

## 41. Aversive Olfactory Conditioning

Valentina Parma, Donald Wilson, Johan N. Lundström

The mammalian olfactory system is intertwined with emotional and memory centers of the brain, thus providing an ideal model to study olfactory-based fear conditioning, a behavior lying at the intersection of perception, emotion, and cognition. In the present chapter, we first outline a brief overview of the olfactory system's anatomy, and then, we define the structural and functional changes induced by aversive olfactory conditioning with a clear focus on rodent and human models. In detail, we discuss aversive experience-dependent modulations at each level of the olfactory pathway, differentiating between experimentally presented (shock) and naturally occurring aversive pairings (toxicosis). Whenever possible, developmental trajectories are reported. The description of aversive olfactory conditioning mechanisms are finally used to provide insights on psychiatric and medical conditions characterized by aversive odor memories which may open up future possibilities of developing novel treatment options.

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*But as present pleasures are tremendous reinforcers, and present pains tremendous inhibitors of whatever action leads to them, so the thoughts of pleasures and pains take rank amongst the thoughts which have most impulsive and inhibitive power.*  
James [41.1, pp. 550]

Valence – the affective evaluation centered on liking – is arguably the dominant dimension in olfactory perception [41.2, 3]. Although lately it has been suggested that odor valence is hard-coded into its chemical properties [41.4], perception of odor valence is commonly thought to be predominantly derived from a learned association with the emotional context in which an odorant is encountered [41.5–7]. The emotional context can be related to positive and negative experiences, and the ability to discriminate between the two is an adaptive trait that promotes reproductive fitness [41.8]. Indeed, organisms who correctly distin-

guish safe from threatening stimuli can more strategically guide perception and attention to the environment, and as a consequence, anticipate and escape harmful events [41.9].

Pavlovian conditioning is the prototypical form of all types of learning [41.10, p. 103], resulting from exposure to relations among events in the environment. Such learning is a primary means by which the organism represents the structure of its world. [41.11]. It is such a fundamental form of learning that it is expressed between species (from invertebrates to humans) as well as within species, in all individuals [41.12].

Aversive olfactory conditioning is a specific form of Pavlovian learning. It involves an unpleasant unconditioned stimulus (US), that produces a vigorous negative response irrespective of training (or unconditionally) and a neutral cue that acts as a conditioned stimulus (CS) [41.13]. The CS is a stimulus that at first induces only a minor orienting response. However, fol-

lowing contingent associations with the US (such that the CS predicts the occurrence of the US), the CS can acquire aversive properties itself and evoke an aversive conditioned response (CR). Imagine a rat wandering in his cage and suddenly receiving a foot shock. Without any previous exposure to this aversive stimulus, the rat freezes. Freezing, the behavioral counterpart of acute stress responses in many prey animals, is a typical measure for unconditioned responses (UR) in rodents. If the same rat is exposed to a stimulus neutral in valence, such as a colored light, an auditory tone, a tactile stimulation, a flavored solution, or a smell, no negative unconditional reaction (no freezing) is expected. However, if the presentation of the neutral stimulus – such as rose – is paired with the foot shock in such a way that a clear association can be established between the two events, the neutral stimulus will acquire aversive properties. In other words, after a certain number of pairings between rose and foot shocks, the sole presentation of the rose odor will trigger a freezing reaction in the rat. Thus, the rose odor has become a conditioned stimulus, a stimulus whose response has acquired an aversive power by the repeated pairing with the stressful event (foot shock). However, by virtue of their rich affective connotation, odors can additionally play the role of US. When odors are perceived as markedly unpleasant – such as, for instance, in the case of rotten eggs for humans – odors can act as an aversive stimulus.

Pavlovian aversive olfactory conditioning is a unique source of information for unveiling the rules and functions underlying sensory-mediated learning processes for several reasons. For example, olfaction is the most archaic sense, thought to be the earliest to appear during ontogeny and the oldest sensory informant from a phylogenetic perspective [41.14, 15]. In virtue of this, the olfactory sense has evolved to a complex and highly sensitive organ [41.16]. In all vertebrates, olfactory information is rapidly distributed to multiple central targets, which are confined to the anteromedial temporal and posterior orbitofrontal lobes rather than being widespread across the whole brain [41.17, 18]. In fact, the first central brain area that process odors is situated only one synapse away from the olfactory receptor body, a distinctively short pathway between the periphery and the central sensory brain [41.17]. Furthermore, olfactory information does not require a mandatory thalamic relay from the periphery to the cortex, as for our other sensory modalities [41.19]. In addition, even if ancient, olfaction can be considered the most *dynamic* modality. Neurons in the olfactory epithelium uniquely regenerate on a monthly basis [41.20] and experience-dependent morphological and functional changes in the adult olfactory system have been revealed at many different stages of the

pathway [41.21, 22]. This flexibility is essential to sustain the highly complex and versatile representation of odors in the brain [41.22].

As reviewed in Chap. 38 as well as elsewhere [41.23], cerebral areas in the inferotemporal and frontal lobes are linked to lower and higher order emotional and memory processes and are profoundly related to odor processing. It will suffice to mention the famous Proustian effect – in which smells have the power to unleash a flood of emotional memories, present in the life of almost every normosmic person [41.24]. To add biological credence to the anecdotal connection between olfaction and emotions is the fact that neural representations of odors with different valence are separable in the olfactory structures also implicated in emotional processing [41.25]. The nature of this architectural feature, that again makes olfaction a special sense as compared with other modalities, raises interesting questions about the peculiarity of olfactory-mediated aversive learning.

Olfaction also offers an exclusive prenatal-postnatal sensory continuity, which allows for the development of adaptive behavioral and neural mechanisms *in utero* [41.26–28]. Prenatal olfactory learning favors adaptation to the postnatal environment and the development of the neural structures supporting that learning. Critically, within the early postnatal period when altricial neonates are entirely dependent on the mother for food, warmth and protection, odor learning is heavily biased to produce an attraction to the maternal odor, regardless of whether the mother causes the infants pain or not [41.29, 30]. Thus, at a crucial period during early development, aversive olfactory conditioning is suppressed to prevent infants from learning an aversion to an odor their life depends on.

Olfaction is further the only sense that allows the receiver to have a dual experience of a unique stimulus. On the one hand, when an odor is smelled orthonasally, both animals and humans are able to make sense of it at a relative distance from its source. In an aversive context, this distal feature of the system allows for the implementation of actions that more successfully will attain the goal of avoiding the threat. On the other hand, food odors can access the system through an additional route – the retronasal pathway, which is also characterized by an internal (or proximal) evaluation of the stimulus. Humans experience this retronasal smell as flavor. Perceptual as well as neural underpinnings of the two routes are not completely overlapping and therefore can contribute differently to olfactory learning mechanisms [41.31–33].

