Adult-neurogenesis allows for representational stability and flexibility in early olfactory system

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Acknowledgments

This study was supported by funding from the National Institutes of Health (NIH) and the National Science Foundation (NSF). KP was funded by NIH R01 MH113924, NSF CAREER 1749772, the Cystinosis Research Foundation, and the Kilian J. and Caroline F. Schmitt Foundation. This manuscript has been released as a pre-print.

Author contributions

K.P. conceived and supervised the project. Z.C. performed the experiments and analyses. Z.C. and K.P. created the figures and wrote the manuscript. Both authors approved the submitted version.

Competing interests

The authors declare no competing interests.

Abstract

In the early olfactory system, adult-neurogenesis, a process of neuronal replacement results in the continuous reorganization of synaptic connections and network architecture throughout the animal's life. This poses a critical challenge: How does the olfactory system maintain stable representations of odors and therefore allow for stable sensory perceptions amidst this ongoing circuit instability? Utilizing a detailed spiking network model of early olfactory circuits, we uncovered dual roles for adult-neurogenesis: one that both supports representational stability to faithfully encode odor information and also one that facilitates plasticity to allow for learning and adaptation. In the main olfactory bulb, adult-neurogenesis affects neural codes in individual mitral and tufted cells but preserves odor representations at the neuronal population level. By contrast, in the olfactory piriform cortex, both individual cell responses and overall population dynamics undergo progressive changes due to adult-neurogenesis. This leads to representational drift, a gradual alteration in sensory perception. Both processes are dynamic and depend on experience such that repeated exposure to specific odors reduces the drift due to adult-neurogenesis; thus, when the odor environment is stable over the course of adult-neurogenesis, it is neurogenesis that actually allows the representations to remain stable in piriform cortex; when those olfactory environments change, adult-neurogenesis allows the cortical representations to track environmental change. Whereas perceptual stability and plasticity due to learning are often thought of as two distinct, often contradictory processing in neuronal coding, we find that adult-neurogenesis serves as a shared mechanism for both. In this regard, the quixotic presence of adult-neurogenesis in the mammalian olfactory bulb that has been the focus of considerable debate in chemosensory neuroscience may be the mechanistic underpinning behind an array of complex computations.

Introduction

In the rodent brain, the main olfactory bulb (MOB) is one of two regions where neurogenesis persists throughout the animal's lifetime [1]. Adult-born cells in the sub-ventricular zone migrate to the MOB, where nearly 95% differentiate into inhibitory adult-born granule cells (abGCs) forming reciprocal dendro-dendritic connections [2,3] with the principal excitatory cells of the MOB, the mitral and tufted (M/T) cells. M/T cells in turn relay the chemosensory information to the downstream targets including the olfactory or piriform cortex (PCx) [4–6]. Although both the cellular composition and synaptic organization of this circuit undergo constant changes due to adult-neurogenesis [7], animals are nonetheless able to perform incredibly complex behavioral tasks related to the determination of odor identity and concentration, suggesting that they maintain stable representations of odors. This raises two critical questions: Does the encoding of odors via patterns of neural activity throughout the early olfactory system undergo changes as a result of this ongoing plasticity, and if so, how? If changes in neural activity due to adult-neurogenesis percolate throughout early olfactory circuits, what computational principles allow the system to represent the same odor stably over time?

Previous studies have primarily explored the plasticity at synapses between M/T cells and abGCs, particularly in relation to olfactory learning [8–10]. It is known that sensory experience influences the survival and synaptic turnover of abGCs with M/T cells [7,11], impacting both the normal activity of these cells [12] and animal's performance in odor discrimination tasks [13]. However, the implications of these local synaptic changes in the bulb on the downstream areas, including in the PCx, which is critical for olfactory perception and learning [14,15], remain largely unexplored.

The three-layer PCx is thought to be a region where the components of an odor are assembled into an olfactory percept or representation. Subsets of piriform cells (PCs) respond when multiple M/T cells are activated in complex temporal sequences [16–18]. A given population of M/T cells from a single glomerulus, a neuropil like structure where inputs from individual olfactory receptor neuron types converge [19,20], project randomly to a distributed array of PCs [4–6]. As odor information in PCx is coded for through the combinatorial activity of PCs [21,22] it is hypothesized that PCx is where stable representations of odors are maintained [23]. However, recent evidence is beginning to challenge this idea [24]. First, NMDA mediated long-term potentiation (LTP) in both afferent and associate fibers to PCx [25,26] is similar to that observed in the CA1 region of hippocampus. PCs thus undergo synaptic plasticity on scales observed in other regions where representations are not stable [27]. Second, recent studies examining the responses of PCs over months demonstrate that patterns of activity in both individual cells and populations of cells can drift over time [24]. This representational drift has led to the hypothesis that PCx, rather than being a primary sensory area, may be more like an association cortical region. However, the mechanisms by which this drift in PCx occurs remain unknown.

One clue that adult-neurogenesis in MOB may be the mechanism underlying these diverse processes is that neurogenesis occurs on a similar time scale to the representational drift in PCx, and the turnovers of abGCs is highly experience dependent [9] which is also reflected in the PCx drift [24]. More frequent exposure to the same odor slows down the representational drift in PCx, while the drift rate increases again once this frequent exposure was halted [24].

We therefore hypothesized that the long-term plasticity conferred by adult-neurogenesis in MOB percolates through the olfactory system serving as the mechanism of representational drift in PCx. To test this hypothesis, we adapted a spiking neuronal network model that replicated the circuit architecture within and between the MOB and PCx, integrating both the ongoing network restructuring due to adult-neurogenesis and the short-term plasticity of abGCs. We found that adult-neurogenesis differentially modulated odor responses and representations in M/T cells in the MOB and PCs in PCx. While the MOB maintained stable population representations despite changes in individual M/T cell responses due to neurogenesis, the PCx shows variation at both individual and population levels, leading to representational drift. Furthermore, when we incorporated spike-timing-dependent plasticity (STDP) at the synapses on abGCs, repeated odor exposure stabilized the PCx representations resulting in a reduction in drift rate. Taken together, we identified how the rules of plasticity on short-term time scales such as STDP and long-term time scales like adult-neurogenesis allow networks to both preserve sensory representations in some circuits like the MOB, while allowing other representations to change like those in PCx. Our work reveals the nuanced role played by adult-neurogenesis in balancing stability and adaptability in the chemosensory system.

Results

Spiking network model of adult-neurogenesis in early olfactory system

To understand the functional role of adult-neurogenesis of GCs on the odor representations in both MOB and PCx, we used a detailed spiking neural model [28] that recapitulates the circuit architecture and neural dynamics of the early olfactory system (**Fig.1A1**, Methods). To this, we added adult-neurogenesis by replacing the existing GCs with abGCs (**Fig.1A1**) [7,29]. On each day, we randomly changed 10% of the synaptic weights with between GCs and M/Ts, GCs and other GCs or short axon cells (SACs), and the top-down feedback projections from PCs to GCs (**Fig.1A2**); an implementation that effectively added new cells and replacing old ones. We simulated a total of 11 days of neurogenesis from Day-0 and Day-10, over the course of which synaptic weights between M/Ts and GCs, GCs/SACs and GCs, PCs and GCs were changed to match the observed changes in experiments (**Fig.1B1-1B3, FigS1**). These gradual changes in the network connectivity allowed us to probe the long-term effect of adult-neurogenesis on odor processing and the effect it had on modulating odor representations in MOB and PCx over time.

Odors drive coordinated activity in structures called glomeruli from which M/T cells receive their information about the odors. To match the glomerular activation patterns both in terms of the identify and onset timing in response to real odors [30–32], we generated a panel of 100 model odors where each one activated 6%~20% of the total 50 glomeruli in the model with different onset latencies (**Fig.1C1, FigS1**). Each model odor was presented during a 250ms time window (4Hz sniff), corresponding to a single sniff that is ethologically and behaviorally relevant time-scale for rodents [33–35]. Our generated panel of model odors spanned a wide range of similarity, ranging from distinct odor pairs with low pairwise correlations (see Methods) to highly similar odor pairs with high pairwise correlations (**Fig.1C2**). The input to our network, the model odors at the glomerular level, remained unchanged across simulated days consistent with previous observations of stable odor responses of glomeruli [36]. Using this experimental paradigm, we could study

how the same odor inputs were differently encoded for over the course of adult-neurogenesis by both the principal cells in the main olfactory bulb and the piriform cortex [14,37].

Modulation of individual cell responses and preservation of population representations in MOB

First, we examined how adult-neurogenesis affected the responses of both individual M/T cells in the bulb and the population. We found that individual M/T cells changed their responses to the same odor across days due to adult-neurogenesis, with some cells decreasing the firing rate responses (**Fig.2A1** top) while other cells increased the magnitude of their responses (**Fig.2A2** bottom, **Fig.S2**), similar to what has been observed by others using calcium imaging of M/T cell activity [36,38]. These changes in gain are consistent with a model of normalization, wherein the firing of an individual neurons is modulated within a regime. However, when we examined the M/T responses to the same odor across the population (**Fig.2B2**), we found that the overall pattern of population responses was preserved across days despite the ongoing neurogenesis. In this example, the odor activated 6 of the 50 glomeruli. Although individual M/T responses changed (**Fig.2A1, 2A2** arrows), the groups of M/T cells driven by the same glomerulus preserved the temporal structure of their firing as a whole. This preservation of M/T population responses was due to the invariant glomerular input to the M/T cells.

