
In the auditory system, early neural stations such as brain stem are characterized by strict tonotopy, which is used to deconstruct sounds to their basic frequencies. But higher along the auditory hierarchy, as early as primary auditory cortex (A1), tonotopy starts breaking down at local circuits. Here, we studied the response properties of both excitatory and inhibitory neurons in the auditory cortex of anesthetized mice. We used in vivo two photon-targeted cell-attached recordings from identified parvalbumin-positive neurons (PVNs) and their excitatory pyramidal neighbors (PyrNs). We show that PyrNs are locally heterogeneous as characterized by diverse best frequencies, pairwise signal correlations, and response timing. In marked contrast, neighboring PVNs exhibited homogenous response properties in pairwise signal correlations and temporal responses. The distinct physiological microarchitecture of different cell types is maintained qualitatively in response to natural sounds. Excitatory heterogeneity and inhibitory homogeneity within the same circuit suggest different roles for each population in coding natural stimuli.


of PVN frequency tuning should render pup odor-induced disinhibition more effective for high-frequency stimuli, such as ultrasonic vocalizations. Indeed, pup odors increased neuronal responses of PyrNs to pup ultrasonic vocalizations. We conclude that plasticity in the mothers is mediated, at least in part, via modulation of the feedforward inhibition circuitry in the auditory cortex.

2014

Mizrahi, A, Shalev A, Nelken I. 2014. *Single neuron and population coding of natural sounds in auditory cortex* [31]. *Current Opinion in Neurobiology*. 24:103-110. Abstract [32] RTF [33] Tagged [34] XML [35] BibTex [36] Google Scholar [37] The auditory system drives behavior using information extracted from sounds. Early in the auditory hierarchy, circuits are highly specialized for detecting basic sound features. However, already at the level of the auditory cortex the functional organization of the circuits and the underlying coding principles become different. Here, we review some recent progress in our understanding of single neuron and population coding in primary auditory cortex, focusing on natural sounds. We discuss possible mechanisms explaining why single neuron responses to simple sounds cannot predict responses to natural stimuli. We describe recent work suggesting that structural features like local subnetworks rather than smoothly mapped tonotopy are essential components of population coding. Finally, we suggest a synthesis of how single neurons and subnetworks may be involved in coding natural sounds.

Livneh, Y, Adam Y, Mizrahi A. 2014. *Odor Processing by Adult-Born Neurons* [38]. *Neuron*. Abstract [39] RTF [40] Tagged [41] XML [42] BibTex [43] Google Scholar [44] The adult mammalian brain is continuously supplied with adult-born neurons in the olfactory bulb (OB) and hippocampus, where they are thought to be important for circuit coding and plasticity. However, direct evidence for the actual involvement of these neurons in neural processing is still lacking. We recorded the spiking activity of adult-born periglomerular neurons in the mouse OB in

Adam, Y, Livneh Y, Miyamichi K, Groysman M, Luo L, Mizrahi A. 2014. *Functional transformations of odor inputs in the mouse olfactory bulb* [45]. *Frontiers in Neural Circuits*. 8 Abstract [46] RTF [47] Tagged [48] XML [49] BibTex [50] Google Scholar [51] Sensory inputs from the nasal epithelium to the olfactory bulb (OB) are organized as a discrete map in the glomerular layer (GL). This map is then modulated by distinct types of local neurons and transmitted to higher brain areas via mitral and tufted cells. Little is known about the functional organization of the circuits downstream of glomeruli. We used in vivo two-photon calcium imaging for large scale functional mapping of distinct neuronal populations in the mouse OB, at single cell resolution. Specifically, we imaged odor responses of mitral cells (MCs), tufted cells (TCs) and glomerular interneurons (GL-INs). Mitral cells population activity was heterogeneous and only mildly correlated with the olfactory receptor neuron (ORN) inputs, supporting the view that discrete input maps undergo significant transformations at the output level of the OB. In contrast, population activity profiles of TCs were dense, and highly correlated with the odor inputs in both space and time. Glomerular interneurons were also highly correlated with the ORN inputs, but showed higher activation thresholds suggesting that these neurons are driven by strongly activated glomeruli. Temporally, upon persistent odor exposure, TCs quickly adapted. In contrast, both MCs and GL-INs showed diverse temporal response patterns, suggesting that GL-INs could contribute to the transformations MCs undergo at slow time scales. Our data suggest that sensory odor maps are transformed by TCs and MCs in different ways forming two distinct and parallel information streams.
In the mouse olfactory bulb, information from sensory neurons is extensively processed by local interneurons before being transmitted to the olfactory cortex by mitral and tufted (M/T) cells. The precise function of these local networks remains elusive because of the vast heterogeneity of interneurons, their diverse physiological properties, and their complex synaptic connectivity. Here we identified the parvalbumin interneurons (PVNs) as a prominent component of the M/T presynaptic landscape by using an improved rabies-based transsynaptic tracing method for local