The functional role of olfaction is differently expressed in mammals at different levels of the phylogenetic scale. Although humans have been demonstrated

to outperform many nonhuman species in odor sensitivity [41.34], certain animals, such as rodents, depend heavily on olfactory information to navigate the world, whereas humans are considered to be less reliant on orthonasal olfactory cues [41.35], though may be expert at retronasal olfaction. A comparative perspective can offer the opportunity to study the impact of this aversive olfactory information in the full behavioral context and account for the variability that can specifically be found within species. As an example, animal models are critical for the definition of the molecular and physiological mechanisms of aversive olfactory conditioning, whereas humans offer the possibility to directly assess how the participants evaluate the nearby stimuli [41.3]. If on one hand, defining how mice pair the smell of banana with gastric malaise using single cell recordings can help us determine the neuronal mechanisms of aversive olfactory learning [41.36], it would prove fairly difficult to acquire a verbal report of the animal's preference of said odor. On the other hand, one can simply ask human participants to gain information about odor pleasantness; however, obtaining information from single neurons using the same gastric malaise paradigm as for the mouse would face rejection by most ethical committees.

From a theoretical standpoint, defining how specific olfactory memories are created and stored represents an opportunity to better define cognition in rodent models, which show impressive odor-based memory abilities [41.37]. From the clinical (human) perspective, aversive olfactory conditioning represents the key to unveiling mechanisms that promote and maintain certain pathologies, such as post-traumatic stress disorder (PTSD) [41.38, 39], multiple chemical sensitivity (MSC) [41.40] and pretreatment chemotherapy nausea [41.41]. Historically, the scientific community has primarily relied on animal models to uncover etiopathogenetic and maintenance mechanisms of fears and phobias. However, given that humans exhibit behavioral vulnerability to odors in certain instances, it is timely

to validate the functional anatomy of human olfaction and olfactory memory to unveil how aversive olfactory conditioning contributes in humans to the etiology and the treatment of fear-related disorders [41.42], in which odors might play a critical role.

Considering the nature of the olfactory system's architecture and its close anatomical connections to emotional and memory brain centers, it seems to us that olfaction is the sense allowing for the most reductionist and naturalistic study of aversive conditioning processes. It is worth noting, however, that this observation should not be interpreted as derived from the principle of Occam's razor. As Occam stipulated, in the absence of certainty among competing options, the one with the fewest assumptions [aka the simplest] should be selected. However, complexity has its intrinsic value and alternatives with a greater number of assumptions may ultimately prove correct. Indeed, olfaction is a simple, yet not a trivial system. Instead, it is characterized by a level of complexity that needs to be valued and manipulated to extend the boundaries of our actual knowledge on this system, whose potential is still underappreciated. Aversive olfactory conditioning is particularly interesting because it allows us to join sensory, cognitive, and emotional information to provide an effective model to study where and how these pieces of information are encoded and, importantly, integrated in the brain.

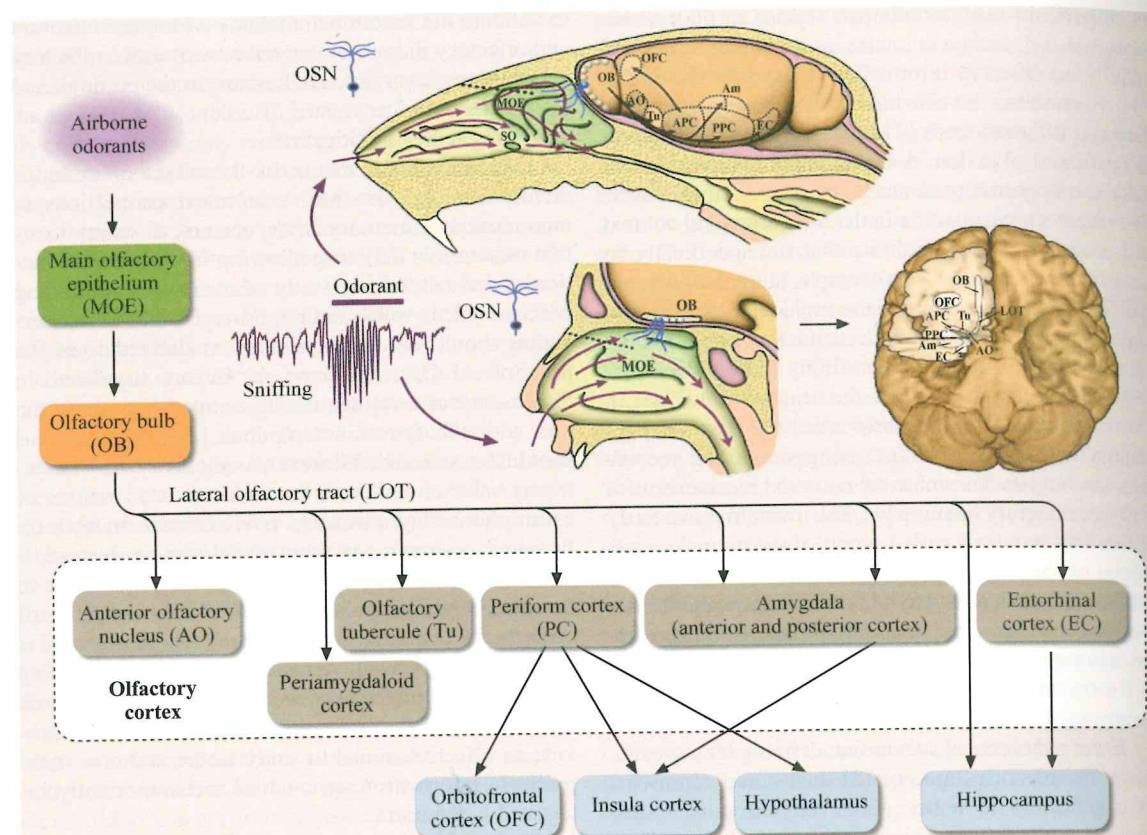
To better account for this holistic view of olfactory aversive experience, in the next section we will first broadly sketch the anatomy of the olfactory system as well as known fear circuits in mammals; then we will review how each structure along the olfactory pathway alters the signal based on experience-dependent dynamic plasticity, according to functionally different types of aversive olfactory conditioning. As we will review, important aspects of this plastic system are age-dependent; therefore, for the sake of completeness, a developmental perspective will be included.

## 41.1 The Anatomy of Neural Circuits Involved in Mammalian Aversive Olfactory Conditioning

The functional and organizational structure of the olfactory system is conserved across the animal kingdom [41.43]. Whether this is the result of homology or it reflects an independent evolution due to similar constraints has yet to be clarified. However, the organizational and structural similarities are an opportunity to explore the neuronal processing of aversive olfactory conditioning between species. The goal of this sec-

tion is not to provide a complete review of the neural systems involved in olfactory perception and aversive conditioning; rather, it is to outline the primary factors underlying olfactory-dependent aversive conditioning. For a more complete overview, please see Chap. 38.