Next, we wanted to quantify the changes in M/T odor response across days due to adult-neurogenesis. We took the odor-evoked firing rate over the 250ms time window across all M/T cells as a high-dimensional population vector, and computed the correlation of the population vectors between Day-0 and each other day. Regardless of using either single-trial (**Fig.2A3**) or trial-averaged responses (**Fig.2A4**), the within-odor correlations decreased significantly over time, and the correlation value on Day-10 dropped to a level similar to experimental observations [38]. The across-odor correlations, computed from responses evoked by different odors, remained low across all days (**Fig.2A4**). Therefore, these results indicated that the gradual changes in the odor-evoked responses of individual M/T cells (**Fig.2A1**) accumulated over time.

However, as we observed above, the overall structure of M/T population responses was preserved (**Fig.2A2**), suggesting that the covariance, a measure of the shared fluctuations across M/T population might remain stable. To test this, we projected M/T population responses into a low-dimensional space (**Fig.2B1, 2B2,** see Methods), where the time varying odor-evoked responses across the population constituted a trajectory in the odor representation space of M/T cell population activity. For the two example odors, the M/T trajectories of the same odor stayed quite close on the two example days (**Fig.2B1**). If we simplified the single-trial trajectories by only plotting the maximal-distance points to the origin (**Fig.2B2**), we found that the points of the same odor (color) stayed clustered together in the space across all days (darkness of the color) despite the ongoing circuit restricting due to adult-neurogenesis. The correlation of the population vectors constructed from these trajectories remained high across all days (**Fig.2B3**), and only dropped to ~0.7-0.8 on Day-10 (**Fig.2B4**). Together, our results showed that although adult-neurogenesis gradually varied the responses of individual M/T cells, the covariance of M/T cells was stable across days despite the changes in local synaptic organization due to adult-neurogenesis.

Modulation of both individual cell responses and population representations in PCx

M/T cells in MOB send random projections to PCx, such that each individual piriform cell receives input from a random subset of M/T cells associated with different glomeruli [4,6]. PCx cells incorporate this feedforward information about odor identity and concentration from the individual M/T cells in the MOB [14] and assembles those components into an olfactory percept [21,23]. Although perceptual stability is a hallmark of sensory processing and piriform cortex has historically been thought to be a place where perceptual stability is established in the population code, recent evidence has started to challenge this idea [24]. We hypothesized that the gradual changes in the individual M/T responses, passed through the nonlinearities of synaptic integration, would affect the responses of PCs at both individual and population level. We studied this by looking at the activity of individual PCs and the ensembles of PCs in PCx.

Similar to M/T cells, the responses of individual PCs to the same odor varied across days. Some PCs increased their responses while others decreased responses (**Fig.3A1**, **Fig.S3**), consistent with recent chronic recordings in PCx (**Fig.S4**) [24]. However, unlike M/T cells, the population firing rate patterns of PCs varied as a result of adult-neurogenesis (**Fig.3A2**). Some PCs responding strongly on Day-1 became inactive on Day-9, whereas some PCs not responding on Day-1 became strongly activated on Day-9. Consequently, the combinatorial patterns of activated PCs by the same odor were reorganized by adult-neurogenesis on different days. Additionally, we also found that the temporal structure of firing rate in individual PCs was highly variable. For example, some PCs changed the onset and duration of their activation over the course of neurogenesis (**Fig.3A2**). As a consequence, the within-odor correlation computed by the high-dimensional population vectors of firing rate showed a significant drop for PCs (**Fig.3A3, 3A4**). This is consistent with recent studies examining the responses of PCs over time and demonstrating that patterns of PCs responses in both individual cells and populations of cells can *drift* over time [24].

Changes in the firing rates reflect the changes in the variance of individual cells (**Fig.S5**), but they do not say anything about the covariance, nor do they capture the nonlinear interactions that shape the representations in PC populations when synaptic information is integrated across M/T cell inputs and passes through the threshold nonlinearity in individual PCs reflective of this integration. To study this, we calculated the covariance across population of PCs was impacted by adult-neurogenesis. In contrast to the M/T population where the representational trajectories of the same odor followed one another closely in the space across different days, we found that the trajectories of PCs showed a large variability across different days (**Fig.3B1**). As a result, the maximal-distance for the trajectories on each day were broadly spread in the space across progressive days of neurogenesis (**Fig.3B2**). These results are consistent with representational drift in the odor encoding space. Quantitatively, the within-odor correlation computed using the PCs trajectories decreased substantially across days (**Fig.3B3, 3B4**). Our data suggest that as a consequence of both the random projections of M/T cells to different PCs and the ways in which the cortical cells integrate those inputs, PCx representations drift with ongoing adult neurogenesis in the bulb.

Next, we asked how adult-neurogenesis geometrically reshaped the odor manifold and representational trajectories in the high-dimensional space? Recent computational models that have been built on longstanding frameworks of population coding suggest that neural representations reside in a high-dimensional manifold [39,40]. First, we reasoned that the structure of the odor manifold would be defined as the aggregation of the odor-evoked temporal responses within a sniff cycle to all the odors based on evidence showing that different odors evoke complex and distinct temporal activities in both M/T cells [41–43] and PCs [28,44,45]. For visualization, we plotted the odor manifold in the three-dimensional PCA space (**Fig.S6**). We found the odor manifolds of M/T cells were highly overlapping with each other, whereas for PCs they were much more separated. Across individual odors, we quantified the geometrical reshaping of representational trajectories by calculating the cosine similarity (see **Methods**) which measures the similarity between two vectors. It has a value 1 if the two vectors have the same direction, and a value 0 if they are orthogonal. We found that cosine similarity using the population firing rate of M/T cells and PCs had a similar degree of decrease as the function of intervals (i.e., number of days between two representations) (**Fig.S7A1**). However, the cosine similarity using representational trajectories remained stable for M/T cell but reduced for PCs (**Fig.S7B1**).

If representations drift as a result of adult-neurogenesis, then behaviors too should be impacted, drifting in a similar time-scale. To unpack this connection, we used the K-nearest neighbor algorithm as the decoder (see **Methods**). We found that the decoding accuracy for discriminating two different odors using M/T cell population responses was high but accuracy in PCs dropped substantially capturing the representational flexibility in PCx (**Fig.S7**).

Experience-dependent plasticity enhances representational stability in PCx

So far, we have shown that adult-neurogenesis, a process that changes the circuit structure of the early olfactory system, is one mechanism by which representational drift in PCx happens. Interestingly, it has been reported that repeated experience of an odorant stabilizes odor representations and thus reduces the drift in PCx [24]. The mechanism which drives drift also appears to stabilize that drift when the olfactory environment is stable, suggesting that a core feature of the mechanism should be plasticity. Since the synapses of abGCs have been shown to be highly plastic and experience-dependent [8,9,46], we reasoned that experience-dependent plasticity of the same abGCs that drive representational in PCx may also stabilize that drift in response to the experience of encountering a stable olfactory environment.

To model experience-dependent changes at the level of synapses, we implemented a spike-timing-dependent plasticity (STDP) rule [47–49] across the diversity of the synapses related to an abGC (**Fig.4A1**). Depending on the spike timing interval of pre- and post-synaptic neurons, the synaptic weight could be either facilitated or suppressed (**Fig.4A2**, see Methods). Experience then was modeled as repeated presentations of the same set of odors every day (50 trials for each odor per day) to our network model, while adult-neurogenesis was occurring as previously described, with the network presumably learning these stable representations in the pattern of synaptic connectivity. In this example GC, the adult-neurogenesis that took place on day-4, resulted in a new cell being added to the circuit, while the existing cell was removed, a

process that randomly reset a group of synaptic weights (say, S1 and S2, **Fig.4B**) across two days of neurogenesis. Without STDP, the synaptic weights S1 and S2 would keep constant or fluctuate by some stochastic process, regardless of what was happening in the environment, including the effects of the repeated experience of an odor (black line, **Fig.4B**). The implementation of STDP meant that the synaptic weight may change on a trial-by-trial basis when an odor was repeatedly presented (blue line, **Fig.4B**). In the end, the weight S1 may be enhanced while the weight S2 may be suppressed. Although odor representations of M/T cells remained stable with and without STDP (**Fig.4C1**), we found that odor representations in PCx was stabilized with STDP (**Fig.4C2**). The correlation drops from day-0 was significantly reduced (0.8 without STDP and 0.4 with STDP by day-10, **Fig.4C2** left), and the drift rate (° per day), which quantified the daily angle changes of the population responses (see **Methods**), was reduced by 26% (7.9 without STDP and 5.8 without STDP, **Fig.4C2** right). Adding STDP to the network and using repeated presentations of an odor meant that the synapses that would otherwise randomly change due to adult-neurogenesis converged asymptotically to some weight (**Fig.S8**). Importantly, we identified that while the brain is constantly undergoing change, especially in the MOB and the PCx due to ongoing adult-neurogenesis, the impact of these changes on both population responses and the representation depends as much on the plasticity rules as it does on the ongoing statistics of the environment.

Discussion

In our study, we modeled adult-neurogenesis as a dynamic reshuffling of granule cells (GCs) within a detailed spiking neuronal network that replicated the circuit architecture of the main olfactory bulb (MOB) and piriform cortex (PCx). This modeling revealed how adult-neurogenesis differentially modulates odor responses and representations in mitral and tufted (M/T) cells and PCs.

In the MOB, individual M/T cells exhibited variable odor responses akin to gain control, altering their firing rate magnitudes over time [36,38]. Despite these fluctuations, the population-level response patterns of M/T cells remained stable. This stability is attributed to consistent glomerular input, as reflected in the covariance of M/T cell populations and their proximity in PCA space. Conversely, in the PCx, both individual and population-level response patterns of PCs were in constant flux due to the ongoing adult-neurogenesis. This resulted in a geometric reshaping of odor representations and a drift in the odor manifold defined by those representations. Our results reveal how the process of adult-neurogenesis may support a number of computations in the early olfactory circuits, including how a sensory representation may remain stable, and how it might change due to plasticity.