The auditory cortex is malleable by experience. Previous studies of auditory plasticity have described experience-dependent changes in response profiles of single neurons or changes in global tonotopic organization. However, experience-dependent changes in the dynamics of local neural populations have remained unexplored. In this study, we examined the influence of a dramatic yet natural experience in the life of female mice, giving birth and becoming a mother on single neurons and neuronal ensembles in the primary auditory cortex (A1). Using in vivo two-photon calcium imaging and electrophysiological recordings from layer 2/3 in A1 of mothers and age-matched virgin mice, we monitored changes in the responses to a set of artificial and natural sounds. Population dynamics underwent large changes as measured by pairwise and higher-order correlations, with noise correlations increasing as much as twofold in lactating mothers. Concomitantly, changes in response properties of single neurons were modest and selective. Remarkably, despite the large changes in correlations, information about stimulus identity remained essentially the same in the two groups. Our results demonstrate changes in the correlation structure of neuronal activity as a result of a natural life event.

The auditory cortex is malleable by experience. Previous studies of auditory plasticity have described experience-dependent changes in response profiles of single neurons or changes in global tonotopic organization. However, experience-dependent changes in the dynamics of local neural populations have remained unexplored. In this study, we examined the influence of a dramatic yet natural experience in the life of female mice, giving birth and becoming a mother on single neurons and neuronal ensembles in the primary auditory cortex (A1). Using in vivo two-photon calcium imaging and electrophysiological recordings from layer 2/3 in A1 of mothers and age-matched virgin mice, we monitored changes in the responses to a set of artificial and natural sounds. Population dynamics underwent large changes as measured by pairwise and higher-order correlations, with noise correlations increasing as much as twofold in lactating mothers. Concomitantly, changes in response properties of single neurons were modest and selective. Remarkably, despite the large changes in correlations, information about stimulus identity remained essentially the same in the two groups. Our results demonstrate changes in the correlation structure of neuronal activity as a result of a natural life event.

The auditory cortex is malleable by experience. Previous studies of auditory plasticity have described experience-dependent changes in response profiles of single neurons or changes in global tonotopic organization. However, experience-dependent changes in the dynamics of local neural populations have remained unexplored. In this study, we examined the influence of a dramatic yet natural experience in the life of female mice, giving birth and becoming a mother on single neurons and neuronal ensembles in the primary auditory cortex (A1). Using in vivo two-photon calcium imaging and electrophysiological recordings from layer 2/3 in A1 of mothers and age-matched virgin mice, we monitored changes in the responses to a set of artificial and natural sounds. Population dynamics underwent large changes as measured by pairwise and higher-order correlations, with noise correlations increasing as much as twofold in lactating mothers. Concomitantly, changes in response properties of single neurons were modest and selective. Remarkably, despite the large changes in correlations, information about stimulus identity remained essentially the same in the two groups. Our results demonstrate changes in the correlation structure of neuronal activity as a result of a natural life event.

The auditory cortex is malleable by experience. Previous studies of auditory plasticity have described experience-dependent changes in response profiles of single neurons or changes in global tonotopic organization. However, experience-dependent changes in the dynamics of local neural populations have remained unexplored. In this study, we examined the influence of a dramatic yet natural experience in the life of female mice, giving birth and becoming a mother on single neurons and neuronal ensembles in the primary auditory cortex (A1). Using in vivo two-photon calcium imaging and electrophysiological recordings from layer 2/3 in A1 of mothers and age-matched virgin mice, we monitored changes in the responses to a set of artificial and natural sounds. Population dynamics underwent large changes as measured by pairwise and higher-order correlations, with noise correlations increasing as much as twofold in lactating mothers. Concomitantly, changes in response properties of single neurons were modest and selective. Remarkably, despite the large changes in correlations, information about stimulus identity remained essentially the same in the two groups. Our results demonstrate changes in the correlation structure of neuronal activity as a result of a natural life event.