As depicted in Fig. 41.1, olfactory perception is initiated in the periphery of the olfactory system with an interaction between volatile odorant molecules and



**Fig. 41.1** Neural organization of the mammalian olfactory system. Sensory pathways in the main olfactory system of mammals are illustrated for mouse (*upper image*) and human (*lower images*). Volatile odorant molecules enter the nasal passages as a result of phasic sniffing, and interact with olfactory sensory neurons (OSNs) in the main olfactory epithelium (MOE). OSNs project into the olfactory bulb (OB). Discrete sets of glomeruli in the OB are targeted by the OSNs expressing the same receptor, forming odotopic spatial maps. Dozen of mitral/tufted (M/T) cells project from each glomerulus to the lateral olfactory tract (LOT), which distributes the information to the olfactory cortex. Major recipients of OB input include the piriform cortex (PC) with anterior (APC) and posterior (PPC) subdivisions, the olfactory tubercle (Tu), the anterior olfactory nucleus (AO), the hippocampus, the amygdala, the periamygdaloid cortex and the entorhinal cortex (EC). From here, odor information is routed to higher-order centers such as the orbitofrontal cortex (OFC), the agranular insula, and the hypothalamus. Adapted with permission from [41.44].

receptors expressed on the cilia of olfactory sensory neurons (OSNs) located in the main olfactory epithelium (MOE). Individual olfactory sensory neurons express a single olfactory receptor gene from the large family of olfactory receptor protein encoding genes. The axons of these bipolar neurons project to a single glomerulus, or module, situated in the olfactory bulb (OB). Each glomerulus is odorant-receptor specific in that it receives input from olfactory sensory neurons all expressing the same receptor gene. This creates an odotopic spatial organization in the OB, similar to what occurs in the visual or somatosensory systems [41.43, 44]. Dozens of mitral/tufted (M/T) cells constitute second-order projections that transmit via the

lateral olfactory tract (LOT) information to the primary olfactory cortices. This group of cortices is dominated by the piriform cortex – structurally and functionally divided into anterior (APC) and posterior (PPC) regions – and it is complemented by the olfactory tubercle, anterior olfactory nucleus (AO), hippocampus, anterior and posterolateral amygdala, periamygdaloid cortex, and entorhinal cortex (EC). Subsequently, the olfactory information is processed in other regions such as the orbitofrontal cortex (OFC), agranular insula, mediodorsal thalamus, and the hypothalamus [41.23, 45].

This system constitutes a powerful tool to model the functional neurocircuitry of fear. In fact, topograph-

ical representations of the olfactory sensory inputs exist only one synapse away from the amygdala, which is considered a key structure enabling aversive conditioning. The main olfactory bulb directly targets the cortical nucleus of the amygdala, which in turn targets the basolateral amygdala (BLA) [41.46]. The central nucleus of the amygdala (CeA) acts as an output regulator for fear responses, by targeting midbrain and brainstem structures that initiate and control the expression of fear or reactions to threat, such as freezing. This neural circuit is identified as the medial hypothalamic defensive cir-

cuit [41.47, 48]. Although it is not involved in cue fear conditioning per se, the hippocampus is a fundamental limbic structure involved in adult contextual aversive olfactory conditioning [41.49].

In the present chapter, we will consider only the structures critically contributing to the learning of representations processed in the context of aversive olfactory conditioning. For the sake of cross-species comparison, we assume that structural changes in the brain have functional correlates, whether behavioral or physiological.

## 41.2 Aversive Olfactory Conditioning-Induced Structural and Functional Plasticity

After repeated pairings with an aversive stimulus (US), a neutral stimulus (CS) develops an emotionally salient response (CR). Electrical shocks or nonlethal levels of toxins are commonly the stimuli that artificially or naturally induce aversive olfactory conditioning. However, in virtue of the hedonic trait of odors, unpleasant odors (and tastants) have been used as behaviorally salient US with unconditioned aversive properties [41.50]. Although few direct comparisons have been reported, the potency of the different aversive stimuli has been deemed equitable [41.25, 50]. However, provided that the acquisition of olfactory object perception is a prerequisite for aversive olfactory conditioning to occur [41.51], the involvement of different brain structures depends on the task used to elicit aversive reactions. We will therefore explore the neural plasticity shaped by the use of different aversive stimuli separately. To this end, we will initially focus on experimental (arbitrarily chosen) stimuli used in pairings or associations, which do not naturally occur in the ecological niche of an organism (electrical shock-odor coupling) with the goal of providing the basic theoretical and mechanistic principles of aversive olfactory conditioning. We will then focus on more ecologically relevant and naturally occurring phenomena of the odor-induced aversive conditioning (toxin effects odor coupling). For the sake of brevity and clarity, we will limit this review to studies using odors that are experimentally paired with aversive stimuli or unpleasant (aversive per se) odors and food-related biologically relevant stimuli (toxicosis).

For odor aversion induced by predator chemosignals, please refer to the thorough review by Staples [41.52]. Since anatomical development is not always matched with functional development [41.53, 54], whenever possible, we will report how the mechanisms change across maturation to approximately define at which

age a brain area is involved, in rodents and humans alike.

### 41.2.1 Somatosensory Stimulation US

Different noxious somatosensory stimuli have been used to induce threat associations with an odor (CS). In adult rodents, the use of strong tail pinches – whose limits rely on the inability of maintaining a constant stimulation over time and across subjects [41.55] – have been attempted. However, the by far most utilized stimuli in both rodent and human studies are electrical shocks of different intensities [41.56–59].

In the following sections, we will consider aversive olfactory conditioning-induced plasticity at different levels of the olfactory system, beginning from the periphery and moving towards the more central cerebral substrates.

#### Olfactory Sensory Neurons

The olfactory sensory neurons constitute the first order of synapses of the olfactory system and they represent the interface between the environment and the central nervous system. Experience-dependent structural plasticity has been revealed as early as at this level during the first phases of development [41.60] and during adulthood in mice [41.61, 62].

For example, mice trained in a fear conditioning paradigm with the odor acetophenone as the CS, an odorant specifically activating the M71 olfactory receptor (M71OR), demonstrated an increase in number of M71 specific sensory neurons within the olfactory epithelium and a related increase in size of the targeted glomeruli within the OB of adult mice [41.61]. This aversive learning plasticity does not appear in untrained mice, mice trained to a non-M71 activating odorant, or mice exposed to nonassociative pairings of

acetophenone, therefore confirming the link to the aversive experience. This hypothesis has also been tested with other odors and demonstrated that synaptic output of olfactory sensory neurons (OSNs) is modulated by odor-shock conditioning [41.62]. In other words, aversive learning-dependent modulation occurs already at the level of the receptor neuron.

Moreover, neonatal exposure to acetophenone in association with aversive olfactory conditioning promotes glomerular refinement, revealing not only experience-dependent structural changes but also modulation of the speed of glomerular development [41.60]. At present, it has not been conclusively settled whether the association between the CS+ and the US takes place in the epithelium or whether it is the result of a top-down link. As demonstrated by Kawai and colleagues [41.63], it is possible that an instantaneous increase in adrenaline in the olfactory epithelium (as a result of the US) might mediate an increase in receptor activity.

Although it is assumed that the human brain is able to similarly adapt its structure following aversive experiences, the technical challenges have so far prevented us from empirically testing this hypothesis, especially at such an initial level of the olfactory system. Nevertheless, it seems plausible that the regeneration of olfactory neurons throughout a lifetime [41.64] will support enhanced olfactory experience.