Second, we found that one for of the roles for STDP in the early olfactory system is reducing representational drift in the PCx. Repeated exposure to an odor significantly reduced the representational drift in the PCx, consistent with experimental observations [24]. Rather counterintuitively, this result suggests that a role of STDP and plasticity in general is stabilizing representations despite ongoing changes in the circuit. Here, representational stability arises because of the stability of the sensory world; Representational permanence, rather than being a feature of the circuit, is a feature of the sensory landscape, a stabilizing force against the inherent variability introduced by

continuous adult neurogenesis. Adult-neurogenesis, which occurs throughout the animal's life, may confer a mechanistically different computational framework as compared to vision or audition, for which critical periods delineate the bounds of plasticity, and define the periods over which sensory representations are changed or stabilized.

In addition to PCx, M/T cells also project to other cortical areas such as the anterior olfactory nucleus (AON). Although in our model we didn't differentiate mitral and tufted cells as did in many early experiment, it has been recently reported that mitral and tufted cells have distinct preferred cortical targets, with mitral cells targeting more at PCx and tufted cells targeting more at AON [50]. The authors also found that tufted cells substantially outperform mitral cells in decoding both odor identity and intensity, suggesting that tufted cells and their targeted AON are more ideal to compute odor identity than the mitral cells and PCx [50]. One possible reason for such differences might be: mitral cells are located in the deeper layers of the bulb and thus they interact primarily with abGCs, whereas tufted cells in the superficial layer preferentially interact with existing GCs that were born in the neonatal period [51,52]. Therefore, the activity of mitral cells may be more impacted by the turn-overs of abGCs, and the effect of adult-neurogenesis then percolates onto PCx. Comparatively, adult-neurogenesis has less impact on the tufted cells targeting more at the AON, potentially contributing to the better performance in encoding odors in AON.

While our study focused on the effects of adult-neurogenesis in the olfactory bulb on odor representations, it does not negate the possibility of other forms of plasticity [53] contributing to the representational drift observed in the PCx [24]. Indeed, similar representational drifts have been noted in other brain areas like the posterior parietal cortex (PPC) [54], primary motor cortex [55], and hippocampus [56,57]. Of these regions, adult-neurogenesis only occurs in the hippocampus, where adult-born granule cells integrate into the existing circuitry of dentate gyrus [58]. Interestingly, similar to what we our model demonstrated for the early olfactory system (i.e., new-born cells in MOB and drift in PCx), the cells downstream of the dentate in the CA3 region [59] and CA1 region [27,56,57] have been found to drift over days and weeks.

Both PCx and hippocampus are evolutionarily old archi-cortical structures. This conservation of adult-neurogenesis in these brain regions may suggest a broader evolutionary strategy. This feature underscores the structural flexibility of these regions, which likely conferred selective advantages in navigating dynamic environments. The PCx specializes in processing olfactory information, enabling organisms to detect and discriminate between volatile chemical stimuli, while the hippocampus is crucial for spatial navigation and memory formation. By maintaining flexible neural structures, such as through adult-neurogenesis, these regions can rapidly update the representations of odors and spatial information, respectively, in response to changing environmental cues. This flexibility may enable the early organisms to effectively represent and adapt to the dynamic worlds they inhabited, enhancing their chances of survival and reproduction across evolutionary time scales [60–62]. However, as organisms evolved, brain regions such as the PPC, lacking significant adult-neurogenesis, might rely on alternative mechanisms to balance plasticity and stability [53].

In conclusion, our study not only elucidates a potential mechanism for representational drift in the PCx but also highlights the nuanced role of adult neurogenesis in maintaining the balance between stability and flexibility in olfactory system. The

incorporation of STDP in abGCs, as evidenced by our model, emerges as a critical factor in modulating this balance, offering a new perspective on how the brain adapts to an ever-changing sensory environment.

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Figures and Tables

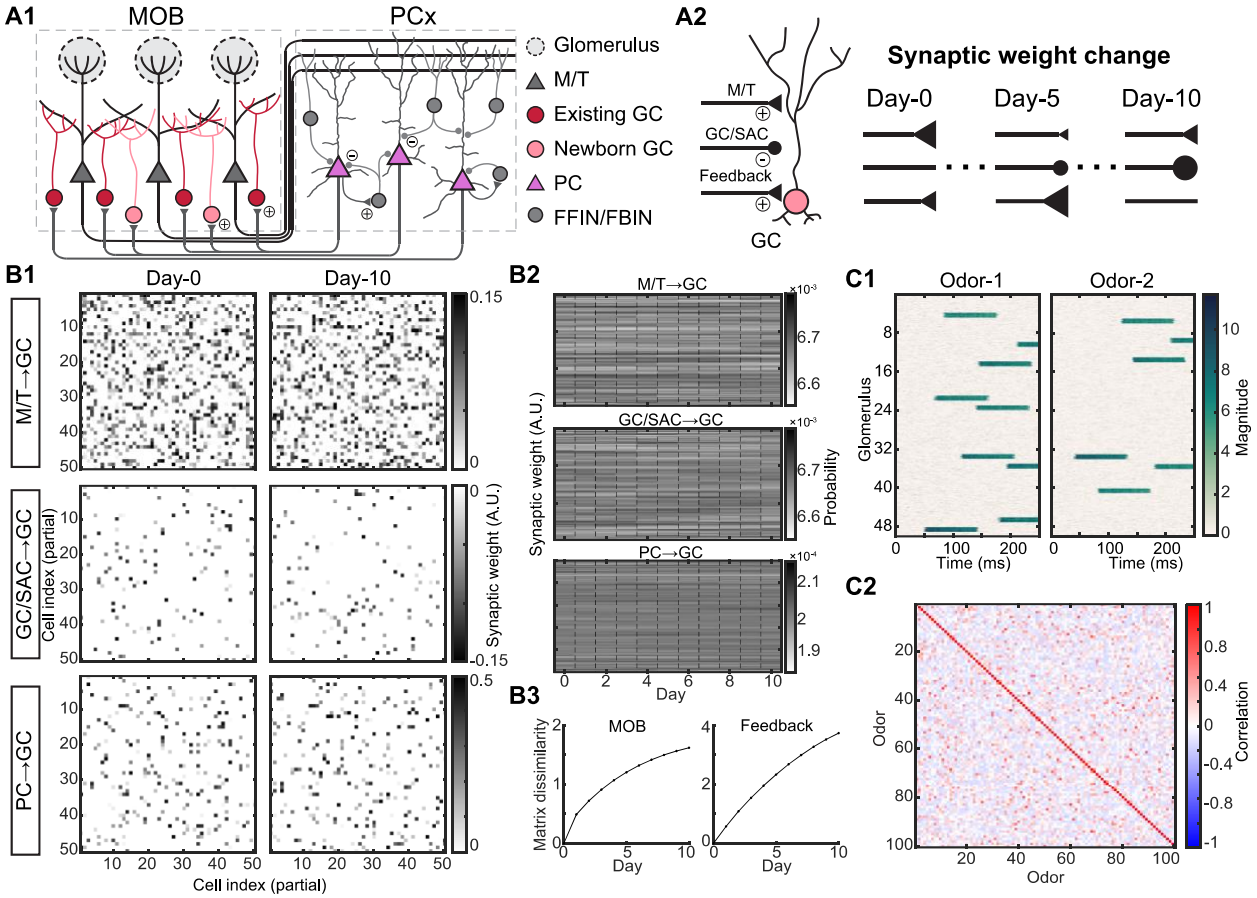

Figure 1. Spiking network model of adult-neurogenesis. (A1). Schematic of early olfactory circuit. M/T: mitral/tufted cells, GC: granule cells, abGCs: adult-born GCs, PCs: piriform cortical cell, FFIN: feedforward inhibitory neuron, FBIN: feedback inhibitory neuron. Example plus signs indicate excitatory synapses and minus signs indicate inhibitory synapses. (A2). Schematic of synaptic reshuffling of GCs due to adult-neurogenesis. On each day, 10% of GCs have their weights reshuffled, including the synaptic weights from M/T cells, other GCs or short-axon cells (SAC), and PCs to GC (feedback). (B1). Partial weight matrix on two example days between GCs and M/T cells (top), other GCs or SACs (middle), and feedback from PCs (bottom). (B2). Histograms of all synaptic weights across days. (B3). Weight matrix dissimilarity between Day-0 and each other day. (C1). An example model odor generated by stimulating different combinations of glomerular identity and timing of activation. (C2). Pair-wise correlations between model odors show the relative similarities and differences across all model odors.

