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Making Memories. On the fly.

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Abstract: Stimulus directed behavior is regulated by communication between neurons within neural circuits throughout an animal's brain. Experience can change the dynamics of neural circuits by modifying specific synaptic connections. However, pinpointing the sites of behavioral-relevant plasticity has proven challenging. Technical advances in controlling and monitoring neural activity in behaving animals have allowed for marked progress in understanding the logic underlying learning and memory in the model system *Drosophila melanogaster*. The fruit fly has a numerically simple brain and probing identified network components has become feasible. Here, we discuss cellular and circuit mechanisms underlying associative learning. We also provide insights into the computational operations encoding associative memories in the fly. Beyond their roles in learning and memory retrieval, these circuit components are recruited for the reevaluation of memories during memory extinction and reconsolidation.

Keywords: Learning and Memory; Dopamine; Mushroom Body; Mushroom Body Output Neurons; Extinction and Reconsolidation

Sensory stimuli are transformed into and represented as activity patterns within neurons in defined neural circuits. Brain regions that are downstream of sensory inputs depict associations and steer subsequent motor programs. Such sites for instance include the hippocampus and the amygdala in mammals (Tovote et al., 2015) or the mushroom bodies in insects (Menzel, 2014; Stevens, 2015). Associative memories can form when valence is attributed to previously meaningless cues. Progress in understanding the underlying principles of such operations has been made over the last years, however this progress has been attenuated partially due to the numerical complexity of and certain accessibility limitations to the vertebrate nervous systems. Localizing the precise cellular and synaptic sites encoding associative memory traces has remained a major challenge in the field.

Neurons connect via synapses to form neural circuits. Memories are widely believed to be written by strengthening or weakening synaptic connections persistently and thus changing the information flow or the make-up of neural ensembles. That said, direct evidence for such a model remains scarse in the behaving animal. Such a configuration however relies on the fact that neurotransmission can be precisely tuned at synapses, and this requires concerted activities of second messenger pathways and intricate protein machineries. Indeed, mutations in genes that encode components involved in such operations can lead to aberrant neural activities (Südhof, 2012). It is thus plausible that the genetic make-up of an animal and the gene expression profiles of individual neurons will influence the transformation of signals from sensory representation to motor output and ultimately account for behavioral traits. To understand how changes in synaptic strength and circuit activity tie to behavioral outcome will thus require manipulating and measuring activity of selected identified neurons *in vivo*.

The foundation for recognizing the close relationship between genetic information and behavioral traits was laid in the early 1970s by the laboratory of Seymour Benzer. The approach taken was simple, yet brilliant. Genetically tractable fruit flies, *Drosophila melanogaster*, were mutagenized and subsequently screened for behavioral alterations. Taking this approach, many genetic programs that are highly conserved at an evolutionary level were discovered – one uncovered locus for instance encodes the circadian clock component Period (Konopka and Benzer, 1971).

Importantly, the behavioral programs investigated also included associative learning and memory paradigms (Quinn and Dudai, 1976). In recent years, genetic advantages and the resulting tools have been coupled to behavioral paradigms and physiological approaches and the field has made considerable progress in not only understanding the network principles of memory reading and writing at the cellular level in the fly, but also has tackled more complex computations involving memory extinction and reconsolidation.

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Excursion 1: Drosophila *can be reared en masse and genetic modifications of certain chromosomes allow for mutations to remain stable over generations. Also,* Drosophila *harbors only three chromosomes (plus a very small fourth), keeping genetic complexity to an overseeable level.*

The advent of transgenesis (Rubin and Spradling, 1982) and binary expression systems, has allowed for major breakthroughs in understanding cellular and network components underlying specific behaviors in the fruit fly. One can create transgenes with relative ease and thus encode effector proteins that allow for the blockade of neurotransmission or activation of cells in a light- (optogenetics) or temperature- (thermogenetics) dependent manner. These tools are of tremendous value when probing the active involvement of a neuron or a set of neurons in a behavioral program. Transgenesis also allows for the use of binary expression systems (Brand and Perrimon, 1993) in which transcription factors and their responsive DNA-elements are borrowed from other organisms and cloned downstream of Drosophila *enhancer sequences. Such expression systems allow precise temporal and spatial control of gene expression. Using several refinements of this system enables the activation of specific transgenes, such as those encoding for optogenetic tools, in sparse, identified, neuronal populations [for review (Owald et al., 2015b)]. Such an approach was for instance used to initiate flight in headless flies by optogenetically activating motor neurons with light (Lima and Miesenböck, 2005). These genetic principles not only allow for direct manipulation of neurons, but importantly also can be used to monitor activity patterns in defined neurons. The combined use of effectors and activity reporters, which include genetically-encoded calcium indicators, has proven invaluable for neural circuit mapping.*