#### Olfactory Bulb

The axons projecting from the olfactory sensory neurons terminate within specific glomeruli in the OB, and synapse with M/T cells and juxtaglomerular interneurons [41.65–67]. Considering that each glomerulus represents input regarding a single odorant receptor, the glomerular and M/T layers of the OB constitute odorant receptor maps [41.68], which can be molded by experience. Studies conducted in rodents demonstrated that early in postnatal development, the repeated, daily exposure to odor-shock pairings induces fear responses in the pups. It also intensifies the CS+ odor-evoked brain activity as measured by an increase in focal uptake of glucose (precisely, 2-deoxy-D-glucose, 2-DG) in the OB glomerular layer, as well as changes in M/T cell responses [41.69]. In adult rats, even a single exposure to an odorant paired with shock will result in subsequent CS-evoked freezing and increased odor-evoked 2-DG uptake in OB glomeruli [41.70].

These aversive olfactory conditioning-induced changes in OB response to the CS may be mediated by long-term potentiation-like mechanisms within the olfactory bulb [41.71, 72], as well as learned changes in olfactory sensory neuron input [41.61, 62]. Importantly, the olfactory bulb also undergoes continued neurogenesis of inhibitory granule cells throughout

life, and several studies have demonstrated that the incorporation of these newborn neurons into the OB circuit is shaped by odor experience and learning, and the inclusion of these new neurons significantly contributes to the odor memory [41.22, 73, 74]. This effect is true for both appetitive odor conditioning and aversive olfactory conditioning [41.75]. Although aversive conditioning does not reorganize the glomerular representation, mice exposed to the odor-shock pairings demonstrate an increase in the size of glomeruli within the specific odor representation [41.61, 76]. Moreover, the activation of glomeruli that were originally only weakly activated by the CS pre-training increased after conditioning [41.76]. Together, these data suggest that aversive olfactory conditioning, even in immature animals, helps tune the olfactory bulb to an increased and more specific representation of the CS odor. The tuned representation is expressed at the level of both glomerular layer spatial activity patterns and M/T output activity, and includes neuroanatomical changes such as local addition of granule cells.

At present, noninvasive neuroimaging techniques that can be applied in human studies do not allow for the characterization of the functional plasticity of the OB in an aversive olfactory conditioning paradigm. However, it seems plausible that humans do also show some sort of learning-dependent OB plasticity after aversive olfactory conditioning. This area deserves further study.

#### Piriform Cortex

Second-order projections bridge the information from the OB to the primary olfactory cortices, by means of the lateral olfactory tract (LOT) [41.77]. In contrast to the odor-specific spatial maps expressed in the OB, both connections in the olfactory cortex [41.78, 79] and odor-evoked activity are distributed in the piriform cortex [41.80–82], revealing the presence of diffuse projections and an internal system of long association fibers. In other words, as theorized by Haberly [41.83], the olfactory cortex acts as a *content-addressable memory* in which each site in the system contains information about the entire input. The anterior piriform cortex (APC) receives strong afferent inputs from M/T neurons and is hypothesized to play a primary sensory cortical role in olfaction [41.84–87], as well as having some functions in odor memory. For example, single-unit recordings showed post-conditioning changes at [41.87–90] the level of the APC in awake rats [41.91, 92]. In animals trained to fear a specific odor (CS+) and not fearing a similar odor that was not paired with shock (CS-), APC expressed more selective odor coding. In contrast, rats trained to have a generalized behavioral fear response demonstrated impaired odor discrimination at the level of APC single units [41.92].

Contrary to the APC, the anatomy and the functionality of the posterior part of the piriform cortex (PPC) are reminiscent of higher-order associative areas and are thought to be responsible for odor quality and categorization. The PPC receives a relatively strong input from the basolateral amygdala, while the APC does not [41.93, 94]. As postulated by Li [41.95], this may be the primary locus of representation for olfactory aversive stimuli in humans. Since early development (post natal (PN) day 7–8), odor aversion learning is associated with PPC activity [41.96]. This is maintained around the weaning age (PN12–13) with shocks of different intensity (0.5 and 1.2 mA). Post-conditioning plasticity in this area has been repeatedly demonstrated via different techniques. Animals trained with odor-shock conditioning display stronger local field potentials [41.97, 98], higher synaptic plasticity as measured via the expression of brain-derived neurotrophic factor (BDNF) [41.99], increased gamma-aminobutyric acid (GABA) and glutamate concentrations that resist approximately for 30 minutes [41.100]. Also, lesions at the level of associative olfactory cortices (PPC included) one month after training eliminate the CR [41.101]. Taken together this indicates that the piriform cortex is an essential structure for long-term storage and retrieval of odor-paired threat. In other terms, the synthetic function of the piriform cortex as a whole complements the specificity of elaboration found in previous stages of the olfactory system (OB) and promotes a more comprehensive and stable representation that serves as the base of the holistic perceptual experience of the odor object [41.102]. Furthermore, convergent support of this statement comes from the study of the slow-wave sleep (SWS) activity in an aversive olfactory conditioning paradigm. Even if PC is usually hyporesponsive to odors during SWS, during post-conditioning its activity is enhanced and significantly correlates with subsequent memory performance [41.91]. In other words, it is possible that the PC's reduced reactivity during SWS indicates a preferential mechanism to facilitate memory consolidation of relevant information (threat) while external noise can remain unattended [41.91].

In agreement with findings from the rodent literature, the human piriform cortex has been identified as a key structure in aversive odor conditioning. PPC, but not APC, exhibits odor-paired specific plasticity [41.103] that seems to be based on response enhancement following prolonged exposure to an odor [41.104]. Critically, the PPC post-conditioning odor plasticity is evident also when the initial neural (and perceptual) representation of the odor to-be-paired with the shock (CS+) and the odor to-be-unpaired with the shock (CS-) are not discriminable [41.103].

Associating one of two enantiomers, odors with chemical mirror non-superimposable images, with a shock significantly increases discrimination performance of the paired odor [41.103]. This elegantly suggests that human aversive olfactory conditioning is based on sensory augmentation processes that are independent of attention [41.103]. In line with the above-mentioned studies demonstrating that aversive olfactory conditioning-plasticity is present already at earlier stages of the system, Åhs and colleagues [41.105] demonstrated in human participants that the increase in discriminatory performance after aversive olfactory conditioning was based on an odorant-dependent shift in absolute sensitivity rather than on a change in discrimination performance per se. Interestingly, eight weeks after the documented aversive olfactory conditioning-dependent increase in sensitivity, the increase was no longer present [41.106]. This indicates that these effects of rapid plasticity may be of a transient rather than permanent nature.

At present, while aversive olfactory conditioning-induced changes can occur throughout the piriform cortex (especially in rodents), the site of most likely anatomical convergence between threat signals and the odor CS is the posterior part of the piriform cortex. Accordingly, the PPC is the structure that most reliably demonstrates odor-shock induced plasticity in humans.