The auditory cortex is malleable by experience. Previous studies of auditory plasticity have described experience-dependent changes in response profiles of single neurons or changes in global tonotopic organization. However, experience-dependent changes in the dynamics of local neural populations have remained unexplored. In this study, we examined the influence of a dramatic yet natural experience in the life of female mice, giving birth and becoming a mother on single neurons and neuronal ensembles in the primary auditory cortex (A1). Using in vivo two-photon calcium imaging and electrophysiological recordings from layer 2/3 in A1 of mothers and age-matched virgin mice, we monitored changes in the responses to a set of artificial and natural sounds. Population dynamics underwent large changes as measured by pairwise and higher-order correlations, with noise correlations increasing as much as twofold in lactating mothers. Concomitantly, changes in response properties of single neurons were modest and selective. Remarkably, despite the large changes in correlations, information about stimulus identity remained essentially the same in the two groups. Our results demonstrate changes in the correlation structure of neuronal activity as a result of a natural life event.
primary auditory cortex (A1). Using in vivo two-photon calcium imaging and electrophysiological recordings from layer 2/3 in A1 of mothers and age-matched virgin mice, we monitored changes in the responses to a set of artificial and natural sounds. Population dynamics underwent large changes as measured by pairwise and higher-order correlations, with noise correlations increasing as much as twofold in lactating mothers. Concomitantly, changes in response properties of single neurons were modest and selective. Remarkably, despite the large changes in correlations, information about stimulus identity remained essentially the same in the two groups. Our results demonstrate changes in the correlation structure of neuronal activity as a result of a natural life event.

### 2012

Kopel, H, Schechtman E, Groysman M, Mizrahi A. 2012


### 2011

Cohen, L, Rothschild G, Mizrahi A. 2011

Multisensory Integration of Natural Odors and Sounds in the Auditory Cortex [90]. Neuron. 72(2):357-369. Abstract [91]
mothers were more sensitive to sounds as compared to those from experienced mice, independent of the odor effects. These uni- and multisensory cortical changes may facilitate the detection and discrimination of pup distress calls and strengthen the bond between mothers and their neonates.

Livneh, Y, Mizrahi A. 2011 Long-term changes in the morphology and synaptic distributions of adult-born neurons. Abstract. The Journal of comparative neurology. The adult mammalian olfactory bulb (OB) is continuously supplied with adult-born neurons. While some new neurons die shortly after arrival into the OB, others persist throughout the life of the animal. Here, we followed the long-term morphological changes in adult-born periglomerular neurons and granule cells from the mouse OB well after they mature. We present a dataset of dendritic morphology and synaptic distributions from >100 adult-born neurons as imaged in vivo, and reconstructed in 3D. The dataset currently includes a substantial range of neuronal ages (0.5-11 months old). Using this dataset, we show that the morphological steady-state which adult-born periglomerular neurons reach soon after maturation is not maintained in older neurons. Rather, total dendritic length decreases after 6 months of age. We find that this morphological decrease in "old" periglomerular neurons is regulated by the age of the animal, and is independent of neuronal age. This suggests that morphological development of adult-born neurons is regulated extrinsically. Our dendritic morphology dataset of 3D reconstructions is made available to the scientific community so it may serve as a useful resource for comparative morphological studies of the OB, and in particular of adult neurogenesis. J. Comp. Neurol., 2011. © 2011 Wiley-Liss, Inc.

Adam, Y, Mizrahi A. 2011 Long-term imaging reveals dynamic changes in the neuronal composition of the glomerular layer. The Journal of neuroscience : the official journal of the Society for Neuroscience. 31(22):7967-73. The mammalian olfactory bulb (OB) contains a rich and highly heterogeneous network of local interneurons (INs). These INs undergo continuous turnover in the adult OB in a process known as "adult neurogenesis." Although the overall magnitude of adult neurogenesis has been estimated, the detailed dynamics of the different subpopulations remains largely unknown. Here we present a novel preparation that enables long-term in vivo time-lapse imaging in the mouse OB through a chronic cranial window in a virtually unlimited number of sessions. Using this preparation, we followed the turnover of a specific neuronal population in the OB, the dopaminergic (DA) neurons, for as long as 9 months. By following the same population over long periods of time, we found clear addition and loss of DA neurons in the glomerular layer. Both cell addition and loss increased over time. The numbers of new DA cells were consistently and significantly higher than lost DA cells, suggesting a net increase in the size of this particular population with age. Over a 9 month period of adult life, the net addition of DA neurons reached ?13%. Our data argue that the fine composition of the bulbar IN network changes throughout adulthood rather than simply being replenished.