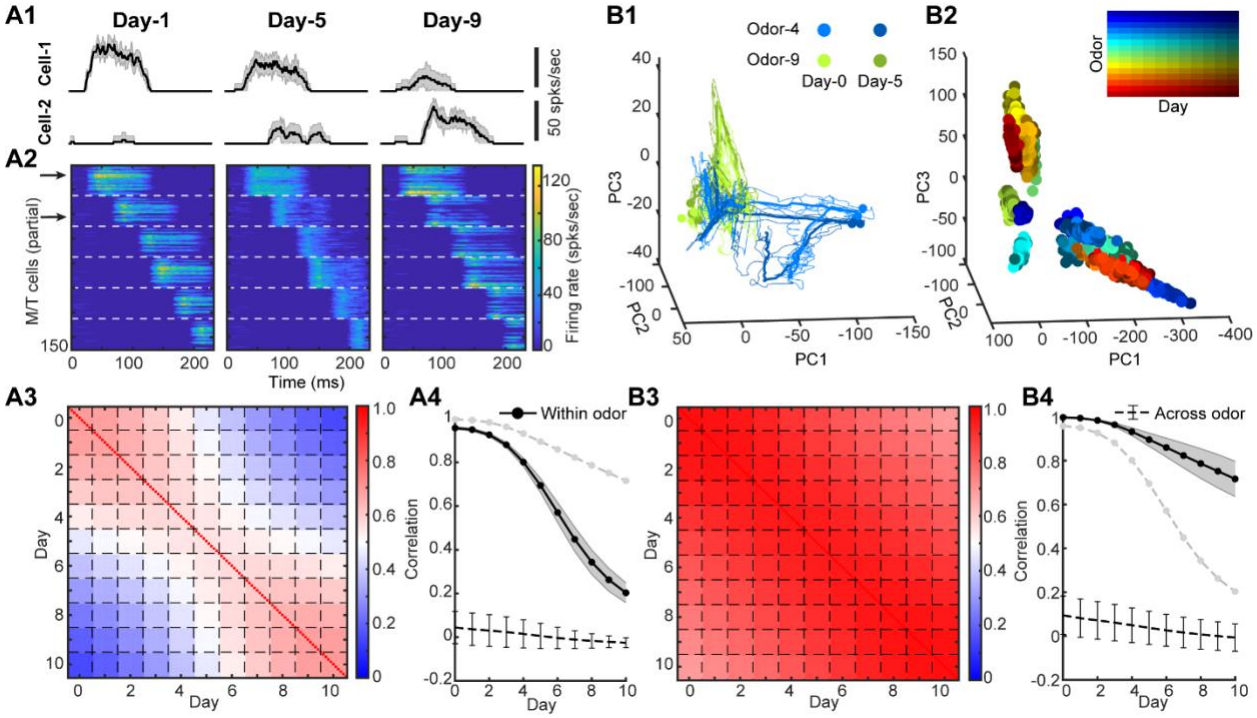

Figure 2. Adult-neurogenesis modulates individual M/T cell responses but preserves population representation. (A1). Trail-averaged firing rate of two example M/T cells responding to the same odor (within-odor) on three different days (mean ± SD, n = 10 trials). (A2). Firing rate patterns of odor-activated M/T cells to the same odor on three days. M/T cells driven by different glomeruli are separated by white dashed line. The two arrows correspond to the two example cells in (A1). (A3). Pairwise within-odor correlation of the single-trial population firing rate of all M/T cells between each day averaged across all odors (n = 100). Each small box separated by the dashed lines is a 10x10 matrix (n = 10 trials) corresponding to autocorrelation (same day on diagonal) and cross-correlation (different days off diagonal). (A4). Pairwise within-odor correlation of trial-averaged population firing rate of all M/T cells (black solid line) between Day-0 and each other day (mean ± SD, n = 100 odors). Black dashed line with error bar: pairwise correlation of M/T cell responses to different odors (across-odor), mean ± SD, n = 10 pairs. Grey dashed line with no error: same as the black solid line in (B4). (B1). Low-dimensional trajectories of M/T responses to two example odors (color) on two different days (darkness of color). Thin curves: single-trial trajectories, thick curves: trial-averaged trajectories, points: maximal-distance points on trajectory to the origin. (B2). Only maximal-distance points are shown for different odors on different days. (B3). Similar to (A3) but computed using the low-dimensional M/T trajectories (single-trial). (B4). Similar to (A4) but computed using the low-dimensional M/T trajectories (trial-averaged). Grey dashed line with no error: same as the black solid line in (A4).

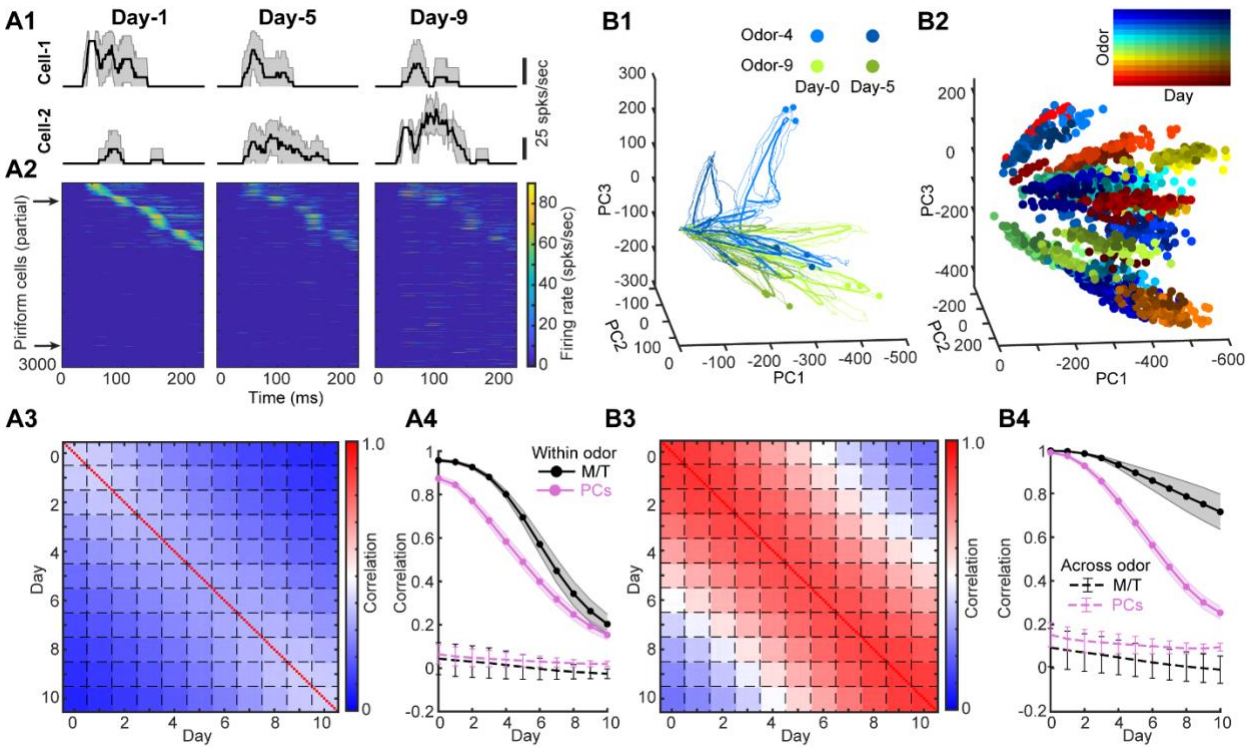

Figure 3. Adult-neurogenesis modulates both individual PCs responses and population representations. (A1). Trail-averaged firing rate of two example PCs responding to the same odor on three different days (mean ± SD, n = 10 trials). (A2). Firing rate patterns of partial PCs responding to the same odor on three days. The two arrows correspond to the two example cells in (A1). (A3). Pairwise within-odor correlation of the single-trial population firing rate of all PCs between each day averaged across all odors (n = 100). Each small box separated by the dashed lines is a 10x10 matrix (n = 10 trials) corresponding to autocorrelation (same day on diagonal) and cross-correlation (different days off diagonal). (A4). Pairwise within-odor correlation of trial-averaged population firing rate of all PCs (purple solid line) between Day-0 and each other day (mean ± SD, n = 100 odors). Purple dashed line with error bar: pairwise across-odor correlations of PCs, mean ± SD, n = 100 pairs. Black lines: M/T cells, same lines as in Fig.2. (B1). Low-dimensional trajectories of PCs responses to two example odors (color) on two different days (darkness of color). Thin curves: single-trial trajectories, thick curves: trial-averaged trajectories, points: maximal-distance points on trajectory to the origin. (B2). Only maximal-distance points are shown for different odors on different days. (B3). Similar to (A3) but computed using the single-trial PCA trajectories of PCs. (B4). Similar to (A4) but computed using the trial-averaged PCA trajectories of PCs.

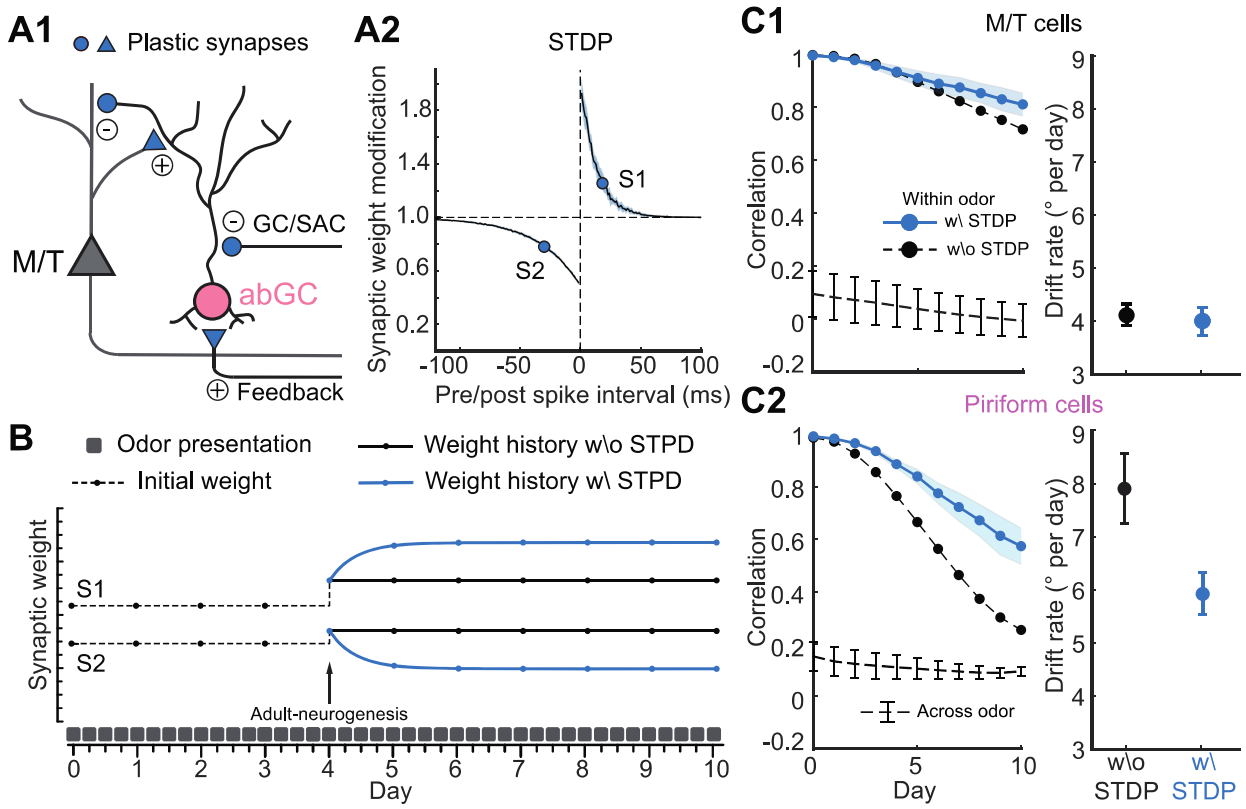

Figure 4. Experience-dependent plasticity enhances representational stability in PCx. (A1). Different types of plastic synapses (blue) related to an abGC. Circle: inhibitory; triangle: excitatory. (A2). Dependence of synaptic modification on pre/post inter-spike interval used for the spike-timing-dependent plasticity (STDP). S1 and S2 are two example synapses with different modification – S1: facilitated; S2: suppressed. (B). Weight history of the two example synapses in A2 when an odor is repeatedly presented. Adult-neurogenesis happens on day-4 which randomly resets the weights. The synaptic weights stay constant without plasticity (black) while change trial by trial with plasticity (blue). (C1). Left: pairwise within-odor correlation of trial-averaged low-dimensional M/T trajectories between Day-0 and each other day. Blue solid line: with STDP (mean ± SD, n = 10 odors); black dashed line with circles: without STDP. Black dashed line with error bar: pairwise correlation of M/T cell responses to different odors (across-odor), mean ± SD, n = 10 pairs. Right: drift rate for M/T trajectories with and without STDP. (C2). Same as C1 but for PCs trajectories.

Methods

Architecture of spiking network model and single-neuron model

We adapted the spiking network model of the main olfactory bulb (MOB) and piriform cortex (PCx) from the published work [28]. For details of the model, see the Methods in paper [28].

Model odor definition

Model odors are defined by the combinatorial patterns of glomeruli which are activated successively with different glomerular timing, a pattern recapitulating the spatiotemporal structure of odor inputs (Rubin and Katz, 1999; Meister and Bonhoeffer, 2001). Specifically, when a model odor is presented, 3~10 glomeruli will be activated ($6-20\%$ of all glomeruli) and all the M/T cells associated with those glomeruli will receive correlated glomerular input I^{osn} which lasts for 90ms. A table of 100 model odors were defined as the odor inputs to our network.

Modeling adult-neurogenesis as weight reshuffling

Adult-neurogenesis of the granule cells constantly removes old granule cells and replace them with adult-born ones. As a consequence, all the synapses from and onto old granule cells are removed and new synapses with adult-born ones are built. We modeled this process by weight reshuffling in the network with the total number of granule cells fixed. On each simulation day, 10% of the granule cells had their synaptic weights reshuffled. For each granule cell, the values of synaptic weights changed randomly on each day. The distributions from which new synaptic weights were sampled from were the same distributions as building the network (see Table 3.2). We only reshuffled the individual weight values without changing the whole weight distributions.

Principal component analysis (PCA)

Spiking activity of each mitral/tufted cell and each piriform cell was binned into a $5ms$ sliding time window and averaged across trials (each model odor was presented in 10 trials). To perform the PCA analysis, we concatenated the trial-averaged responses of all mitral/tufted cells to all 100 model odors on all simulation days, resulting in a large matrix of 1250 cells by 247 time bins $\times$ 100 odors $\times$ 11 days. Response covariance matrices (1250 by 1250) were computed for this concatenated matrix (after subtracting the mean responses averaged across time bins, odors, and days). This gave us a single set of eigenvectors, thus the same eigenspace into which cell responses for all days can be projected and compared. Each 1250-dimensional cell response vector was then projected onto the first 3 principal eigenvectors for visualization and the first 50 principal eigenvectors for computations. The same procedure was also done for piriform cells.

Population vectors of firing rates and PCA trajectories

We constructed the population vectors using either the firing rates of all cells or the PCA trajectories of the first 50 dimensions. When using the firing rates, for each odor on each day, the single-trial responses all the cells was a matrix of 1250 cells by 247 time bins for M/T cells or $10{,}000$ cells by 247 time bins for piriform cells. We then converted the matrix into a long vector of lengths 1250×247 for M/T cells and $10{,}000 \times 247$ for piriform cells.

When using PCA trajectories, the same procedures were applied, with only the cell number replaced by the reduced dimensionality.

Pairwise correlation between population vectors

To measure the similarity of population responses over time, we computed the Pearson's pairwise correlations of the population vectors constructed either by firing rates or PCA trajectories on two comparison days (for example, day-i and day-j). For within-odor correlation, the two population vectors were the responses (either single-trial or trial-averaged) to the same odor on day-i and day-j. For across-odor correlation, the two population vectors were the responses to any given two different odors on day-i and day-j, and we computed that for all different odor pairs on those two days. When $i = j$, the within-odor correlation was computed by comparing responses of even and odd trials.

Cosine similarity between population vectors

To gain a geometric perspective of the drift over days, we computed the cosine similarity of the population vectors by $\theta_{i,j} = \boldsymbol{u}_i \cdot \boldsymbol{u}_j / \|\boldsymbol{u}_i\| \times \|\boldsymbol{u}_j\|$, where $\theta_{i,j}$ is the cosine similarity between day-i and day-j, and $\boldsymbol{u}_i$ ($\boldsymbol{u}_j$) is the trial-averaged population vector on day-i (day-j). We also estimated the within-day variability for each odor on each day by computing the cosine similarity between the even trial-averaged and odd trial-averaged responses. For within-day cosine similarity when $i = j$, we subtracted the estimated within-day variability from the computed cosine similarity.

Decoding analysis: K nearest neighbor algorithm

The K nearest neighbor approach was used to decode odor identity from the projected ensemble responses of PCs to any given odor pair [63]. Consistent with the computation of symmetrized Kullback–Leibler divergence D_{KL}, analysis was performed in the space of the first 50 principal components. The original data was broken up into testing and training sets. The training sets established the location of PC responses to known odors (i.e., known PC responses) in the principal component space and the testing sets were probed with respect to these known PC responses. The Euclidian distance of the unknown odors to all PC responses was then calculated and the K nearest neighbors were used to determine to which odor the unknown PC activity was responding to. This process of generating testing and training sets was repeated 30 times, with each repeat reflecting a different random population of testing and training to ensure that the decoding accuracy was not a result of artifacts of selecting a single testing/training population. Free parameters in the K nearest neighbor algorithm include the ratio of testing to training data, and the number of nearest neighbors used in the calculation. For training/testing, we used ratios of 50%, 70% and 90%. We also examined the algorithm's accuracy when 3, 5 and 7 nearest neighbors were used.

Spike-timing-dependent plasticity (STDP)

To model the effect of spike trains on synaptic weights, we used the suppression model given in [47]. Each pre- and post-synaptic spike was assigned with an efficacy $\epsilon_i = 1 - e^{-(t_i - t_{i-1})/\tau_s}$, where ϵ_i is the efficacy of the ith spike, t_i and t_{i-1} are the timing of the ith and $(i-1)$th spike respectively, and τ_s is the suppression time constant. The effect of each pair of pre- and post-synaptic spikes on synaptic modification was given by $\Delta w_{ij} =$

$\epsilon_i^{pre}\epsilon_j^{pos}F(\Delta t_{ij})$, where ϵ_i^{pre} and ϵ_j^{pos} are the efficacies of the ith presynaptic spike and jth postsynaptic spike, respectively, and Δt_{ij} is the interval between the two spikes $t_j^{pos} - t_i^{pre}$. The function F represents the effect of temporal window for STDP, defined as:

$$F(\Delta t)\begin{cases} A_+ e^{-|\Delta t|/\tau_+} & if \quad \Delta t > 0 \\ A_- e^{-|\Delta t|/\tau_-} & if \quad \Delta t < 0 \end{cases} \tag{5}$$

Where A is the scaling factor, τ is the time constant, $+$ means long-term potentiation (LTP) and $-$ means long-term depression (LTD). We chose $\tau_s^{pre} = 34ms$, $\tau_s^{pos} = 75ms$. $A_{+/-}$ and $\tau_{+/-}$ are drawn from normal distributions for each synapse, where $A_+ \sim \mathcal{N}(1.03,0.1)$, $A_- \sim \mathcal{N}(-0.51,0.01)$, $\tau_+ \sim \mathcal{N}(13.3, 1.7)$ (in ms), $\tau_- \sim \mathcal{N}(34.5, 1.6)$ (in ms), and $\mathcal{N}(\mu, \sigma)$ represents normal distribution with mean μ and standard deviation σ.

