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Cortical Odor Processing in Health and Disease

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Abstract

The olfactory system has a rich cortical representation, including a large archicortical component present in most vertebrates, and in mammals neocortical components including the entorhinal and orbitofrontal cortices. Together, these cortical components contribute to normal odor perception and memory. They help transform the physicochemical features of volatile molecules inhaled or exhaled through the nose into the perception of odor objects with rich associative and hedonic aspects. This chapter focuses on how olfactory cortical areas contribute to odor perception and begins to explore why odor perception is so sensitive to disease and pathology. Odor perception is disrupted by a wide range of disorders including Alzheimer's disease, Parkinson's disease, schizophrenia, depression, autism, and early life exposure to toxins. This olfactory deficit often occurs despite maintained functioning in other sensory systems. Does the unusual network of olfactory cortical structures contribute to this sensitivity?

Keywords

piriform cortex; orbitofrontal cortex; entorhinal cortex; mediodorsal thalamus; odor perception

1 INTRODUCTION

Sensory cortices perform a number of functions which result in a transition of information processing from initial highly analytical processing toward more integrative, synthetic processing. Thus, while peripheral receptors may be selectively responsive to specific wavelengths of light or vibration in visual, auditory, and somatosensory systems, cortical areas are often most responsive to more complex patterns of stimulation and ultimately objects. Perhaps the most extreme expression of cortical synthesis relative to peripheral selective analysis is the fact that most "primary" sensory cortices are now known to be multisensory (Man et al., 2013), allowing at least some form of cross modal integration.

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Ultimately, cortical sensory processing provides the information necessary for downstream regions to drive attention, behavioral decision making, and sensory-guided action.

In mammalian olfaction, the sensory cortex is uniquely close to the periphery. Olfactory sensory neurons (OSNs) terminate on olfactory bulb mitral and tufted cells which in turn project directly to olfactory cortex. Although even the olfactory bulb fits the anatomical definition of a laminar, cortical structure, traditionally olfactory cortex is defined as those regions which receive direct, monosynaptic input from the main olfactory bulb. These areas include the anterior olfactory nucleus (a.k.a. anterior olfactory cortex), tenia tecta, olfactory tubercle, cortical nucleus of the amygdala, anterior and posterior piriform cortex, and the lateral entorhinal cortex. Most of these areas in turn feedback to the olfactory bulb. While the sensory physiology of many of these regions is still woefully understudied, the contributions to odor perception of anterior and posterior piriform cortices and entorhinal cortex, and to a lesser degree the olfactory tubercle, are beginning to emerge.

In addition to the traditional olfactory cortex, olfaction also includes a thalamo-cortical component similar to other sensory systems. The mediodorsal nucleus of the thalamus (MDT) receives olfactory input from the traditional olfactory cortex and projects in turn to the orbitofrontal cortex (OFC). The OFC also has direct, reciprocal connections with the anterior piriform cortex. The OFC is a highly multisensory region important for compiling information regarding reward value and important in decision making. As a chemosensory area, the OFC is involved in olfactory and flavor perception, in addition to its roles in decision making and reward. Thus, olfactory cortical areas include both archicortical and neocortical components.

Together, these cortical components of the olfactory system contribute to normal odor perception and memory. They help transform the physicochemical features of volatile molecules inhaled or exhaled through the nose into the perception of rose, coffee, and grandmother’s kitchen. Odor perception involves at least four components—detection, discrimination, recognition, and identification. In addition, it should be noted that odors are also highly effective at evoking hedonic responses, suggesting this may also be a basic component of odor perception. This chapter focuses on how olfactory cortical areas contribute to these different components of odor perception, beyond the extensive processing that already occurs in the olfactory sensory epithelium and olfactory bulb. Furthermore, we will begin to explore why odor perception is so sensitive to disease and pathology. Odor perception is disrupted by a wide range of disorders including Alzheimer’s disease, Parkinson’s disease, schizophrenia, depression, autism, and early life exposure to toxins. This olfactory deficit often occurs despite maintained functioning in other sensory systems. Does the unusual network of olfactory cortical structures contribute to this sensitivity?