#### Hippocampus

A key player in the formation and storage of memories across mammals is the hippocampal formation [41.106]. The hippocampus is thought to be responsible for the acquisition of the association between stimuli, and among stimuli and the context in which they are presented during aversive olfactory conditioning [41.106]. Critically, the development of the hippocampus is responsible for the emergence of contextual aversive olfactory conditioning that appears in rat pups at PN24, but not before that developmental stage [41.49]. Neural and immunohistochemical correlates indicate an increased activity evoked by CS odors after aversive olfactory conditioning in several subregions of the hippocampal formation, such as the Cornu Ammonis (CA) 1, CA3, and the dentate gyrus (DG). This learned odor-evoked activity presumably reflects the fact that the DG receives strong afferent input from the entorhinal cortex, which is a highly multi-sensory cortex including serving as a direct, monosynaptic target of the olfactory bulb and piriform cortex (Fig. 41.1) [41.49]. The DG in turn projects to the CA3.

The GABA<sub>A</sub> agonist muscimol infused into the hippocampus, which silences hippocampal activity, prevents rat pups from coherently representing the stimuli in the environment and therefore inhibits contextual

aversive olfactory conditioning [41.49]. These results are in line with most literature on adult contextual aversive olfactory conditioning.

In human participants, it has been demonstrated that the representation of an object becomes fully consolidated by involvement of the hippocampus [41.107]. In aversive olfactory conditioning, the sensory (piriform) cortex plays a key role in supporting the long-term storage of the representation [41.108], as evident also for other sensory modalities (audition) [41.109]. Recent data also indicate that the strength and precision of aversive olfactory conditioning memories can be modified by sleep [41.110, 111]. Re-exposing adult participants during the sleep stage to the odor associated with threat during the previously wake state induced a reduction in hippocampal activity (as well as a reorganization of neural patterns in the amygdala) prompted by stimulus-specific extinction. Therefore, the extinction of the feared odor can be favored during sleep, simultaneously avoiding the traumatic conscious re-exposure of the threatening odor [41.110].

#### Amygdala

The amygdala has historically been thought to be the key structure for initiating and controlling fear reactions. However, more recent data indicate that the amygdala codes for the biological significance, intensity, or salience of sensory stimuli [41.112, 113]. It projects outputs to the sensory cortices, which may enable perceptual analysis of potentially threatening stimuli [41.112, 114]. Although this is not the only possible pathway enabling threat perception [41.115], the amygdala remains a central area for aversive olfactory conditioning given its role in emotional, memory, and olfactory processes.

Among the amygdalar nuclei, the basolateral complex (BLA), which includes the lateral, basal and accessory basal nuclei, is the area most strongly linked to aversive olfactory conditioning processing [41.116]. The lateral nucleus has been implicated as the primary site of acquisition and consolidation of aversive memories, given its increased spike firing and long-term potentiation [41.117]. This has been confirmed specifically for aversive olfactory conditioning [41.118] as early as in the first stages of development [41.96]. Learning-associated changes in the BLA are impacted by the strength of the shock, but only from PN23–24, when BLA is involved at all intensity levels of electric shock (0.5–1.2 mA) [41.96]. Immunohistochemistry measures further confirm that amygdala involvement critically mediates the development of aversive olfactory conditioning at PN10 [41.119–123]. This structure, although sufficiently mature to respond to aversive odor stimuli during the sensitive period [41.124], is

involved in the mechanisms in interaction with corticosterone levels [41.119, 121, 125–127]. Further, attenuated aversive olfactory conditioning in adulthood has been demonstrated to be associated with a deficit in CS odor-evoked 2-DG uptake in the cortical nucleus of the amygdala and the PPC, effects that have been linked to reduced local inhibition, as assessed by means of electrophysiological techniques [41.128]. In other words, odor-shock pairing experienced early in life induces functional changes in areas beyond those involved in infant learning and they are potentiated by contingencies [41.128].

In adult rats, the amygdala is critical for threat acquisition and consolidation. Pre-training lesions or pharmacological inactivation or inhibition of BLA as well as post-training lesions prevent the full formation of a CS-paired odor aversion [41.129–131]. Increased expression of BDNF [41.99] and heightened concentrations of GABA and glutamate [41.100] in trained rodents are biomarkers of the BLA synaptic plasticity following aversive olfactory conditioning.

Learning-dependent responses in the amygdala are also revealed in human studies showing time-dependent post-conditioning plasticity. In other words, the amygdala response is maximal in early conditioning trials and a progressive decay of activity in this area is subsequently seen [41.103]. This finding is in line with the exponential decay in activity observed in imaging studies using visual stimuli in association with shocks [41.132, 133] and provides an indication of how the aversive experience shapes perception. More recently, it has also been shown that odors paired with painful (trigeminal) stimulation (carbon dioxide, CO<sub>2</sub>) elicits an enhancement of functional activation of the amygdala during conditioning [41.134].

In summary, the amygdala, especially the BLA, is strongly implicated in aversive olfactory conditioning in both humans and rodents. The BLA expresses localized changes in network function that contribute to stored memory and subsequent CR behaviors. Furthermore, BLA output to target areas, such as the PPC, may contribute to learned changes directly within the sensory cortex, a mechanism that can contribute to odor-evoked fear.

#### Orbitofrontal Cortex

The orbitofrontal cortex (OFC) is a vital part of the neural olfactory network in both nonhuman and human animals. In rodents, it receives olfactory input through both reciprocal connections with the piriform cortex [41.135] and via projections from the mediodorsal thalamus [41.136, 137]. The OFC is important for odor-taste multisensory integration [41.138, 139] as well as for olfactory reward evaluation and odor-guided be-

haviors [41.140]. The OFC and its connections with primary olfactory areas [41.135] demonstrates experience-dependent plasticity [41.141, 142] and this may contribute to learned odor behaviors. Important for this discussion, the prefrontal cortex, including the orbitofrontal, is also a strong modulator of amygdala activity and is involved in emotional regulation and anxiety [41.143]. However, to the best of our knowledge, the OFC has received very little attention in aversive olfactory conditioning paradigms in either humans or nonhuman animals.

#### 41.2.2 Chemosensory Stimulation

The extent of the literature covering the use of chemosensory stimuli as the US in aversive olfactory conditioning paradigms is scant when compared to the previous section. Therefore, we present a more integrated view and we merge our discussion of the various neural structures involved. In rodents, although predator odors can be used as US in contextual conditioning paradigms [41.144, 145], we are not aware of any published odor US – odor CS conditioning data. Perhaps the closest example of such work in rodents is the recent work demonstrating transgenerational odor fear [41.146]. Female rats were conditioned (odor-shock) to fear an odor. They were subsequently bred and allowed to have litters. If the mothers were exposed to the CS odor in the presence of her pups, her fearful response to that CS induced odor-specific fear in her pups. The alarm odor she emitted in response to the fearful CS was sufficient to train her pups to fear the CS themselves [41.146]. This form of transgenerational odor fear is amygdala dependent [41.147, 148].

In humans, unpleasant odors have been used as aversive stimuli to produce aversive reactions comparable – although not identical – to those dependent on electrical shocks [41.25, 50, 147]. For instance, odors are stimuli that can induce emotional reactions closer to disgust rather than fear. In fact, simple odor exposure does not induce the same brain activations as revealed by the pairing of a neutral visual stimulus and an aversive odor [41.50]. Gottfried and collaborators [41.50] used neutral faces as CS and paired half of their presentations with 4-methyl-pentanoic acid, a pungent cheese-like odor acting as US and consistently rated as unpleasant. Functional magnetic resonance imaging limits the extent to which we can spatially zoom in on task-related activations and therefore does not allow assessment of learning-dependent plasticity before the information arrives in the piriform cortex, and it does not enable the analysis of single nuclei within subcortical structures. However, the PPC seems to play a critical role in salient associative activity, thus confirming using a different

type of US that this area cannot be considered a strictly unimodal cortex, but rather an associative brain center [41.50]. Amygdala responses were not, however, reported [41.50]. This lack of amygdala activity could potentially be attributed to an insufficient arousal magnitude by the unpleasant odors [41.149], some of which might have triggered disgust rather than fear [41.150].

Further, an interesting aversive olfactory conditioning-dependent effect has been demonstrated in the orbitofrontal cortex (OFC), an area that has been attributed to higher-order complex processing and by some labeled as the secondary olfactory cortex [41.149]. Both the medial and the lateral portion of this cortex have been related to learning-dependent computations that outperform simple odor processing [41.50]. In other words, OFC is an essential contributor to the creation of stimulus-reward associations that are used to organize odor-guided behaviors.

#### 41.2.3 Naturally Occurring CS-US Associations

The prevalence of object learning in the environment makes it a useful heuristic for identifying CS-US pairings in nature [41.51]. An interesting case is represented by conditioned odor aversion (COA). COA is a robust and long-lasting odor association that generates avoidance of the odor stimulus due to the contingent association of an ingested tasteless solution (CS) rapidly followed by toxicosis (US) [41.151]. COA is a phenomenon that has been shown to be present in intrauterine life and throughout development [41.70, 152–160] [41.161]. Although it has been suggested that COA learning depends exclusively on the taste modality [41.162], it is now clear that retronasal olfaction has a significant impact on post-ingestive outcomes [41.36, 163]. In fact, the distal exploration of the food via its odor acquires predictive value of the sensations experienced while consuming the food [41.36].

In the following sections, we will report the characterization of the neural activity associated with olfactory-induced malaise, following the olfactory pathway. It is worth reiterating that for many other paradigms, the investigation of the lower levels of the olfactory hierarchy has yet to be performed on human participants. Researchers working on the topic are in the process of adjusting current techniques or developing new tools to resolve the issues preventing the online neuroimaging of the OSN and olfactory bulb. Nonetheless, a direct comparison between the human and nonhuman literature is often difficult due to the necessity of experimentally inducing the malaise paired with the olfactory stimuli; a practice that is ethically difficult to perform in humans due to the long-term aversive out-

comes [41.164]. For this reason, this section will focus on knowledge derived from experiments in nonhuman animals. Observational information regarding specific cases of odor-malaise associations will instead be provided in the next section addressing the role of aversive olfactory learning in clinical conditions. To the best of our knowledge, the effects of naturally occurring odor CS-US associations on olfactory sensory neurons have not been explored. Therefore, we will start our hierarchical report at the level of the olfactory bulb.

#### Olfactory Bulb

In the rodents, COA has been deemed possible to induce as early as in fetal rats [41.70, 152, 157–161, 165–169] and it relies on the contribution of the OB, at least until the pup approaches weaning age. However, data gathered in older pups and adult rats [41.170] indicate that the plasticity of the OB is reduced as compared to the first phases of development. Critically, in COA paradigms, the contribution of the OB lasts longer as compared to aversive olfactory conditioning paradigms involving shock [41.49, 158, 171]. Considering that COA relies on the olfactory retronasal stimulation of a food item, the nutritional state of the animal is a critical variable in modulating the activity in the OB. As an example, single-cell recordings demonstrate that the activity of the mitral cells increases when an animal is sated and receives an odor previously paired with malaise [41.172]. Taken together, these findings indicate that the activity in the OB reflects the coding of the conditioned relevance of a stimulus induced through natural exposures.

#### Piriform Cortex

Although relatively unstudied, the impact of odor-malaise learning on the APC does not seem to be robust during early development, whereas PPC seems to play a critical role [41.96]. By capitalizing on Fos immunoreactivity, a technique that allows for the quantitative analysis of the neurons activated following stress and pain by visualizing the expression of the c-Fos protein product, it was evident that the odor-evoked trans-synaptic neuronal activity increased in PPC during the retrieval of taste potentiated odor aversion (TPOA) [41.173, 174]. In line with this evidence, *Chapuis et al.* [41.36] demonstrated that COA learning clearly modified transient oscillations reflecting synchronous activities in large-scale neural assemblies. In detail, odor-induced fast oscillations in the beta frequency (15–40 Hz in rats) of local field potentials registered at the level of PPC predicted the aversive behavior to the odor in concert with the emergence of a strong beta oscillatory activity in the OB, OFC, and BLA. Altogether, these pieces of evidence seem to sup-

port the idea that specific neuronal populations in PPC respond to odors paired with aversive stimuli and have enhanced temporal coherence, allowing for experience-dependent odor representations specific to the way the aversion was acquired [41.36].

#### Amygdala

The amygdala contribution to COA arises post-weaning in rat pups [41.96, 158] and is maintained in adult life [41.175]. The BLA, in particular, has been described as the critical structure involved in the acquisition, consolidation, and retrieval of the COA [41.170, 176–179]. *Chapuis* and colleagues also provided evidence of experience-dependent modulation of BLA oscillatory activity in response to odors [41.36]. In line with the idea that this structure integrates the affective salience of chemosensory stimuli [41.180, 181], it is plausible that it plays a role in the representation of a general aversive connotation of the olfactory signal.

#### Insula

The insula, also known to be a prime processor of gustatory information [41.182], is critically involved in aversive paradigms involving tastants [41.183]. With reference to the COA paradigm, the more ventral agranular zone of the insula (an area labeled by some as primary gustatory cortex) is a particular target of projections for primary olfactory areas [41.184, 185]. *Chapuis et al.* [41.36] described how the pattern of beta oscillatory activity in both the agranular and the granular division of the insular cortex are modulated in response to the learned odor cue, but only when ingested before the animal experienced malaise. This would represent the signature of a network supporting odor representation as a consequence of the animal experience [41.36].

#### Orbitofrontal Cortex

The OFC is known to integrate the inputs of various food-related sensory stimulations and has been suggested to play an important role in flavor perception in rodents and humans [41.139, 186, 187]. *Dardou* and collaborators have shown that both olfactory and taste cues activate this structure during taste potentiated odor aversion retrieval [41.174]. Several studies have shown the existence of both anatomical and functional connectivity between the PC, the BLA, and the OFC [41.135, 188], and that these pathways are capable of learning-dependent plasticity [41.141, 142]. Thus, this network is a good candidate for the integration of both sensory and affective signals about food odor cues.

It has been suggested that retronasal stimuli are more effective than orthonasal stimuli in modulating the gustatory or flavor neural code. As an example,

*De Araujo* and colleagues [41.138] measured brain response to retronasally delivered odors in combination with a taste and demonstrated selective activity in an anterior region of OFC, suggesting that the region was therefore important in integration of taste and

smell. Moreover, *Small* and colleagues [41.187] determined that the modulation of preceding experience (whose valence was not, however, taken into account) affects OFC, as well as the insula and anterior cingulate cortex.