Livneh, Y, Mizrahi A. 2011 Experience-dependent plasticity of mature adult-born neurons. Nature neuroscience. 15(1):26-8. The adult olfactory bulb and hippocampus are continuously supplied with newborn neurons that are thought to possess a capacity for plasticity only at a young neuronal age, mainly during the early stages of integration into the network. We find that the two main types of adult-born neurons in the mouse olfactory bulb undergo experience-dependent plasticity long after maturation and integration, as evidenced by stabilization of synaptic turnover rates. Thus, the potential time window for plasticity of adult-born neurons extends well into maturity.
Cortical processing of auditory stimuli involves large populations of neurons with distinct individual response profiles. However, the functional organization and dynamics of local populations in the auditory cortex have remained largely unknown. Using in vivo two-photon calcium imaging, we examined the response profiles and network dynamics of layer 2/3 neurons in the primary auditory cortex (A1) of mice in response to pure tones. We found that local populations in A1 were highly heterogeneous in the large-scale tonotopic organization. Despite the spatial heterogeneity, the tendency of neurons to respond together (measured as noise correlation) was high on average. This functional organization and high levels of noise correlations are consistent with the existence of partially overlapping cortical subnetworks. Our findings may account for apparent discrepancies between ordered large-scale organization and local heterogeneity.

The angiogenic factor vascular endothelial growth factor A (VEGF) has been shown to have a role in neurogenesis, but how it affects adult neurogenesis is not fully understood. To delineate a role for VEGF in successive stages of olfactory bulb (OB) neurogenesis, we used a conditional transgenic system to suppress VEGF signaling at the adult mouse sub-ventricular zone (SVZ), rostral migratory stream (RMS) and OB, which constitute the respective sites of birth, the migration route, and sites where newly born interneurons mature and integrate within the existing (OB) circuitry. Following the development of fluorescently tagged adult-born neurons, we show that sequestration of VEGF that is constitutively expressed by distinct types of resident (OB) neurons greatly impaired dendrite development in incoming (SVZ-born) neurons. This was evidenced by reduced dendritic spine density of granule cells and significantly shorter and less branched dendrites in periglomerular neurons. Notably, the vasculature and perfusion of the (SVZ,) (RMS) and (OB) were not adversely affected when VEGF suppression was delayed until after birth, thus uncoupling the effect of VEGF on dendritogenesis from its known role in vascular maintenance. Furthermore, a requirement for VEGF was specific to newly born neurons, as already established (OB) neurons were not damaged by VEGF inhibition. This study thus uncovered a surprising perfusion-independent role of VEGF in the adult brain, namely, an essential role in the maturation of adult-born neurons.

The rodent olfactory bulb (OB) is becoming a model system for studying how neuronal circuits develop and maintain. The (OB) has typical components of a sensory circuit such as ordered sensory inputs, diverse populations of interneurons, substantial neuromodulatory innervation, and projection neurons that transfer information to higher brain centers. Additionally, the (OB) is unique because its sensory afferents and a subset of its interneurons are continuously replaced throughout adulthood. Here, we review some recent findings on the development and maintenance of the mammalian (OB) circuitry. We review some of the known developmental strategies of the major (OB) components and discuss the ways in which the (OB) circuitry preserves stability in the face of ongoing changes.

Advances in neuroanatomy and computational power are leading to the construction of new digital brain atlases. Atlases are rising as indispensable tools for comparing anatomical data as well as being stimulators of new hypotheses and experimental designs. Brain atlases describe nervous systems which are inherently plastic and variable. Thus, the levels of brain plasticity and stereotypy would be important to evaluate as limiting factors in the context of static brain atlases. In this review, we discuss the extent of structural changes which neurons undergo over time, and how these changes would impact the static nature of atlases. We describe the anatomical stereotypy between neurons of the same type, highlighting the differences between invertebrates and vertebrates. We review some recent experimental advances in our understanding of anatomical dynamics in adult neural circuits, and how these are modulated by the organism’s experience. In this respect, we discuss some analogies between brain atlases and the sequenced genome and the emerging epigenome. We argue that variability and plasticity of neurons are substantially high, and should thus be considered as integral features of high-resolution digital brain atlases.