From stimulus to meaning

The world is full of sensory stimuli. In order to ensure survival and reproduction, animals must learn which cues will guide them to food sources and mating partners and which will predict potential threats. Fruit flies can learn to associate sensory stimuli, such as those of olfactory or visual nature, with a food source (reward) or an unpleasant stimulus (punishment). Decades of research have cemented a third order neuropil, the mushroom body, as the major center for associative learning in the insect brain (Heisenberg, 2003; Menzel, 2014). The fly mushroom body network consists of no more than 3000 neurons per brain hemisphere. Due to this relative numerical simplicity and the advanced genetic tool-box available, a comprehensive understanding of how memories are written at the level of the mushroom body network has surfaced in recent years.

The mushroom body principal cells, the Kenyon cells (KCs, approximately 2000 cells per hemisphere), hold a representation of the surrounding sensory world, particularly of olfactory cues. While airborne odors are perceived at the level of sensory receptor neurons, information is further computed at the next relay station (the antennal lobe), and then conveyed to KCs. A given olfactory cue specifically activates a sparse pattern of KCs; it is this pattern that codes odor identity within the mushroom body network (Stevens, 2015).

The cholinergic (Barnstedt et al., 2016) KCs extend parallel axon bundles that make up the mushroom body lobes. Within the lobes, they form excitatory *en passant* synapses with a small number of downstream partners, the mushroom body output neurons (MBONs; see Figure 1a). The dendritic fields of individual MBONs stereotypically tile the lobes of the mushroom body and mark distinct non-overlapping compartments (Tanaka et al., 2008; Aso et al., 2014b). Based on this anatomy, the thirty-five MBONs per hemisphere can be classified into twenty-one categories (types).

Interestingly, olfactory information gets categorized according to valence at this stage. The activity of specific types of MBONs is sufficient to promote odor driven approach while other types support odor driven avoidance behavior [Figure 1b; (Aso et al., 2014a; Owald et al., 2015a; Perisse et al., 2016)]. Indeed, when naïve flies are given the choice between a clean air stream and a repulsive odor, they predominantly choose to avoid the odor. Acutely blocking synaptic output from avoidance promoting MBONs flips this aversive behavior: flies now approach the repulsive odor. On the contrary, silencing approach-promoting MBONs during a choice situation increases avoidance behavior (Owald et al., 2015a; Perisse et al., 2016). This notion is further supported by optogenetic experiments (Aso et al., 2014a; Owald et al., 2015a): naïve flies expressing light-activatable cation channels (for example CsChrimson) were given the choice between an illuminated and a dark site. If CsChRimson was expressed in avoidance-promoting MBONs, flies would avoid, if the light-activatable channel was expressed in approach-promoting MBONs, flies would approach the light source. These experiments are in line with a model in which the identity of an odor is translated into a meaning at the synapse between KCs and MBONs (Heisenberg, 2003) and we will argue that this behavioral switch from avoidance to attraction behaviorally mimics observed cellular memory traces.

Assigning a value

As in mammals, associative learning in the fly depends on dopaminergic signaling. Interestingly, the compartmentalization of the mushroom body by MBON dendrites is perfectly matched by the presynaptic innervation pattern of

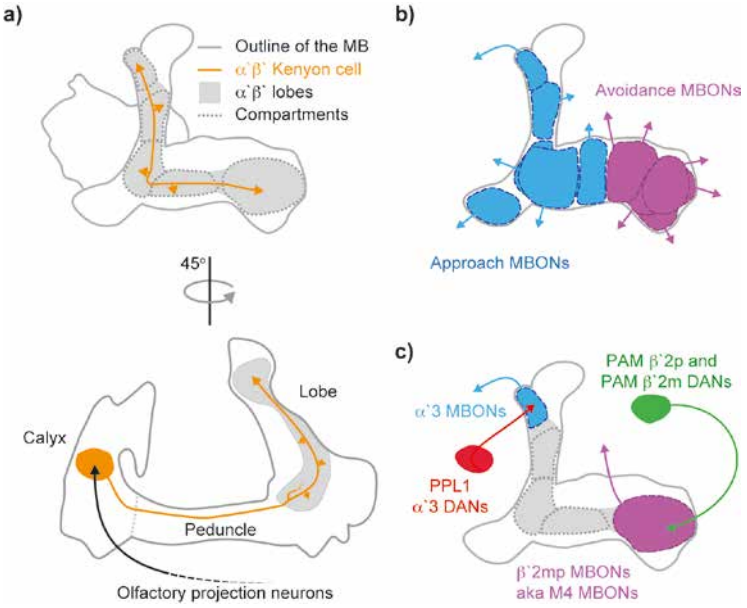

Fig. 1: The major components of the mushroom body. **a)** Kenyon cells (KCs) shape the MBs (grey solid line). There are three major classes of KCs, the αβ, the α′β′ (in purple one example Kenyon cell) and the γ KCs which all receive input from projection neurons at their input region, the mushroom body calyx (black). The KC neurites project along the peduncle into the lobes (grey). Within the lobes KCs make *en passant* excitatory synapses (arrow heads) with downstream neurons, the mushroom body output neurons (MBONs). **b)** Distinct types of MBONs promote avoidance and approach behavior (purple and blue respectively). **c)** The dendritic innervation pattern of each class of MBONs (two examples, blue and purple) is matched by the innervation of a corresponding group of dopaminergic neurons (DANs, red and green). Together they define distinct compartments (dashed lines). The role of some MBONs has been investigated. For instance, the α′3 MBON has recently be shown to be involved in encoding novelty and familiarity (Hattori et al., 2017). However, the role of several remaining MBONs remains to be elucidated.

two major clusters of dopaminergic neurons: a relatively small set of neurons (PPL1 cluster) provides the teaching signal for punishment and dopaminergic neurons of the larger PAM cluster convey rewarding information (Figure 1c). Notably, learning about different punishments, such as electric shock, extreme heat or bitter substances, all depend on the same small set of punishment-coding dopaminergic neurons [for review (Waddell, 2013)]. In contrast, forming associations linked to different rewarding events requires the activity of distinct sets of PAM dopaminergic neurons: the reward-related teaching signal provided by water recruits dopaminergic neurons that are different from those involved in learning about food rewards such as sugars (Burke et al., 2012; Liu et al., 2012; Lin et al., 2014). Reward provided by sugars can be even further distinguished on a neuronal level. Dopaminergic neurons signaling 'sweet' differ from those providing information on the nutritional content (Huetteroth et al., 2015; Yamagata et al., 2015). Because these distinct sets of reinforcing neurons innervate separate non-overlapping compartments, their activity affects distinct synapses between KCs and specific MBONs. Together, such an anatomical separation suggests that memories about punishment and different reward types are stored at specific KC-MBON synapses at defined sites of the respective compartments, thus providing the backbone for a distinguishable memory read and write system.

Reading and writing memories: synapses and networks

Punishment-coding dopamine neurons innervate compartments where approach promoting MBONs extend their dendrites and reward-related dopamine neurons innervate compartments covered by avoidance promoting MBONs. This pattern implies that during olfactory learning, compartment specific dopamine release induces a depression of synaptic connections between KCs coding for the trained odor and the downstream MBONs.

The first evidence for learning induced plasticity at the level of MBONs came from extracellular recordings in the honey bee (Menzel and Manz, 2005). However, studies from *Drosophila* have recently used genetically-encoded calcium indicators to measure neural activity in genetically-identified populations of neurons in trained and untrained flies [for review (Owald and Waddell, 2015)]. Utilizing such experimental strategies, it was recently demonstrated that the responses of specific glutamatergic avoidance MBONs (the so called M4/6 MBONs) downstream of sugar-reinforcing dopaminergic neurons were depressed for an odor that had previously been associated with a reward. Strikingly, the physiological depression observed here matches the behavioral switch from odor avoidance to approach observed when blocking these MBONs in the naïve fly (see above). Because interfering with these neurons during memory recall also abolishes learned behavior, depression of this KC to MBON connection most likely (a) is the site for appetitive memory sto-

rage and (b) is directly causal for the observed behavioral switch (Owald et al., 2015a).