2 THE ROLE OF THE OLFACTORY CORTEX IN ODOR PERCEPTION

In most sensory systems, multiple pathways exist, with different downstream and cortical targets and with the different pathways specialized in different aspects of perception. For example, in mammalian vision, retinal output targets the lateral geniculate nucleus of the

thalamus, which in turn projects to the primary visual cortex. However, a subset of retinal output neurons target the midbrain superior colliculus or the hypothalamic suprachiasmatic nucleus instead of the thalamus. These later projections contribute to eye movements and light-entrained circadian rhythms, respectively, while the thalamic output is involved in classic visual perception. In addition, the projection to the thalamus can also be divided into separate, parallel pathways based on receptor input and neural firing properties, with one providing information about visual spatial detail and color, while the other is more sensitive to spatial movement. These spatial detail versus spatial movement specialized pathways are maintained through higher-order visual cortical areas.

The olfactory system shares many of these properties, though seems to do so in a highly compressed manner (Cleland and Linster, 2003). The traditional olfactory cortex includes all of those areas directly, monosynaptically targeted by the mitral and tufted cells of the main olfactory bulb. This includes a number of archicortical (three layered) structures such as the anterior olfactory nucleus, the olfactory tubercle, cortical nucleus of the amygdala, and the piriform cortex, as well as parahippocampal neocortical areas such as the lateral entorhinal cortex. Different cortical subregions are targeted by different olfactory bulb output neurons, with tufted cell output limited to more anterior structures, such as the anterior olfactory nucleus and olfactory tubercle, and mitral cells more broadly projecting through piriform cortex and entorhinal cortex. In addition, the piriform cortex directly targets the orbitofrontal neocortex as well as its primary thalamic source, the MDT. Thus, within one to two synapses, information from the olfactory bulb is distributed to broad cortical regions with diverse functions ranging from autonomic regulation and emotional processing (amygdala) to motivated behavior (olfactory tubercle), to episodic and working memory (entorhinal cortex–hippocampus), to reward valuation and decision making (OFC), and to more basic odor quality discrimination (piriform cortex). The connections between most of these regions are reciprocal, with, for example, heavy bidirectional connections between the piriform cortex and the entorhinal cortex and between the piriform cortex and the OFC. Finally, most of these areas are at least to some extent multisensory, with, for example, the olfactory tubercle directly responsive to at least odors and sound (Wesson and Wilson, 2010), the piriform cortex responsive to at least odors and taste (Maier et al., 2012), and the orbitofrontal and entorhinal cortices responsive to most sensory modalities (Kadohisa et al., 2004; Rolls et al., 2003; Schoenbaum and Eichenbaum, 1995).

Here, we focus on three major components of cortical olfaction—the piriform cortex, the lateral entorhinal cortex, and the OFC and its thalamic input, the mediodorsal nucleus.

2.1 Piriform Cortex

In most sensory systems, spatial organization is critical to system function and perception. For example, retinotopic, tonotopic, and somatotopic spatial organization is maintained throughout the visual, auditory, and somatosensory systems, respectively. This means that the spatial location of activated neurons within subregions of the sensory pathway provides some information about the stimulus. The same appears to be true in the olfactory bulb. Different volatile molecules evoke unique spatial patterns of glomerular and mitral/tufted cell activity (Bozza et al., 2004; Guthrie et al., 1993; Imamura et al., 1992; Johnson and

Leon, 2007). However, beyond the olfactory bulb in olfactory cortical regions, there is no odotopic organization. This is true both in the anatomy of axonal projections (Mitsui et al., 2011; Sosulski et al., 2011) and in the spatial patterns of stimulus-evoked neural activity as assessed with many techniques (Cattarelli et al., 1988; Datiche et al., 2001; Illig and Haberly, 2003; Rennaker et al., 2007; Stettler and Axel, 2009). For example, individual mitral cells project broadly throughout piriform cortex (Mitsui et al., 2011), and neighboring piriform cortical neurons can show completely different odor tuning and temporal entrainment to the respiratory cycle (Rennaker et al., 2007). Odor responses of piriform cortical neurons reflect both the combinatorial nature of their olfactory bulb afferent input (Apicella et al., 2010) as well as the nature of their intracortical association fiber input (Franks et al., 2011; Poo and Isaacson, 2011), which is also highly distributed and nontopographic (Haberly, 2001; Johnson et al., 2000).