## 41.3 Clinical Applicability

Up to this point, we have reviewed the neural changes associated with aversive olfactory conditioning across different stages of the olfactory pathway and across specific developmental ages. These modifications have a striking impact on the individual's physiology, whether nonhuman or human animals, and on the manifested behavioral correlates. Independently of the sensory modality considered, the fear-conditioning paradigm has proven to be one of the more prolific and valuable experimental models for assessment of human psychiatric disorders associated with abnormally heightened fear, anxiety, and other dysfunctional behaviors [41.189–196]. The natural response to sensory cues, the acquisition of aversive memories, and the extinction of the already acquired fear memories are mechanisms that have characterized the study of aversive olfactory memory and set the base for explaining a range of pathologies and psychopathologies. Besides etiopathogenetic explanations, behavior therapy has used aversive olfactory conditioning to reduce a variety of dysfunctional or unwanted behaviors [41.197]. Below, we will analyze some of the most relevant applications.

### 41.3.1 Anxiety and Trauma-Related Disorders

The range of fears is immeasurable, and some clearly present an olfactory component. Besides phobias triggered by odors of animals (for instance, dog odor for cynophobics) [41.198], post-traumatic stress disorder (PTSD) has a strong olfactory connotation [41.192]. PTSD is a mental sequela that may occur after a traumatic event, such as war, assault, or a natural disaster [41.199]. Experimentally, studies reported in the literature have used combat-related stimuli in different sensory modalities. Odors have long been noted in the clinical practice to have a strong emotional and memory component that seems to precipitate or trigger the individual to re-experience the traumatic event [41.200]. The characterization of the mechanism of aversive olfactory conditioning constitutes a model for threat perception and reaction that can be useful in the explanation of the general principles underlying

these types of fear-related clinical issues. The amygdala and the hippocampus, both of which are central to the mechanism as previously outlined, are structures that have been consistently included in neural models of anxiety and mood disorders [41.201]. Specific to PTSD, a positron emission tomography study revealed a bigger change in cerebral blood flow in the amygdala and odor cues retrieved more memories of life events [41.39]. Furthermore, aversive olfactory conditioning can either induce very stimulus-specific fear (selective to the CS) or generalized odor fear depending on the events during the conditioning (presence of a CS– and a CS+ [41.92]) and experiences during consolidation of those fearful odor memories (during post-training SWS [41.110, 111]). These different features of aversive olfactory conditioning experience can change the precision with which the olfactory system encodes the learned odor. Failure to have precise stimulus control of our learned fears can contribute to PTSD and other fear-related disorders. Thus, understanding how traumatic events affect sensory coding itself will significantly contribute to our understanding of these disorders and will open up the possibility of expanding treatment options.

Well-established treatments for both specific phobias [41.202] and PTSD [41.203] are exposure-based behavioral strategies, which involve the experience of the feared object or situation in a nondangerous, controlled environment. Exposure therapy encourages the systematic confrontation of stimuli associated with fear, with the goal of reducing the person's fearful reaction [41.204]. Confrontation of external (feared objects, activities, situations) or internal feared stimuli (feared thoughts, physical sensations) can occur in imagination or *in vivo* [41.202–205]. Nevertheless, positive therapeutic results are critically dependent on the emotional engagement of fearful memories, [41.206] whose replay is often actively contrasted by patients [41.206]. Smells, in virtue of their automatic emotion-producing feature, are ideal candidates to increase emotional engagement [41.207] and reduce the frequency and the intensity of episodes of anxiety, flashbacks, and dissociation triggered by odors. Attempts have been made to increase the usability of exposure therapy and

the compliance to the therapy by reducing its side effects. As an example, technological advancements offer the opportunity to control odor presentation by exposing patients to sensory rich virtual reality (VR) environments [41.208, 209]. As another example, techniques have been proposed to replay the traumatic event in states of faded consciousness. Besides the scant evidence on hypnotherapeutic olfactory conditioning [41.210], which helps the hypnotized patient to develop new (positive) olfactory associations with the traumatic event, interesting potential comes from the study by Hauner and colleagues [41.110]. The authors exposed their participants to face images and electrical shocks in the presence of an olfactory background. During an afternoon nap, the olfactory cue paired with the aversive association was repropose. In the ensuing wake period, arousal, amygdala, and hippocampal activations were reduced for the feared face. In other words, these findings suggest that odors are sensory cues able to target which memories can be reactivated during sleep and favor fear extinction. Although these results were reported for a group of healthy young adults, they trace a pathway for research including patients with anxiety disorders and, in general, everyone who would like be relieved of an unwanted fear.

### 41.3.2 Multiple Chemical Sensitivity

Another pathology that heavily relies on olfactory-based conditioning issues is multiple chemical sensitivity (MCS) [41.211], also defined as idiopathic environmental intolerance [41.40]. MCS incorporates a range of chronic polysymptomatic conditions among which low levels of common environmental chemicals (pesticides, solvents, etc.) have been reported to cause disabling problems in the sufferers. The high comorbidity with affective disorders [41.212] and the findings from the animal literature of links to the mechanism of kindling (or neurogenic sensitization), support the idea that olfactory-based conditioning and/or sensitization mechanisms might be the base of the disorder. Aside from maladaptive cognitive products (i.e. beliefs, expectations), repeated associations between multi-componential aversive responses (e.g. psychophysiological, motor) and low levels of inhaled and ingested chemicals, may condition aversive response symptomatology [41.40, 213]. In fact, it has been demonstrated that healthy participants exposed to harmless odors (i.e. butanoic acid) in association with CO<sub>2</sub> show post-conditioning somatic symptoms like altered respiratory behavior that can be reduced in a typical Pavlovian extinction paradigm [41.214].

The olfactory-limbic mechanisms previously described, and in particular the use of odors as US

and odor-malaise paradigms, are mechanisms that offer testable hypotheses, which are urged to be explored to better characterize this still controversial syndrome [41.215]. In addition, in rodents it has been reported that norepinephrine, released in response to arousal, can prevent habituation and/or induce dishabituation of odor evoked neural [41.90] and behavioral [41.216] responses. Thus, cognitive factors could differentially maintain or heighten olfactory responsiveness to odors in individuals predisposed to MCS via elevated norepinephrine levels. This should be the target for future studies.

### 41.3.3 Pretreatment Chemotherapy Nausea

The odor-malaise condition type is an optimal model to explain the phenomenology of anticipatory nausea in patients undergoing cancer chemotherapy. Many cancer chemotherapy drugs provoke nausea and stimulate the emetic reflex [41.217], resulting in approximately 25% of patients developing anticipatory nausea and vomiting [41.218]. The most common cause of pretreatment nausea has been found in the odor that the patients associate with the clinical environment or odors previously associated with a vomiting experience [41.219]. Given the repetitive aversive association with the treatment and the emetic episodes, the patients might refuse or experience the treatment as disgusting. Therefore, the patient's compliance in the treatment, essential for the recovery process, is threatened and quality of life impaired [41.40]. At present, antiemetic drugs acting on the neurochemical control of vomiting are primarily used to treat chemotherapy nausea [41.220]. However, some types of administrations, such as intramuscular delivery, prove to be painful and carry a plethora of side effects (e.g. erratic absorption of drug, sterile abscess formation, fibrosis of the tissues, etc., [41.221]). Therefore, understanding the learning mechanism of the conditioned response offers the possibility of making behavioral recommendations [41.218, 222].