Input to other sets of MBONs that promote approach and are downstream of punishment-coding dopaminergic neurons, is typically depressed after associating an odor with an electric shock (Séjourné et al., 2011; Hige et al., 2015; Perisse et al., 2016). Together these findings suggest synaptic depression as the major motif of synaptic plasticity in the mushroom body network. However, for some MBONs (for instance V2-MBONs, γ2α'1-MBONs) odor responses were potentiated after training (Bouzaiane et al., 2015; Owald et al., 2015a; Felsenberg et al., 2017). Indeed, some MBONs (like M4/6) show bidirectional plasticity: they are depressed after reward learning, but show an enhanced response for an aversively trained odor. The mechanisms underlying these plasticity traces, however, are not solely confined to local synaptic phenomena: enhanced responses after aversive conditioning more so seem to arise from a network effect (Owald et al., 2015a; Perisse et al., 2016). Depression of approach-promoting GABAergic MBONs ('MVP2') after aversive learning changes the inhibition these MBONs feed-forward onto avoidance MBONs. This disinhibition effectively leads to a potentiation of the latter class of neurons. Importantly, both sets of MBONs receive input from the odor-coding KCs, so that information of odor-identity can still be retrieved through such a network motif.

Together, these findings give rise to an integrative model, which predicts that olfactory memories are manifested as a skew in the mushroom body output network [Figure 2; (Owald and Waddell, 2015)]. Odors with no assigned learned value drive approach and avoidance MBONs with equal strength. During associative learning an odor activates a specific set of KCs concurrent with the presence of a meaningful cue. The latter in turn drives the respective dopaminergic neurons innervating a specific compartment and induces synaptic plasticity at the underlying odor specific KC to MBON synapses. The change of odor drive to a particular group of MBONs biases the network either towards approach MBONs after reward learning, or towards avoidance MBONs after punishment learning. This skew then elicits the learned stimulus-driven behavior of the fly.

The anatomy of MBONs, however, suggests that they not only project out of the mushroom body to pre-motor areas, but also connect to the dopaminergic neurons that feed back to the mushroom body (Aso et al., 2014b; Lewis et al., 2015; Owald et al., 2015a; Eichler et al., 2017). Given that learning changes the drive of specific MBONs, the feedback to the dopaminergic systems is also changed when a fly encounters the learned odor again (Riemensperger et al., 2005). This motif of recurrent feedback loops turns out to be essential for the re-evaluation of learned behavior (Felsenberg et al., 2017).

Reconsidering what is true

In an ever-changing world, reliability of learned information must constantly be re-assessed to ensure adequate behavior. Thus, one of the most crucial aspects of memory to grant behavioral flexibility is that it is malleable. If an animal encounters a situation in which the stored information does not match the actual outcome (a mismatch condition which can be computed as the so called prediction error), learned information and previous memories need to be adjusted. In general, this can be achieved in two ways, either by updating the original memory or by the formation of a new opposing memory, an extinction memory. It seems to depend on the extent of the prediction error occurring during memory recall, which of the two processes is utilized. In *Drosophila*, an extinction memory can be formed by re-exposing flies to a previously rewarded odor in the absence of the expected food reward. Such an incongruity changes the behavior of flies; it nullifies the learned approach behavior (Tempel et al., 1983; Felsenberg et al., 2017). The new learning event, the extinction learning, depends on the teaching signal from punishment-coding dopaminergic neurons which are driven by the skew in the output network established during initial learning. Thus, the omission of reward is coded as a punishment and leads to the formation of a parallel aversive extinction memory which opposes the initial appetitive reward memory [Figure 3; (Felsenberg et al., 2017)].

Expectance and reality do, however, sometimes match. If flies experience a reminder of their positive memories, which does not strongly conflict with the learned information, the memory undergoes a cycle of de- and re-stabilization. This process, called reconsolidation, is understood to be a well conserved memory update mechanism to integrate minor adjustments to the destabilized and therefore changeable memory (Nader, 2015). In flies, stabilized memories are insensitive to cooling-induced anesthesia. However, the application of a reminder renders the memory vulnerable, it is destabilized. If cooling is applied within a critical time window after the reminder, it interferes with the re-stabilization process of memory and hence erases the reward memory. Within this time window, temporally orchestrated activity of a specific MBON and distinct groups of dopaminergic neurons are required to ensure successful memory reconsolidation [(Felsenberg et al., 2017)].