The adult mammalian brain maintains a prominent stem cell niche in the subventricular zone supplying new neurons to the olfactory bulb. We examined the dynamics of synaptogenesis by imaging the formation and elimination of clusters of a postsynaptic marker (PSD95), genetically targeted to adult-born neurons. We imaged in vivo adult-born periglomerular neurons (PGNs) during two phases of development, immaturity and maturity. Immature PGNs showed high levels of PSD95 puncta dynamics during 12-72 h intervals. Mature PGNs were more stable compared with immature PGNs but still remained dynamic, suggesting that synaptogenesis persists long after these neurons integrated into the network. By combining intrinsic signal and two photon imaging we followed PSD95 puncta in sensory enriched glomeruli. Sensory input upregulated the development of adult-born PGNs only in enriched glomeruli. Our data provide evidence for an activity-based mechanism that enhances synaptogenesis of adult-born PGNs during their initial phases of development.


We present a new method to study the three-dimensional (3D) spatial distribution patterns of newborn neurons in the mouse olfactory bulb (OB). Newborn neurons were transduced, in vivo, using lentiviruses to express green fluorescent protein (GFP). Two-photon (2P) microscopy was used to image thick (OB) slices (approximately 250 microm) at single cell resolution. Image-stacks were captured semi-automatically, and concatenated offline, to create larger image-stacks containing the positional information of all the labeled neurons. Serial reconstruction of the large image-stacks resulted in a three-dimensional virtual model, containing the exact position of all the labeled newborn neurons within large volumes of the OB. The feasibility of this method was demonstrated by analyzing the cell distributions of thousands of
(GFP) labeled newborn neurons. This analysis identified 3D clusters in which the newborn cells' density is significantly higher than the mean density. We show that our method reveals information that is overlooked when sampling only a small fraction of the tissue in 2D. This method may serve as a valuable tool, not only for analyzing newborn neurons in the OB, but also for other neuronal types as well as for other brain regions.

2007


The mammalian brain maintains few developmental niches where neurogenesis persists into adulthood. One niche is located in the olfactory system where the olfactory bulb continuously receives functional interneurons. In vivo two-photon microscopy of lentivirus-labeled newborn neurons was used to directly image their development and maintenance in the olfactory bulb. Time-lapse imaging of newborn neurons over several days showed that dendritic formation is highly dynamic with distinct differences between spiny neurons and non-spiny neurons. Once incorporated into the network, adult-born neurons maintain significant levels of structural dynamics. This structural plasticity is local, cumulative and sustained in neurons several months after their integration. Thus, I provide a new experimental system for directly studying the pool of regenerating neurons in the intact mammalian brain and suggest that regenerating neurons form a cellular substrate for continuous wiring plasticity in the olfactory bulb.

2006


As a consequence of adult neurogenesis, the olfactory bulb (OB) receives a continuous influx of newborn neurons well into adulthood. However, their rates of generation and turnover, the factors controlling their survival, and how newborn neurons intercalate into adult circuits are largely unknown. To visualize the dynamics of adult neurogenesis, we produced a line of transgenic mice expressing GFP in approximately 70% of juxtaglomerular neurons (JGNs) a population that undergoes adult neurogenesis. Using in vivo two-photon microscopy, time-lapse analysis of identified JGN cell bodies revealed a neuronal turnover rate of approximately 3% of this population per month. Although new neurons appeared and older ones disappeared, the overall number of JGNs remained constant. This approach provides a dynamic view of the actual appearance and disappearance of newborn neurons in the vertebrate central nervous system, and provides an experimental substrate for functional analysis of adult neurogenesis.
It is now widely accepted that deciphering the enigma of the brain is the most challenging intellectual endeavor of the 21st century, "The Century of the Brain" - Join our quest and become a friend of ELSC.

Our Int'l Ph.D. program provides outstanding students with top-notch courses in computational neuroscience.

The Jerusalem Brain Sciences Building will provide a state-of-the-art research and teaching facility for the Edmond and Lily Safra Center for Brain Sciences.

Get into our media channel and investigate ELSC's latest videos: seminars, public lectures, courses and video articles.

Source URL: http://elsc.nc.huji.ac.il/mizrahi/science/publications

Links: