubule severing provides an important mechanism to maintain the cell surface delivery of synaptic proteins and this might explain the cognitive deficits observed in mice lacking the microtubule-severing protein spastin.

Molecular organization of taste cells

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The sense of taste enables organisms to identify and consume nutrients as well as electrolytes and to avoid toxins. The five basic taste qualities are thought to depend on dedicated populations of specialized epithelial cells assembled into taste buds in the oral cavity. One of the cell types residing in taste buds is known as taste receptor cell or type II cell based on morphological criteria and expresses the components required for signaling through taste G protein-coupled taste receptors. Based on the expression of the receptors for sweet (Tas1r2-Tas1r3), umami (Tas1r1-Tas1r3), or bitter (Tas2rs) this cell population is further subdivided into three subsets. Another cell population which, by morphological criteria, is termed presynaptic cells or type III cells detects sour stimuli through acidification of the cytosol which blocks resting potassium currents. A subset of these cells characterized by the expression of carbonic anhydrase 4 (Car4) represents a sensor for the perception of carbonation. Type III cells also express a number of neuronal marker proteins and form conventional synapses with afferent nerve fibers. Moreover, based on input from taste-activated type II cells, they produce secondary taste responses to sweet, umami, and bitter stimulation. However, genetic ablation of type III cells abolishes sour taste and the taste of carbonation, yet leaving the other basic tastes unaffected obscuring the importance of the secondary taste responses for taste quality coding. Finally, the detection of amiloride-insensitive salt stimuli was shown to be facilitated by two distinct subsets of type III cells, in contrast to amiloride-sensitive salt recognition, which could not been assigned to a particular class of taste cells, although the functional identification in specialized taste cells was possible. Together these observations indicate that type III cells form a functionally heterogeneous and poorly understood cell population. Towards a better understanding of type III cell function we generated and analyzed a strain of mice carrying a modified allele of the Car4 gene, by adding the sequence coding for mCherry red fluorescence protein following an internal ribosome entry site. These mice allow us to visualize Car4-expressing cells. Car4 driven mCherry auto-fluorescence and Car4-like immunoreactivity was almost always co-localized with the type III cells markers aromatic L-amino-acid decarboxylase, synaptosomal-associated protein 25, or glutamic acid decarboxylase 67 in fungiform papillae and taste buds of the palate and naso-incisor duct. In vallate and foliate papillae only 84 % of the Car4 expressing cells were co-localized with these type III cell markers, indicating that Car4+ cells represent a distinct subpopulation of the type III cells in the posterior lingual papillae as well as a type III cell-independent population. In comparison to that, type III cell markers aromatic L-amino-acid decarboxylase, synaptosomal-associated protein 25, and glutamic acid decarboxylase 67

co-localized always with each other (99 %), independent of the type of taste papillae. Thus, our data confirm the heterogeneous character of the type III cell population and offer a tool to investigate them in great detail. Additional experiments will be necessary to figure out, how the determined molecular differences of the type III cell subpopulations relate to the functional properties outlined above. Aside from the oral cavity, we detected mCherry auto-fluorescence of Car4-knock-in animals in several extra-oral tissues like kidney, pancreas or epididymis, indicating the relevance of carbonic anhydrases in various biological processes.

Qualitative and differentiated impact of sensory input on hippocampal information processing

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The hippocampus plays an essential role in the integration of sensory information such that spatial representations and declarative memory are retained. One means through which it does this comprises long-term alterations of synaptic efficacy in the form of synaptic plasticity. We have observed that the precise nature and modality of sensory cues, as well as informational pre-processing in the primary sensory cortices are key determinants of the level of detail, the longevity and the content of spatial memories that are enabled by hippocampal synaptic plasticity. Furthermore, the role of synaptic plasticity in processing and enabling storage of elements of a cognitive representation is determined by the distinct hippocampal subfields and their related circuitry. Data will be presented that describe how synaptic plasticity, in the form of long-term potentiation (LTP) and long-term depression (LTD), enables storage and/or updating of different components of a spatial experience, and how the different hippocampal subfields contribute to these phenomena. The influence of local and/or distal visuospatial, audiospatial and olfactospatial sensory cues, as well as informational pre-processing by the visual or piriform cortices, on hippocampal information processing will also be described, derived from field and single-unit electrophysiological recordings from rodents during spatial learning.

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SHANK3 structure reveals a ras-association domain regulating integrin activation in neurons

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SHANK genes code for scaffolding proteins of the postsynaptic density of glutamatergic synapses. Mutations of the SHANK3 gene have been reported in patients with intellectual disability or autism spectrum disorders. The consequences of these mutations remain largely elusive. Clarifying the three dimensional structure of the SHANK3-N terminal region showed that the SPN domain is an unexpected Ras-association domain with high affinity for GTP-bound Ras and Rap G-proteins. Interestingly, autism-associated mutations within the SHANK3 SPN domain (R12C and L68P) interfere with binding to G proteins. Rap1 is known to play a role in integrin activation. Here, we report that SHANK proteins inhibit integrin activation by blocking active Rap1; L68P mutant Shank3 fails to counteract Rap1 signaling and integrin activation. In agreement, overexpression of Shank3 wt but not the L68P mutant blocks formation of filopodia in rat hippocampal neurons cultured on a laminin substrate. Taken together, we identify SHANK proteins s as crucial regulators of G-protein signaling and integrin activation in neurons.

Fast dynamics of endoplasmic reticulum in relation to spine plasticity

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The precise role of intracellular organelles in spines is poorly understood, but there is evidence for effects on synaptic plasticity. The presence of endoplasmic reticulum (ER) allows mGluR-dependent depression and local calcium signalling in voluminous dendritic spines which bear strong synapses (Holbro et al., 2009 PNAS). Knocking out synaptopodin, a protein that is essential for ER organization into a 'spine apparatus', has modest effects on synaptic plasticity (Deller et al., 2003 PNAS; Vlachos et al., 2008 Hippocampus). However, what determines acquisition or loss of the endoplasmic reticulum by dendritic spines and the impact on synaptic properties remains unanswered. Therefore, we set out to monitor the temporal dynamics of ER and synaptic structure. Using multiphoton microscopy, we

followed GFP-labelled ER and the volume of dendritic spines over time in organotypic hippocampal slices at physiological temperature. ER movements in and out of spines were much more dynamic than previously thought, occurring on a time scale of minutes rather than days (Toresson and Grant, 2005 EJN). We could distinguish 2 classes of ER dynamics: In some spines (~10%), the ER remained present for hours. The majority of ER intrusions, however, were short-lasting (< 20 min). About 20% of CA1 hippocampal spines possess ER at any given time point but more than 50% were visited within 2 hours, and progressively more in longer time periods. Interestingly, the volume of dendritic spines was at its maximum at the time of ER insertion, pointing to a tight correlation between ER and structural plasticity (see example shown below). A spine apparatus, revealed by the simultaneous presence of ER and synaptopodin, was mostly found in spines that contained stable ER. Inducing spine structural plasticity (sLTP) by repetitive two photon glutamate uncaging, we observed that spines were typically invaded by ER immediately after sLTP induction. Spines that contained stable ER before sLTP induction did not grow further. We found that fast ER dynamics depended on myosin Va activity and were positively modulated by glutamate receptors. Expressing in single CA1 neurons a myosin Va (MyoVa) dominant negative (DN) pointed to a role of this molecular motor in spine ER insertion. MyoVa DN abolished the aforementioned fast ER dynamics, reduced the fraction of the stable ER-positive spines and blocked LTP induction as revealed by whole cell patch clamp. Our time-lapse analysis agrees with the concept that spine ER acts as a 'brake' on spine growth and synaptic potentiation (Holbro et al., 2009 PNAS).

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Chronic manipulation of activity at identified synapses

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Neuroplasticity refers to the brain's ability to reorganize itself by forming new neural connections throughout life. In particular, long term plasticity of synaptic connections between neurons is generally believed to be a key mechanism for learning and memory. What is unknown, however, is whether information storage in the brain relies on the analog strength of synapses or whether changes in neuronal connectivity underlie a more stable, binary form of memory. Altered neuronal activity is known to affect the turnover of dendritic spines, but little is known about the specificity and molecular mechanisms of this process. Previous studies in hippocampal slice cultures have shown that long term

depression (LTD), induced by stimulating Channelrhodopsin2-expressing CA3 neurons at 1 Hz, leads to increased elimination of Schaffer collateral synapses during the following days, whereas activation at higher frequencies prevented removal. In addition, it was found that initial low release probability is associated with higher elimination probability after LTD suggesting that the rate of ongoing synaptic transmission determines whether a depressed synapse is retained in the circuit, or not.

Based on this assumption, by chronically changing activity levels at identified synapses during the days following plasticity induction, we can directly assess whether this is the case. Here, we combine optogenetic stimulation of identified Schaffer collateral synapses and two-photon imaging of postsynaptic calcium signals with DREADD technology to chronically dampen synaptic transmission selectively in the pathway under scrutiny. After a first electrophysiological characterization of the hM4D-DREADD silencing tool, we tested the effect of such manipulations on synapse survival by following the fate of individual synapses for 7 days.

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Biophysical mechanisms of the microtubule network in synaptic transport processes

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Synapses are major sites of neuronal communication by transducing electrical and chemical signals. In order for the brain to adapt to multiple activity-dependent stimuli, they have the ability to strengthen or weaken over time, which is known as synaptic plasticity. Whether and how plasticity related proteins are transported to synapses is regulated by different mechanisms.

In this study, we address the function of microtubules in transport processes. Microtubules are part of the cytoskeleton and consist of alpha- and beta-tubulin dimers, which assemble into tube-like filaments with an intrinsic orientation. Newly synthesized neurotransmitter receptors are transported from the Golgi to the neurites by molecular motors along this microtubule network. Through their dynamics (growth, shrinkage, movement) and several posttranslational modifications microtubules themselves might act as regulators of these transport processes. Several alpha- and beta-isoforms of tubulin exist, from which tubulin-beta3 is selectively expressed in neurons. Tubulin-beta3 mutations are known to cause neurological syndromes in patients, such as congenital fibrosis of the extraocular muscle and congenital oculomotor nerve hypoplasia. To analyze the functional role of beta3-tubulin

in neuronal transport, we established shRNA-based knockdown of beta3-tubulin gene expression in mouse cultured hippocampal neurons. We subsequently analyzed the dynamics of the microtubule +TIP protein EB3, as a measure of microtubule growth. In addition we studied the transport of the microtubule-dependent motor protein KIF5 and a KIF5-dependent cargo protein, heading to the neuronal plasma membrane.

Our experiments aim to investigate the contribution of tubulin-beta3 in neuronal transport. Future experiments will ask whether beta3-dependent deficits in disease may be due to transport problems through microtubule-dependent motor protein complexes.

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Myosin Id and myosin XVI as potential regulators of postsynaptic function and plasticity

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Myosins are a large family of actin-based cytoskeletal motors. The functions of myosins are diverse, with some playing an important role in actin-dependent regulation of synaptic strength and morphology. Here, we investigate the hypothesis that two myosins (myosin Id and XVI) that are expressed in the brain of vertebrates and whose function is largely unknown are novel regulators of postsynaptic function and plasticity. Observations such as a role of myosin Id in endosomal trafficking and an interaction of myosin XVI with the actin regulatory machinery (the WAVE regulatory complex; WRC) support this hypothesis. Both the actin cytoskeleton and the endosomal pathway are crucial for the regulation of synaptic AMPA receptor content, and consequently for phenomena such as synaptic plasticity. We are using cerebellar Purkinje cells as a model system. Employing a cell specific promotor to induce miRNA-mediated knockdown of myosin Id or XVI we are able to specifically target the Purkinje cells in heterogenous dissociated cerebellar cultures without altering other (e.g. presynaptic) cell types. Interestingly, we observed that the dendritic complexity of Purkinje neurons is altered upon myosin Id or myosin XVI knockdown as quantified via Sholl analysis. This suggests an important role of these myosins in Purkinje cells. Branching of dendrites is at least partially actin depended as is the formation and plasticity of spines. To investigate whether filamentous actin (F-actin) turnover in spines depends on one of the myosins, we used fluorescence recovery after photobleaching (FRAP) on single spines of Purkinje cells expressing mGFP-tagged actin. Interestingly, upon myosin Id as well as myosin

XVI knockdown we detected changes in the turnover of F-actin in spines. We will follow up on the idea that myosin XVI influences F-actin via regulating the WRC and consequently the actin-nucleating activity of the Arp2/3 complex. To further characterize the functions of myosin Id and myosin XVI on a cellular level, we will perform electrophysiological recordings from slices of knockout mice that are generated using the CRISPR/Cas9 system. These mouse models will also be important to understand if myosin Id and XVI are essential for cerebellar network function as changes in motor learning can be directly linked to Purkinje cells. In conclusion, our results so far show that myosin Id and XVI knockdown alters F-actin dynamics and induces changes in cellular morphology.

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Activity-dependent spatially localized miRNA maturation and protein translational repression in neuronal dendrites

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Activity-dependent dendritic protein synthesis plays a key role to support structural and molecular changes during synaptic plasticity. However, how synaptic activity controls the regulatory mechanisms involved in local protein synthesis is not clear. miRNA activity is one mechanism by which protein synthesis can be acutely regulated. To explore activity-dependent local miRNA regulation of protein synthesis, we developed a fluorescent probe to report miRNA biogenesis and examined local translational regulation by synaptic activity. The reporter probe contains the backbone of pre-miR181a that gives a fluorescent signal upon maturation. The mature miR181a is known to regulate expression of CamKIIa and GluA2, two of the well-known mediators of synaptic plasticity. We show that the pre-miRNA-181a probe, delivered intracellularly during whole-cell recordings, exhibited an activity-dependent increase in fluorescence, indicating the stimulation of miRNA maturation by external stimuli. Single-synapse/spine stimulation by glutamate uncaging resulted in a local maturation of miRNA-181a that required the activity of NMDA receptors. The local maturation of miRNA-181a was associated with a spatially restricted and dramatic reduction in the protein synthesis of CamKIIa. Thus, the data indicate that neurons employ miRNA mediated local translational repression as a tool to increase the precision and robustness of synaptic modifications during plasticity.