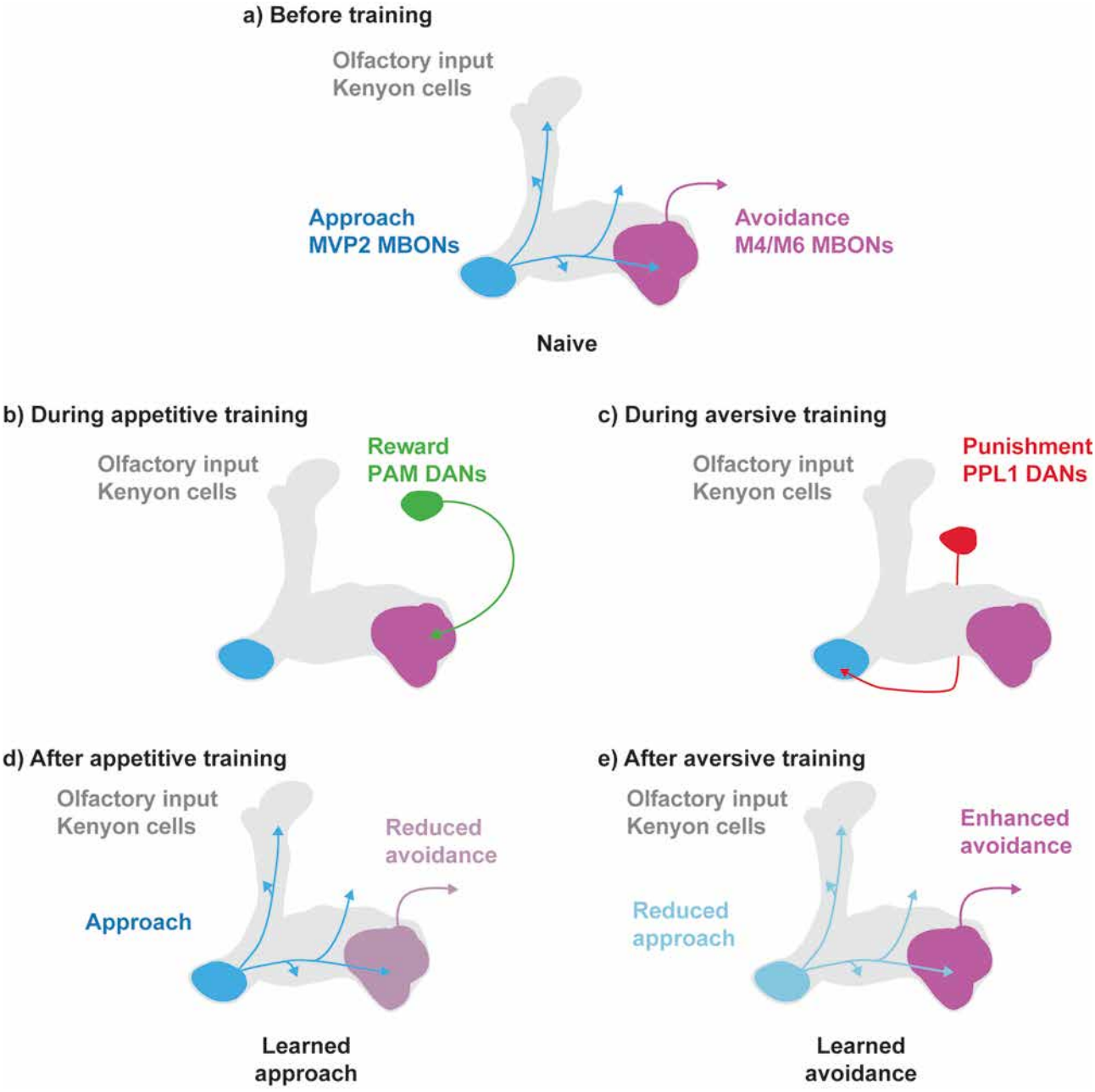

Fig. 2: Olfactory memories are stored as a skew in the mushroom body output network. Olfactory input drives activity in a specific set of KCs (not shown), which in turn activate all classes of downstream MBONs. The approach promoting GABAergic MVP2 MBON (blue, also known as MBON γ1pedc>α/β) provides feed-forward inhibitory input to the avoidance promoting M4/6 MBONs (purple, also known as MBON β′2mp, MBON β2β′2a, MBON γ5β′2a). **a)** In the current skew model for a fly that is naïve for a presented odor activity of approach and avoidance promoting MBONs is balanced. This balance translates into no contribution of the mushroom body to odor driven behavior (arrows, blue for approach behavior and purple for avoidance behavior). **b)** During appetitive training an odor is presented coincidently with a reward. Thus, sugar reward activates dopaminergic neurons (DANs), which innervate compartments in which the odor driven KCs connect to avoidance promoting MBONs. **c)** During aversive training an odor coincides with punishment such as an electric shock, which drives dopaminergic neurons innervating compartments where KCs connect to approach MBONs. **d–e)** After training, synapses between the KCs activated by the trained odor and the respective MBONs are depressed. This learning induced synaptic plasticity skews the MBON network towards either approach after appetitive learning or towards avoidance after aversive learning when the fly encounters the trained odor again. This skew in the network leads to the expression of learned behavior.

Although processes underlying memory re-evaluation provide opportunities to alleviate problematic memories in humans, the mechanistic insight into these processes is sparse. Since the phenomena of extinction and reconsolidation are conserved across species (Eisenhardt, 2014; Nader, 2015) it might well be that the findings obtained in *Drosophila* represent coding principles that might help to unravel general mechanisms underlying memory reevaluation.

Outlook

The increasing knowledge of where and how memories are stored in the *Drosophila* brain, combined with genetic accessibility of the involved structures, provides a unique possibility to gain further mechanistic insights. Recent work has identified specific synapses as part of reward and punishment related memory traces. This offers the opportunity to investigate the molecular machinery and the cell specific genetic settings underlying learning-induced synaptic plasticity. Behavioral experiments linked with high resolution microscopy could determine the structural changes shaping synaptic efficacy. Precise knowledge of the involved network components will allow us to further tackle the coding principles of important processes involved in memory retrieval, consolidation and reevaluation.

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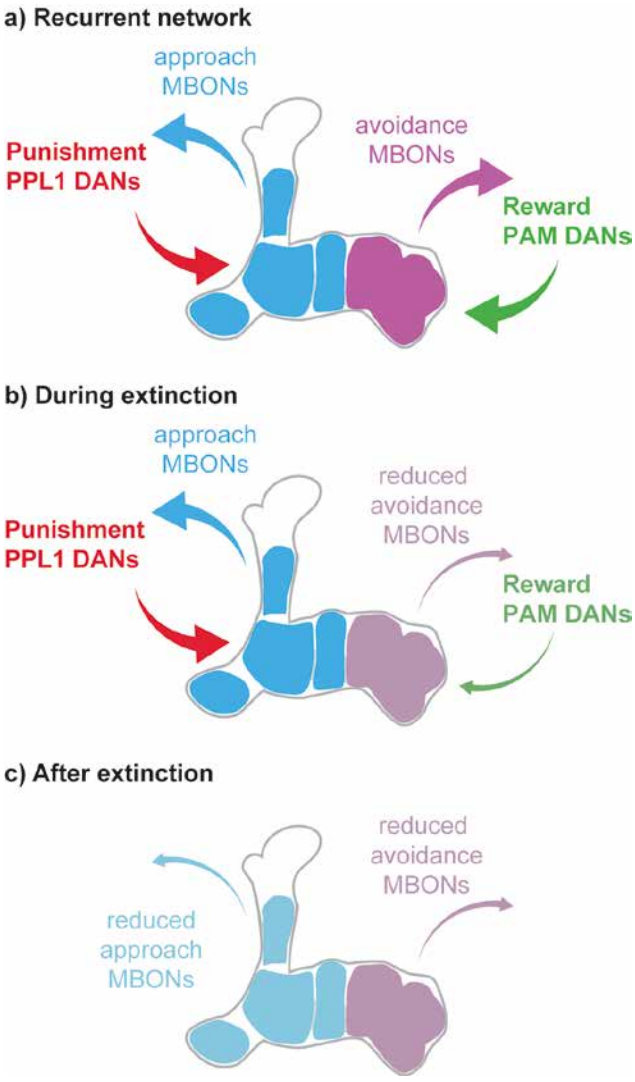

Fig. 3: Extinction of reward memory is driven by the punishment system. **a)** MBONs form recurrent feedback loops with dopaminergic neurons (DANs), which provide the teaching signal during associative learning: approach MBONs drive punishment-coding neurons and avoidance neurons are connected to reward-related dopaminergic neurons. **b)** After learning the response of the MBON network to the reward-associated odor is skewed towards approach MBONs. This skew translates into a relatively stronger drive of the punishment dopaminergic neurons during extinction learning. **c)** Rather than going back to the naïve state, a parallel, aversive memory for the trained odor is formed which annuls the skew in the MBON network (Felsenberg et al., 2017).

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