Supplemental information

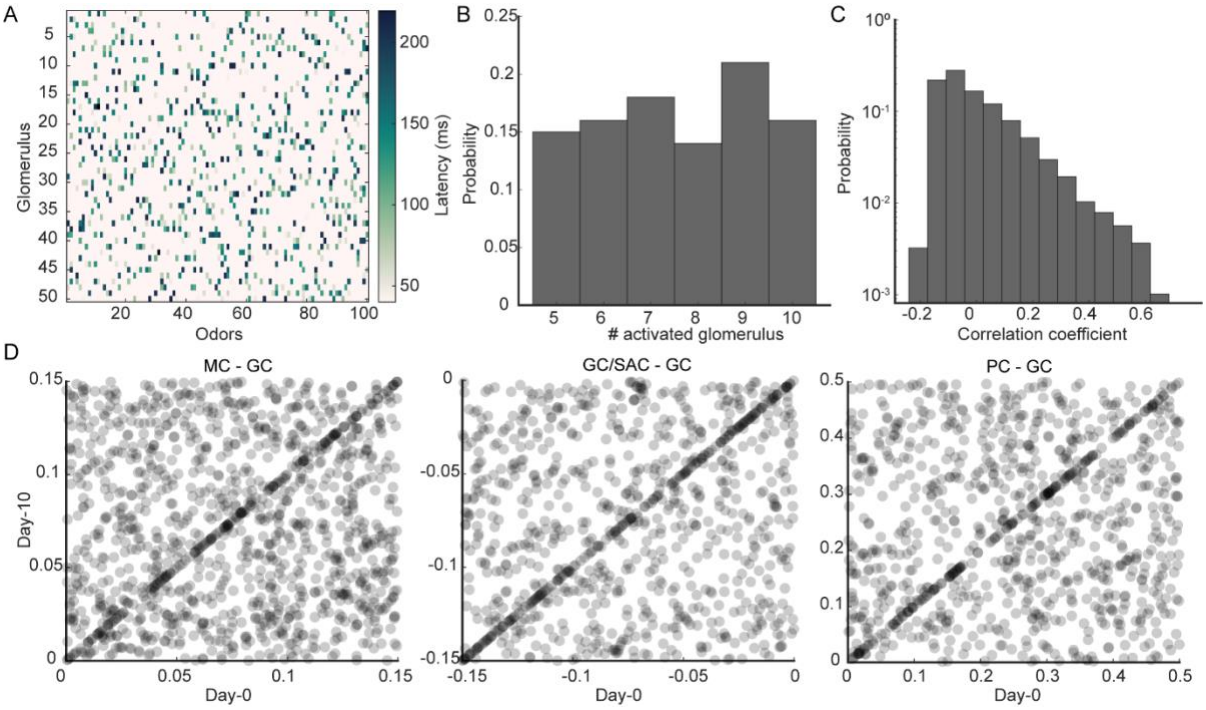

Fig.S1 Odor definition and synaptic weight changes

(A). Glomerular activation latency for all 100 odors we defined. Each column corresponds to one odor. (B). Histogram of the number of activated glomeruli by all odors ($n = 100$ odors). (C). Histogram of correlation coefficients between each pair of odors, measuring the similarity between odors. (D). Sparsely sampled synaptic weights on day-0 (x axis) and day-10 (y axis). Each dot is a synapse. Left: M/T to GCs; middle: GC/SAC to GCs; right: PCs to GCs.

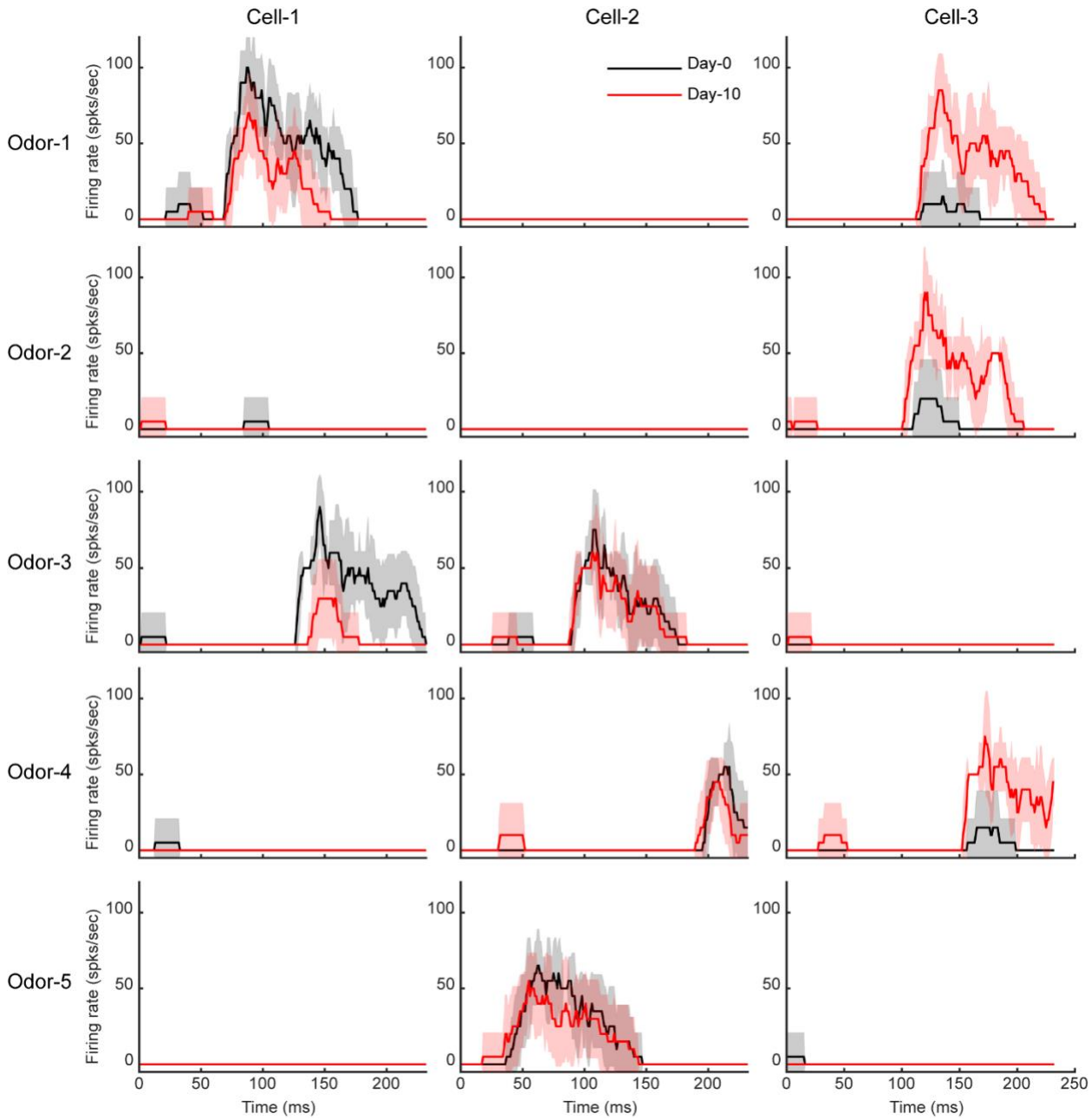

Fig.S2 Example M/T cell responses on day-0 and day-10

Three example M/T cells (column) in response to the five example odors (row). Black: response on day-0; red: response on day-10. Some cells increase their responses while some cells decrease their responses from day-0 to day-10 (mean $\pm$ SD, $n = 10$ trials).