The evolutionary transcriptomic landscape of mammalian olfaction

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The importance of sensing the molecular environment is reflected in the genetic investment in encoding olfactory receptors (ORs), which constitute the largest mammalian gene family. The OR gene repertoire is largely species-specific, and shaped by the nature and necessity of chemosensory information for survival in each species' niche. In addition to differences in the ORs, the morphology, size, neural projections and organization of chemosensory epithelia vary remarkably across mammals, suggesting differences in wider gene expression networks. By combining RNA-seq with FACS in a hierarchical fashion from whole olfactory mucosa (WOM) to single olfactory sensory neurons (OSNs), we have identified the complete transcriptional profile of mouse OSNs, and their heterogeneity at the single cell level. But 25 years after the discovery of the ORs, the interspecific molecular heterogeneity of the olfactory system still remains largely unknown. To study the evolutionary dynamics of gene expression in the olfactory system among species with different chemosensory niches, we performed RNA-seq of the WOM of six species of rodents, carnivores and primates (including humans). Our comparative transcriptome-wide analysis reveals a high degree of molecular conservation across 95 million years of mammalian evolution.

We found that ORs are expressed across a large dynamic range in these six species. RNA abundances correlate well with the number of OSNs expressing an OR. Combining RNA-seq with a phylogeny-based method that classifies ORs into orthologous gene groups (OGGs), we found that phylogenetic conservation does not imply conservation in OR gene expression: we find numerous examples of highly-expressed ORs specific for a single species or order. Our data further suggests that some highly expressed ORs are involved in the detection of food odorants. This experimental strategy has identified OR genes that may have been selected for different niches, and identified food odorants' detection as one of the possible driving evolutionary forces contributing to a better understanding of the evolution of olfaction.

Glutamate dynamics in the cleft of Schaffer collateral synapses

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Glutamate release may be indirectly detected by electrophysiological recordings of postsynaptic AMPA receptor mediated currents (EPSCs). The complex nature of postsynaptic responses makes it difficult to distinguish between multisynaptic connections and multivesicular release from a single synaptic site. Here we show that it is possible to monitor neurotransmitter release at individual Schaffer collateral synapses is using the genetically encoded glutamate indicator iGluSnFR (Marvin et al., Nat. Meth. 2013) and two-photon microscopy. We expressed the indicator in CA3 pyramidal neurons via single cell electroporation. The method is sensitive enough to detect the release of single transmitter vesicles at individual presynaptic terminals.

To investigate the influence of glutamate diffusion, indicator kinetics and cleft orientation on the optical signals, we set up a Monte Carlo-type simulation of molecular events occurring at an archetypical bouton-spine contact site. The stochastic nature of spatial locations of molecules and binding events reflects some of the variability seen at the experimental level. Combining microscope specific focus size (PSF) and calculated 3D positions of iGluSnFR in both glutamate unbound and bound state can be used to simulate two-photon fluorescence transients which then can be compared to experimental data. The results of the simulation suggest critical parameters for further development of genetically encoded glutamate sensors. Furthermore, we quantified the effect of fusion site variability on AMPA receptor activation.

Phosphorylation of focal adhesion kinase at Y925: Role in radial neuronal migration

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The adult mammalian cerebral cortex consists of six layers. During development, cortical neurons originating from the ventricular zone migrate radially towards the marginal zone. Cajal-Retzius cells in the marginal zone express Reelin, an extracellular matrix protein. Reelin has been shown to play an important role in the control of neuronal migration. It has been suggested that neuronal migration requires proper successive attachment and detachment of migrating neurons from radial glial cells, which is largely dependent on adhesion proteins. Focal Adhesion Kinase (FAK), one of the tyrosine kinases localized to focal adhesions, has been shown to be activated by Src at tyrosine residue 925. Src is an important downstream molecule of Reelin signaling. Up to date, the precise molecular function of FAK and its phosphorylation at Y925 during development has remained unclear. Using in utero electroporation and live imaging, we have demonstrated that overexpression of FAK and a point mutation at Y925A in late-born neurons disrupted radial neuronal migration. Compared to control neurons, overexpression of FAK and FAK Y925A induced migration defects of late born neurons. Time-lapse imaging demonstrated that these neurons showed abnormal migratory behaviors. Taken together, our findings indicate that FAK and phosphorylation of FAK at Y925 is required for radial neuronal migration and might be regulated by Reelin signaling.

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The descending pathway to the piriform cortex of freely behaving rats engages in synaptic plasticity in contrast to the ascending pathway

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All areas of the cortex are believed to undergo experience-dependent modification mainly deriving from sensory inputs. The underlying mechanisms for encoding of sensory information into representations in the CNS still have to be uncovered. In freely behaving rats, the visual cortex for example engages in pre-processing of sensory information by means of persistent synaptic plasticity

(Tsanov & Manahan-Vaughan 2007, J. Neurosci). So far, it remains to be determined if this property of the visual cortex is emulated by other sensory cortices.

This project investigates the olfactory system by examining persistent synaptic plasticity in the ascending and descending pathway to the piriform cortex. Field excitatory postsynaptic potentials were recorded in rats with chronic implantation of a stimulation electrode in either the olfactory bulb or the orbitofrontal cortex and a recording electrode in the anterior piriform cortex (coordinates modified from Cohen et al. 2008, J Neurosci) and patterned afferent stimulation in a large range of frequencies was applied.
Applied in the ascending pathway patterned afferent stimulation cannot induce persistent synaptic plasticity in the piriform cortex. In contrast, the descending pathway to the piriform cortex engages in persistent synaptic plasticity. Altogether these findings supports that top-down control may be the final determinant for the expression of persistent synaptic plasticity in the piriform cortex.

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Myosin VI regulates AMPA receptor-mediated synaptic function and plasticity in Purkinje cells

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Myosin VI is an actin-based cytoskeletal motor that is known to form a complex with AMPA-type neurotransmitter receptors (AMPARs). The complex also comprises the synaptic scaffolding protein SAP97/DLG1 that binds both the myosin and the GluA1 AMPAR subunit. Here we aim to examine whether AMPAR-mediated synaptic function and plasticity depend on myosin VI. As a neuronal model system we focus on Purkinje cells (PCs) that are the central signal integrators in the cerebellum. Notably, AMPAR-mediated plasticity at parallel fiber (PF) to PC synapses is thought to be crucial for motor learning. Using cultured PCs derived from Snell's waltzer mice (functional myosin VI null), we find evidence suggesting that myosin VI promotes synaptic incorporation of PC AMPARs during basal conditions. Myosin VI has previously been implicated in clathrin-mediated endocytosis (CME) of

AMPARs. Since postsynaptic plasticity in the form of long-term depression (LTD) at PF-PC synapses is driven by CME of AMPARs in PCs, we tested whether LTD at the PF-PC synapse is affected in acute cerebellar slices of Snell's waltzer mice. Strikingly, our data show a severe impairment of PF-PC LTD in the absence of myosin VI, suggesting that the myosin is needed for the CME of AMPARs that takes place in PCs during LTD. Given these findings, we examined whether PC-specific knockout of the myosin's heavy chain (Myo6) leads to motor learning deficits. However, accelerating rotarod tests and analysis of vestibulo-ocular reflex adaptation did not reveal major deficits in the conditional Myo6 knockout mice. This suggests that myosin VI in PCs is not essential for motor learning. We currently address whether the myosin acts in AMPAR trafficking in a cell-autonomous fashion in PCs and which of its molecular properties are required for AMPAR CME. In conclusion, our results show for the first time that the AMPAR-interacting cytoskeletal motor myosin VI is crucial for a form of postsynaptically expressed LTD.

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Taste categorical information is encoded in the delta band

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The ability to detect the presence of a chemical in the mouth plays a crucial role in nutrient sensing and identification of toxins. Little is known about the cortical dynamics of taste processing which represents the least studied sensory system in humans. We have recently shown that the earliest taste-evoked neural responses obtained from the human cortex code taste quality information (sweet, sour, salty, bitter; Crouzet, Busch, & Ohla, 2015). Yet, advances in the field have been greatly hampered due to poor signal-to-noise ratio of gustatory-evoked responses. We measured multi-channel head-surface electroencephalographic (EEG) in human participants while they were to detect tastants inducing salty, sweet, sour, or bitter sensations. Using multivariate pattern analysis of large-scale electrophysiological responses we show that taste quality information is largely contained in the lower (delta) frequency band and that isolating information in the delta band improves classification performance significantly.

Given that delta oscillations have been implicated in the integration of cerebral activity with homeostatic processes such as hunger and also food reward processing (Knyazev, 2012) the current result suggests a previously unknown role of delta oscillations in food-related sensory processing.

Long-lasting memory of salt chemotaxis learning in C. elegans

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The soil nematode Caenorhabditis elegans is an appropriate model organism for analyzing the function of neural circuits because all hermaphrodites invariably have 302 neurons, whose connections are fully described. Despite its relatively simple neural structure, C. elegans shows several types of experience-dependent behavioral plasticity. For example, C. elegans can learn to associate salt concentration of the environment with food availability. After being exposed to a particular concentration of NaCl with food, they come to be attracted to that concentration of NaCl. On the contrary, if exposed to a particular NaCl concentration under starvation conditions, they avoid that NaCl concentration.

It is well known that in many organisms duration of memory depends on the number of and conditions of training: memory lasts longer after repeated training when compared to a single training. In C. elegans, this phenomenon has been observed in odorant learning (Kauffman et al. 2011) and mechanosensory learning (Rose JK et al. 2011). Here, we report a long-lasting behavioral plasticity in salt chemotaxis learning. Repeated alternating exposure to high NaCl concentration with food and low NaCl concentration without food generated a 4 hour-lasting NaCl preference. Interestingly, food deprivation intervals were critical for memory elongation, while the NaCl concentration during starvation was not.

de novo synthesis of gene products are also involved in elongation of memory. crh-1, the C. elegans ortholog of CREB transcription factor is known to be required for long-lasting odorant memory (Kauffman et al. 2011). In salt chemotaxis learning, however, crh-1 mutants showed a slight delay in behavioral adaptation to food-associated low concentrations of salt. On the other hand, overproduction of crh-1 resulted in preference of low salt concentrations. These results suggest that crh-1 can regulate salt preference.

LTP in the mouse barrel cortex driven by cooperative lemniscal and paralemniscal pathway activity

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Long term potentiation (LTP) underlies changes in synaptic efficacy during cortical plasticity and learning. Our lab has shown in vivo that repeated sensory input, or 8-Hz rhythmic whisker stimulation (RWS), induces synaptic LTP in layer (L) 2/3 pyramidal cells of the somatosensory barrel cortex (BC).

Whisker sensory information is primarily processed by the lemniscal pathway, which comprises neurons in the ventral posteromedial (VPM) thalamus that project to BC L4 and L5B. L4 cells synapse on L2/3 pyramidal cells. Whisker stimuli also recruit activity in paralemniscal circuits, which contain projections from the posteromedial complex of the thalamus (POm) to BC L1 and L5A. Our lab has found that RWS evokes coactivity of these pathways, which is necessary to drive sensory-evoked LTP, however, the exact synaptic circuit remains elusive. Here, using whole-cell patch clamp in thalamocortical slices, we tested if rhythmic coincident pairing (RCP) at 8Hz of L4 and POm synapses onto L2/3 pyramidal cells is sufficient to drive LTP. RCP efficiently induced LTP of postsynaptic potentials (PSPs) in the L4-L2/3 synapses. Activity was paired by electrical stimulation of L4 and optical stimulation of channelrhodopsin-2 expressing POm axons. RCP while suppressing POm neurotransmission using Designer Receptors Exclusively Activated by Designer Drugs (DREADDS), or blocking NMDA receptors, failed to induce LTP.

We then tested to what extent GABAergic inhibition on L2/3 dendrites regulates this LTP. It has previously been shown that L2/3 pyramidal dendrites are efficiently inhibited by somatostatin (SST) expressing interneurons, which are inhibited by vasoactive intestinal peptide (VIP) expressing interneurons. Thus, VIP cells disinhibit L2/3 pyramidal dendrites, which could gate activity- dependent synaptic plasticity.

Data suggest that inhibition of VIP or SST interneuron activity using DREADDS in CRE mouse transgenic lines bidirectionally alters LTP. Our data identifies excitatory and disinhibitory microcircuits whose synergistic activity may facilitate sensory-driven LTP in the BC.

Cognitive impairment and autistic-like behaviours in SAPAP4 deficient mice

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SAPAPs constitute a family of scaffold proteins promoting the assembly of signalling complexes within the postsynaptic density (PSD) of excitatory synapses. In humans, mutations in genes encoding various synaptic components, including scaffold proteins, have been associated with different neurodevelopmental and psychiatric conditions, such as autism spectrum disorders (ASDs). Pathogenic mechanisms that may result from these genetic alterations are largely unknown. ASDs are a group of neurodevelopmental conditions characterized by deficits in social interaction and communication as well as stereotyped repetitive behaviours. Here, we show that functional loss of SAPAP4 triggers profound behavioural changes in mice, including severe learning and memory deficits as well as impaired vocal communication and social interest, alterations also found in patients with ASD. In adult mice, these behavioural changes are associated with larger PSDs, enhanced α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor-mediated currents, altered N-methyl-D-aspartate receptor subunit composition and impaired long-term depression, features not seen in SAPAP2 or SAPAP3 deficient mice. Notably, alterations in the pattern of in vivo network activity are already detectable during neonatal brain development. Taken together, our data indicate that SAPAP4 performs unique roles at excitatory synapses. These data indicate that SAPAP4 performs unique roles at excitatory synapses that not only control the size and function of hippocampus excitatory synapses, but neuronal network functions that underlie the appearance of aberrant behaviours and reduced cognition seen in patients with ASD.

Targeting the spine apparatus to dendritic spines via synaptopodin and the actin cytoskeleton

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Synaptopodin is an actin-associated protein that is present in pyramidal neurons of the cortex and hippocampus. It is essential for the formation of the so-called spine apparatus (SA), a specialized, stacked form of endoplasmic reticulum, which is present in a subset of adult mushroom-shaped spines and can additionally, be found in the axon initial segment. SA functions are still enigmatic; however, it has been implicated in the delivery of receptor subunits to the PSD and as a regulator of the calcium concentration in spines. Synaptopodin also plays a role in synaptic plasticity; spines of synaptopodin-deficient mice completely lack the SA and show a reduction of long-term potentiation that might be related to its role as an internal source of calcium ions.

Prior work has shown that general overexpression of synaptopodin in neurons of knockout mice is sufficient to rescue the stack-organization of the ER that is typical for the SA. STED nanoscopy revealed that synaptopodin immunoreactivity is always in close proximity to actin filaments. To identify potential factors that might be responsible for synaptic targeting of synaptopodin we performed a mass spectrometry analysis of potential binding partners which were pulled down from mouse brain using synaptopodin as bait. Interestingly, several myosins where identified as novel synaptopodin binding partners. Myosins are ATP-dependent motor proteins involved in actin-dependent transport and anchoring of organelles. By using biochemical methods, cell biological and live imaging techniques we are trying to address if the interaction between synaptopodin and myosin V is required for synaptic targeting of synaptopodin into the spine apparatus or might play a role in the localization and stabilization of the SA, possibly mediating its attachments to the F-actin cytoskeleton via actin binding proteins.

Functional characterization of CASK missense mutations

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The calcium/calmodulin-dependent serine protein kinase (CASK) is a member of the Membrane Associated Guanylate Kinase (MaGuK) family of proteins. CASK plays a structural role in synapses through interactions with other synaptic proteins including the membrane protein Neurexin (which reaches across the synaptic terminal and binds to Neuroligin), and SAP97. SAP97 bound by CASK preferentially binds to NMDA receptors, which favours their transport to the postsynaptic terminal. Finally, CASK may act in the nucleus where it is known to form a complex with CINAP and Tbr1, the ladder being a transcription factor of the NR2B subunit of the NMDA receptor.

Mutations in the X-linked CASK gene are associated with a severe neurodevelopmental phenotype; both loss of function, and missense mutations have been described. For missense mutations, the molecular pathogenic mechanisms of these mutations have yet to be elucidated. Here, we investigate the functional consequences of CASK missense by coexpressing wt and mutant CASK proteins with selected interaction partners, and by analyzing their interactions through co-immunoprecipitation and Western Blot. Our data show that the CASK-SAP97 interaction is decreased in the presence of an L354P mutation in CASK's L27 domain where SAP97 binds. The CASK-Neurexin interaction is decreased by the R489W and G521V mutations, which are located within the PDZ domain of CASK where Neurexin binds. Unexpectedly, the CASK-Neurexin interaction is also affected by the Y723C and W914R mutations which flank CASK's GK domain, well outside the PDZ domain. The Tbr1-CASK interaction, which occurs at the GK domain, is also greatly reduced by the Y723C and W914R mutations. Interestingly, the CASK-CINAP interaction, which also occurs at the GK domain, is greatly increased by the same Y723C and W914R mutations that decreased the interaction between CASK and both Tbr1 and Neurexin. The relevance of missense mutation in GK and PDZ domains for the nuclear function of CASK is currently investigated by luciferase reporter assays in 293 cells and cultured neurons.

Our data show that most missense mutations analyzed here affect interactions with specific binding partners of CASK and provide functional evidence of the pathogenicity of these mutations. In addition, our data suggest strong cooperativity between different domains of CASK (such as PDZ and GK domains), which has also been indicated by structural analysis of other MaGuK proteins

Genetic depletion of the catalytic subunit of katanin, p60

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Microtubules (MTs) are highly dynamic structures that contribute to cargo transport and cell morphology. They constitute polymers of □- and □-tubulin that bind to MTs-associated proteins (MAPs), such as tau and undergo post-translational modifications, (acetylation, polyglutamylation and detyrosination). These interactions and modifications are thought to affect MTs stability, which is further regulated by a family of MTs-severing enzymes, such as katanin, spastin or fidgetin. Previous studies suggest that MT severing generates new nucleation points for MT outgrowth and is involved in different cellular processes such as mitosis, meiosis, and cell migration. Katanin is a heterodimer formed by a catalytic p60 subunit that contains a triple ATPase domain and a regulatory p80 subunit. Here, we report the generation of a novel p60-katanin conditional knock-out mouse. Using molecular and in vivo techniques, we characterize the role of p60 in brain development and synaptic plasticity. Preliminary results have shown that homozygous mutants are not viable; however reveal specific phenotypes at the heterozygous KO level. On the other hand, conditionally depleted p60 in a brain region-specific manner shows structurally altered synapses and impaired LTP maintenance. Altogether, our results underline p60 katanin role in development and plasticity.

Regulation of $GABA_A$ receptor clustering by gephyrin S-nitrosylation, dynein light chain and alternative gephyrin splicing

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Inhibitory transmission in the central nervous system depends on the strength and plasticity of synaptic contacts, balancing the activity of neuronal excitation. Gephyrin, the principal scaffolding protein at inhibitory synapses, is essential for postsynaptic clustering of glycine (GlyRs) and GABA type A receptors ($GABA_ARs$). Synaptic localization and clustering of gephyrin, determining the strength of inhibitory transmission, are highly dynamic processes that are regulated by protein-protein interactions, posttranslational modifications and alternative splicing.

We found gephyrin to be associated with the neuronal nitric oxide synthase (nNOS), causing gephyrin S-nitrosylation and thereby affecting receptor clustering and synaptic plasticity at GABAergic synapses (Dejanovic and Schwarz, J Neurosci 2014). nNOS overexpression decreased the size of postsynaptic gephyrin clusters in primary hippocampal neurons, while nNOS inhibition conversely increased gephyrin cluster size and number. Similar effects were observed on gephyrin clustering upon knockdown or overexpression of dynein light chain (DLC), a multifunctional protein, initially believed as gephyrin-cargo adaptor to the dynein motor and furthermore reported as nNOS inhibitor. We demonstrate the formation of a ternary complex between gephyrin, DLC and nNOS and a reduction of gephyrin S-nitrosylation upon DLC-mediated nNOS inhibition. In aggregate, these findings reveal a novel molecular mechanism of DLC-mediated gephyrin clustering by regulating nNOS-dependent gephyrin S-nitrosylation at the inhibitory postsynapse. Furthermore, we studied gephyrin splice variants in hippocampal neurons and monitored their respective cluster formation and co-localization with pre- (VGAT) and postsynaptic markers (alpha2 subunit-containing $GABA_AR$ clusters). For all C4 splice cassette containing gephyrin splice variants we observed an increased synaptic localization accompanied by an induced alpha2 subunit-containing $GABA_AR$ cluster formation. In contrast, gephyrin containing the C3 splice cassette formed a high number of large clusters that were not synaptically localized. Finally, using qRT-PCR we found a developmental expression of all gephyrin C4 cassette variants in hippocampal neurons suggesting an important developmental role of the orchestrated expression of gephyrin splice variants in inhibitory synapse formation.

Transcription factors to define taste versus somatosensory neurons of the geniculate ganglion.

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The geniculate ganglion is formed of chemosensory neurons innervating taste buds of anterior tongue and palate, and somatosensory neurons innervating the ear. Because neuronal diversity is defined by transcription factors (TFs), we sought to identify TFs that distinguish taste from somatosensory neurons in the geniculate ganglion of mice. First, we identified candidate TFs by differential expression in RNAseq of geniculate and trigeminal ganglia. Second, we tested up to 20 candidates to identify those expressed in discrete subsets of neurons. By single-neuron RT-PCR, mRNAs for Phox2b and Drg11 were detected respectively in 11 and 12 non-overlapping sets of neurons. Similarly, immunoreactivity for Phox2b and Drg11 was detected in separate populations of neurons, and accounted for all ganglion neurons. To assess if either of these two TFs is restricted to taste neurons, we co-stained for the taste afferent receptor, P2X2. Phox2b-immunoreactive nuclei were detected in 97% (of 138) of P2X2-immunoreactive neurons. Immunoreactivity for another TF, Brn3b, also did not overlap with Phox2b-expressing cells. Our results suggested that Phox2b may serve as a marker for taste neurons while Drg11 and Brn3b may be markers for somatosensory neurons in the ganglion. To test this, we anterograde-labeled chorda tympani (CT) and greater superficial petrosal (GSP) taste nerves with fluorescent (Al488, TRITC) dextrans and subjected the ganglia to immunostaining. Drg11 was detected in only 1% (of 300) labeled taste neurons. Conversely, over 90% (of 83) GSP- and CT-labeled neurons included Phox2b-positive nuclei. Thus, Phox2b and Drg11 can serve as validated markers for taste and somatosensory neurons respectively. Recently, 5HT3A was shown to be expressed in a subset of geniculate ganglion neurons. To assess if this receptor is associated with one of the above groups, we immunostained ganglia from Htr3a-GFP mice. Only GFP-bright neurons were consistently positive for P2X2 and Phox2b; GFP-faint neurons were distributed in both the taste and somatosensory neuron populations. Thus, Htr3a-expressing neurons are likely a heterogeneous group of neurons with varying significance.

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