Systematic desensitization processes contrast the maladaptive learned responses of anticipatory nausea and vomiting with relaxation under the assumption that fear and relaxation cannot coexist at the same moment [41.205]. This process, which often happens in imagination, facilitates the creation of an alternative response to the dysfunctional behavior. Specifically to anticipatory nausea and vomiting, olfactory stimuli associated with the chemotherapy sessions can be presented to the patient who has reached a deep stage of relaxation, promoting the counterconditioning of the unwanted response. This behavioral approach has been proven more effective than other treatments such as counseling [41.223] and relaxation alone [41.224].

### 41.3.4 Addiction and Substance-Related Disorders

Conditioning mechanisms involving olfactory stimuli can be used, as just reviewed, to reduce nausea and vomiting but they also have often been used to produce them in order to avoid other sorts of unwanted behaviors. Classically, aversion therapy has been an effective approach to reduce excessive drinking in alcoholics [41.225]. Pairing the odor of alcohol with electrical shocks as US has been one of the techniques [41.226], although not the most successful. Indeed, chemically based aversions, appropriately pairing the smell (or the taste) of alcohol with other chemical cues such as ammonia-like smelling salts [41.227] or with emetic drugs [41.225] resulted in longer-lasting alcohol avoidance. Aversion therapy lived its golden age between the 1940s and the 1950s, and then progressively declined. Recently, few to no uses of this technique have been reported [41.228].

Odor-based aversion therapy was not only confined to alcoholism issues but it proved useful in reducing other types of addictions [41.228, 229]. For instance, isovaleric acid, a cheese or sweat-like foul smell, presented during covert sensitization, namely the mental rehearsal of the undesired behavior, discouraged cigarette and marijuana smoking as well as paint and glue sniffing [41.230]. It successfully reduced both manifest and implicit behaviors (thoughts) [41.230]. A naturally occurring aversive therapy has been described in smoking pregnant women who after associating the cigarette odor with nausea reactions will temporarily and spontaneously terminate their smoking [41.229]. Interestingly, Arzi and colleagues [41.231] offered an opportunity for a broader number of smokers. In a group of nicotine addicts who wanted to quit smoking, Arzi et al. [41.231] presented the cigarette's odor paired with two nonarousing, yet disgusting, odors (ammonium sulfate and rotten fish) during short-wave sleep. In the following wake period, participants exposed to the negative conditioning during their natural sleep reduced the number of reported cigarettes smoked (as compared to baseline) without any additional aid.

Smoking cessation persisted for a week. These promising findings open up future research endeavors to fully disentangle the physiological process and evaluate the feasibility of sleep learning as a therapy.

### 41.3.5 Inefficient Therapeutic Use of Olfactory Aversive Conditioning

Besides the important insights that olfactory aversive conditioning has brought to the understanding and treatment of a variety of mental health disorders, the cases in which aversive therapy using olfactory stimuli has been attempted have not always been successful. As in the case of excessive drinking, overeating is a dysfunctional behavior that has often been treated with aversion therapy involving olfactory stimuli. Cole and Bond [41.232] paired appealing foods with noxious odors and temporarily succeeded in facilitating weight loss in a group of obese patients. They also demonstrated that at the end of the eight-week program, olfactory aversion therapy produced the highest weight loss as compared to two control groups (placebo and waiting list) not exposed to the foul odors [41.232]. Measurements at the eight-week follow up revealed, however, no differences with pretreatment weight levels, thus suggesting that olfactory aversion therapy is not efficient in targeting obesity long term [41.232].

Even considering the momentum gained by olfactory aversive therapy throughout a series of behaviors considered dysfunctional, it is striking that such a technique has been widely applied to limit non-canonical sexual practices [41.197]. Sadistic sexual arousal [41.233] and homosexual behaviors [41.234], have been routinely treated by behavioral therapists by associating the unwanted behavior with unpleasant olfactory stimuli such as ammonia or sulfurous compounds (rotten egg smell). In none of these studies can the therapy be considered as successful, either short or long term. Only in a single case study of child harassment tendencies did olfactory-induced aversions, in concert with other simultaneously proposed approaches, reduce the dysfunctional behavior [41.235].

## 41.4 Conclusions

The ensemble of the evidences reported here leads us to conclude that the olfactory system in rodents and humans alike is dynamically regulated at all (testable) levels of the olfactory system, starting from prenatal development and lasting throughout adult life. Indeed, tentative evidence even suggests that aversive odor

learning transcend generations via epigenetic modulation [41.148].

The same core brain areas (PPC, amygdala) are responsible in all types of olfactory-based aversive learning mechanisms for mediating the association between the odor and the negative emotional experience. The

changes induced in the piriform cortex by the aversive experience have a cascading impact on a large network of cerebral areas, including the reciprocal ascending connections to OB and the descending connections from OFC [41.188]. As a result, the rich experience-dependent and plastic responses have the ability to associate memories with emotional content. As recently proposed by Li [41.95], a sensory-cortex-based threat perception model would explain the constitution of aversive experiences. Life experiences will form negative odor-threat associations that will first be stored at the level of the olfactory cortex, enabling encoding of threat cues as early as the first stages of sensory processing. Subsequently, as the representation of the odor-threat association is consolidated in the amygdala and elsewhere, the piriform cortex may undertake both rapid and long-term plastic changes, ultimately resulting in modified neural response patterns underlying the association. Unfortunately, limits to now available methods and usability in respect to ethical standards prevent research from extending this model to the lower levels of the olfactory pathway in humans, such as the olfactory sensory neurons. Moreover, as we highlighted above, whether the stimuli to be associated with the threat (either a shock, or a toxin) are presented orthonasally or retronasally will differently impact the neural network underlying the experience both in animals and in humans.

From a developmental perspective, the literature indicates that different conditioning methods trigger different neural pathways for odor aversion learning, each demonstrating different developmental trajectories [41.96]. The amygdala is a structure whose activation is highly sensitive to the specific learning protocol involved (aversive shock as compared to odor-malaise associations) and the reinforcement condition being assigned. Unfortunately, insights on developmental trajectories of human aversive olfactory conditioning are currently lacking.

Finally, a thorough characterization of aversive olfactory conditioning mechanisms constitutes a model for threat perception that can be useful in the explanation of the general principles underlying a variety of mental health disorders and their treatment. Specifically, a detailed knowledge of these mechanisms will be vital to solve problems related to memories triggered by odors in a variety of psychiatric and medical conditions, thus opening the possibility of developing novel therapies, even directly involving aversive olfactory conditioning. Considering the peculiarity of odor-based aversive learning mechanism, an experimental model with a high ecological relevance, it is our belief that there is an urgent need to fully uncover the behavioral psychophysiological and neural underpinning underlying aversive olfactory conditioning and that the field is set for major discoveries in the near future.

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