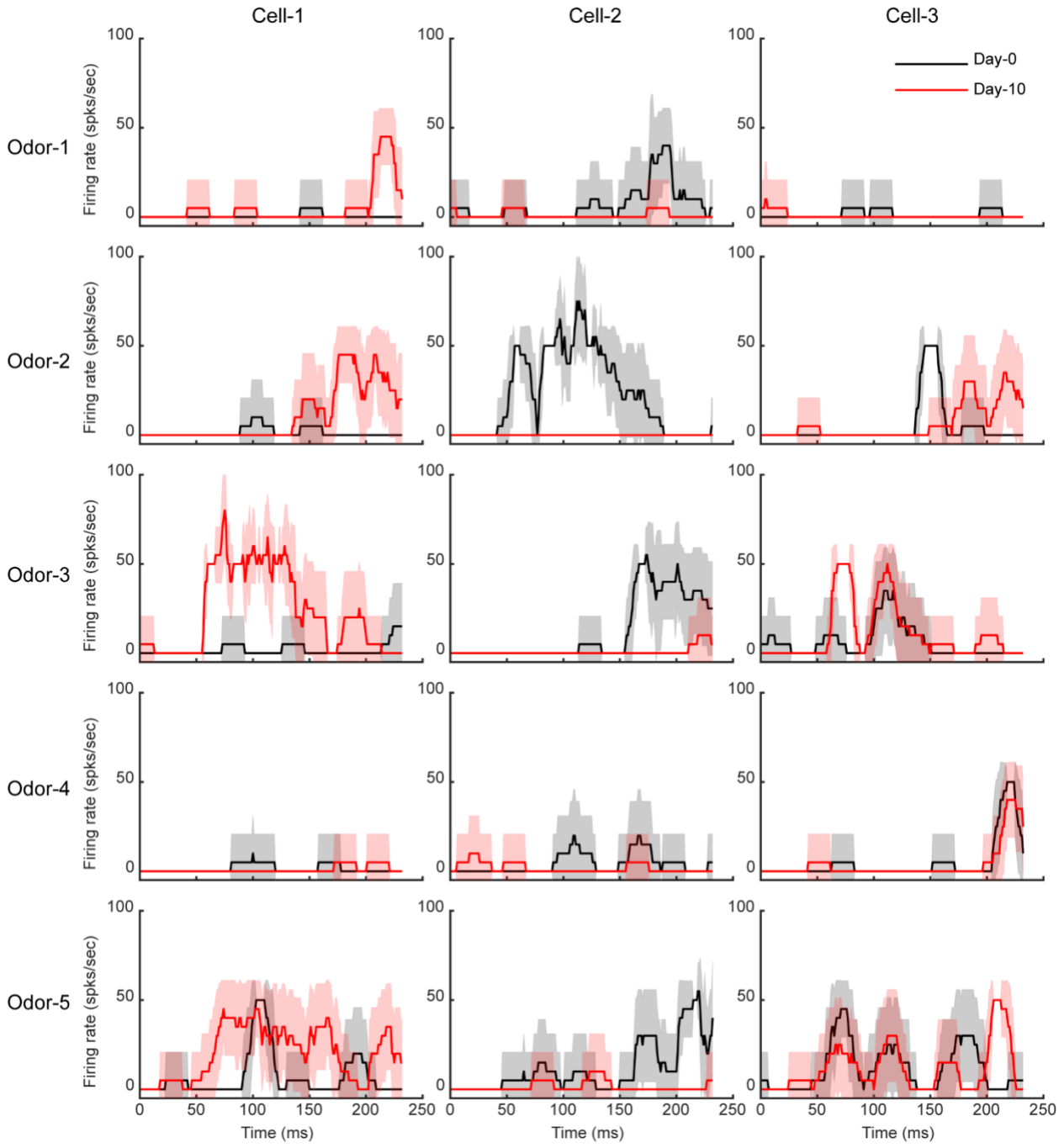

Fig.S3 Example Piriform cell responses on day-0 and day-10

Three example piriform cells (column) in response to the five example odors (row). Black: response on day-0; red: response on day-10 (mean $\pm$ SD, $n = 10$ trials).

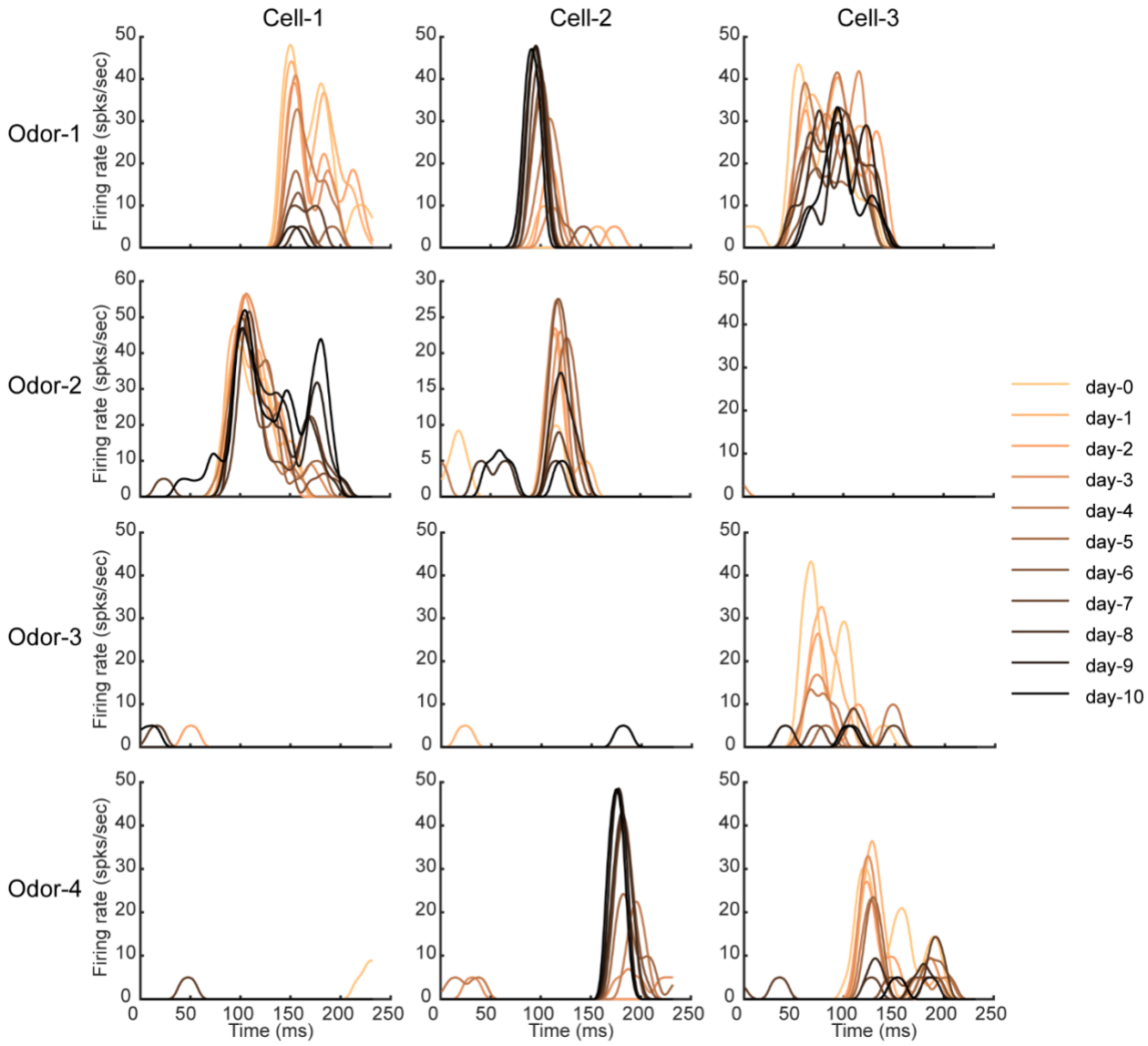

Fig.S4 Example piriform cell responses (trial-averaged) on all 10 days

(A). Another three example piriform cells in response to four odors from day-0 and day=10. Each curve is the response averaged across 10 trials (smoothed by a gaussian kernel with 20ms width). Note some piriform cells increase or decrease their responses, while some cells change their temporal profile (cell-3).

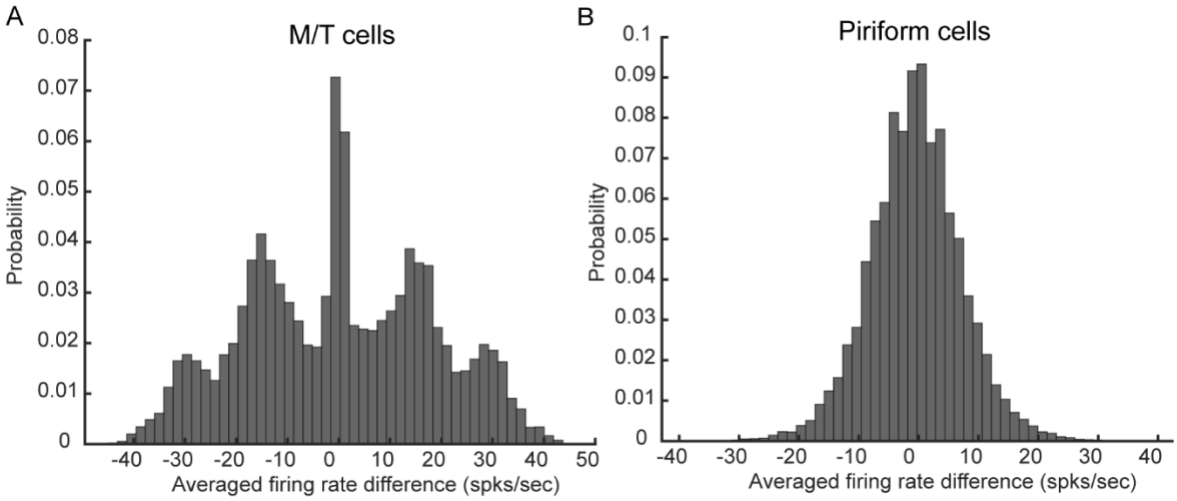

Fig.S5 Cell response changes between day-0 and day-10

(A). Histogram showing the differences between the trial-averaged response on day-10 and the trial-averaged response on day-0 for each odor-activated M/T cell (n=100 odors). Positive values indicate that the responses on day-10 are larger than day-0. (B). Same as (A) but for piriform cells.

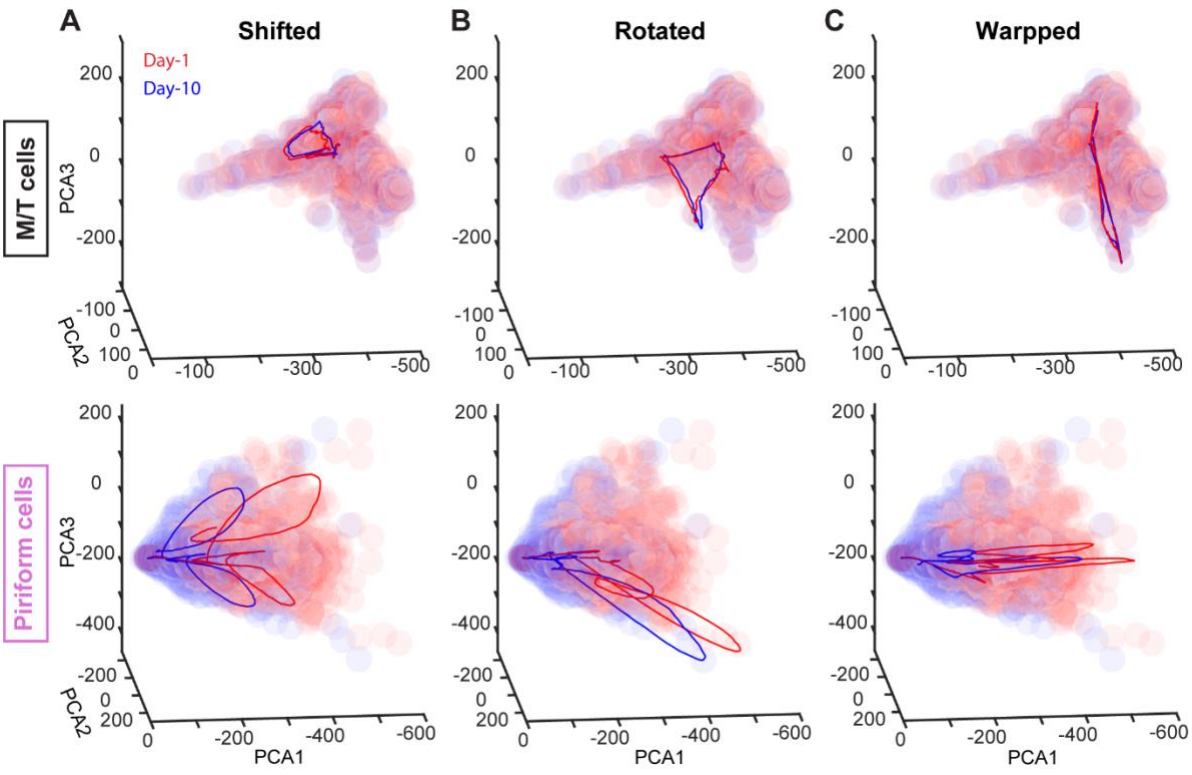

Fig.S6 Odor manifold and geometric reshaping of odor representations in PCx.

Odor manifolds of M/T cells (top) and PCs (bottom) on two example days (red and blue) are plotted by clusters of transparent round dots in the PCA space. Each column contains the trial-averaged trajectories on two days (red and blue) evoked by three example odors. M/T trajectories stay close while PCs trajectories are reshaped in different ways: shifted (A), rotated (B), and warped (C).

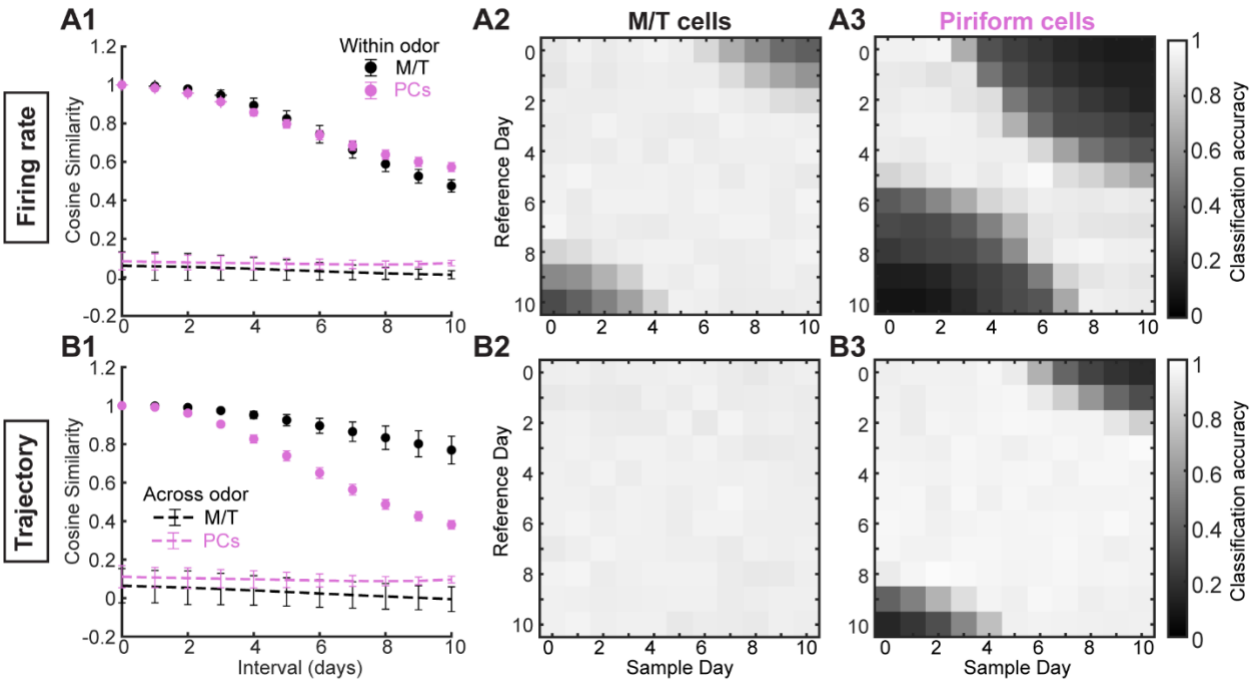

Fig.S7 Quantifying geometric reshaping and decoding analysis on M/T and PCs

(A1). Cosine similarity to quantify the geometric reshaping using population firing rate as a function of intervals (number of days separated). (A2). Decoding accuracy by K-nearest neighbors algorithm trained on M/T population firing rate of each sample day and tested on M/T population firing rate of each reference day. (A3). Same as (A2) but using PCs population firing rate. (B). Same as (A) but using PCA trajectories.

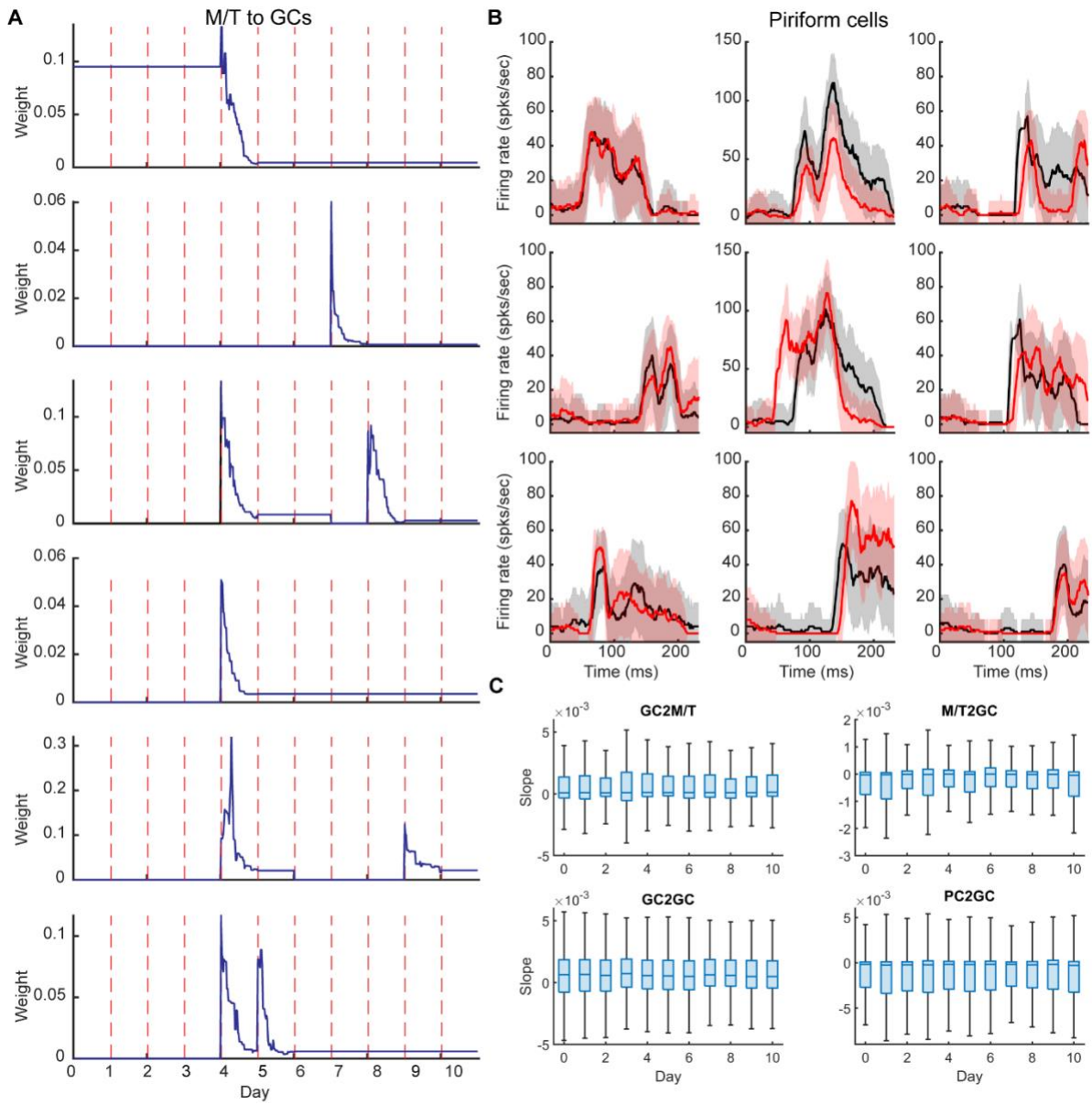

Fig.S8 Synaptic weight history of STDP

(A). Traces of five example synapses from M/T cells to GCs. STDP was applied when adult-neurogenesis happened at the start of the day. STDP drove the synaptic weight (y axis) to certain values through trial-by-trial exposure to certain odors. For some synapses, adult-neurogenesis only happened on one day while for other it happened on multiple days. (B). With STDP applied, three example piriform cells (column) in response to the three example odors (row). Black: response on day-0; red: response on day-10 (mean ± SD, n = 10 trials). (C). Slope of the synaptic weight traces over the last five trials of odor exposure with STPD applied. The slopes were all close to zero indicating the convergence of synaptic weights.