The lack of spatial information in sensory cortex increases the importance of temporal structure and spike rate on information processing (Friedrich and Laurent, 2001; Gire et al., 2013a; Lepousez and Lledo, 2013; Shusterman et al., 2011; Smear et al., 2013; Stopfer et al., 1997). Thus, rather than having a localized population of cortical neurons tuned to a specific odorant molecule providing information about stimulus quality, the piriform cortex utilizes a broadly distributed population of coactive cells to provide that information. The information is thus hypothesized to be encoded by the coactivation of a distributed neural population—the timing of firing of distributed cells is more important than the location of those cells. This is one of the features of an autoassociative, distributed array network (Haberly, 2001; Marr, 1971). An outcome of a circuit like this is that many different stimuli can be encoded simply by having different, overlapping ensembles of neurons coactivated by particular odorant input patterns. Recent estimates suggest that a given odorant will activate 3–15% of piriform cortical neurons (Stettler and Axel, 2009), although ensembles composed of as few as 50–100 neurons (Miura et al., 2012) may be sufficient to encode unique odors (though ensemble size may be dependent on the required precision). Given that the piriform cortex is hypothesized to have many more than 50,000 pyramidal neurons (Neville and Haberly, 2004), this allows a nearly unlimited number of overlapping ensemble representations of different odorants.

In addition to simple convergence of afferent and association fiber input to individual neurons in shaping piriform cortical neural response to odor, synaptic plasticity also plays a major role in odor processing (Wilson and Sullivan, 2011). Distributed ensembles of coactive neurons can become linked through associative plasticity of their connecting synapses. Through experience-dependent synaptic plasticity, encoding of stimuli shifts from a feature-based process to an object-based process, similar to that observed in visual object recognition. This allows refinement of piriform cortical ensembles responsive to specific odors and can support perceptual learning (Chapuis and Wilson, 2012; Chen et al., 2011; Wilson and Stevenson, 2003; Zelano et al., 2011). Such synaptic plasticity can also promote perceptual stability by allowing pattern completion wherein activity within an ensemble of activated neurons can be completed despite degraded input (Barnes et al., 2008; Chapuis and Wilson, 2012).

Importantly, given the rich association fiber system and the strong reciprocal connections with other olfactory, limbic, and multisensory structures mentioned above, these odor object representations may include nonolfactory components. Thus, piriform cortical neurons can not only differentially respond to odor quality, but also differentially respond to the learned meaning of the odor (Chapuis et al., 2009; Gire et al., 2013b; Martin et al., 2006; Moriceau and Sullivan, 2004). Given the limited ability to analyze components of complex mixtures (Laing and Francis, 1989), these hedonic and multisensory features may become integral components of the odor object percept itself (Yeshurun and Sobel, 2010) or at least very strongly tied to the object (Olofsson et al., 2012).

In several systems, synaptic plasticity and memory consolidation have been shown to be sleep dependent (Rasch and Born, 2013; Stickgold and Walker, 2007). Recent work from several labs has demonstrated that sleep also plays an important role in piriform cortical function and odor memory. During slow-wave sleep, the piriform cortex displays sharp-wave activity (Manabe et al., 2011; Wilson, 2010), similar to that observed in the hippocampal formation (Buzsaki, 2006). During this state, the piriform cortex is hyporesponsive to odors (Murakami et al., 2005; Wilson, 2010), perhaps due to changes in cholinergic input (Hasselmo and McGaughy, 2004), and more strongly functionally coherent with other limbic structures and neocortical structures (Wilson and Yan, 2010; Wilson et al., 2011a). Following associative odor learning, the time spent in slow-wave sleep is enhanced, and how long slow-wave sleep is extended predicts future memory strength (Barnes et al., 2011). These phenomena are consistent with a potential role for replay of learned odors within cortical circuits during posttraining sleep. Such replay can occur with relatively little interference from odors from the external environment given the reduced cortical response to odors (Carskadon and Herz, 2004). Cortical neurons that were coactive during odor learning can fire coherently during sharp waves (Wilson, 2010), enhancing their synaptic connectivity and the fidelity of the ensemble representation of that odor—and its associations. Several labs have now demonstrated that if contextual odors present during training are reexposed during posttraining sleep, consolidation of memories learned in that odor context is modified (Hauner et al., 2013; Rasch et al., 2007). In a more direct test of the odor replay hypothesis, recent work from our lab suggests that imposed replay of learned spatial patterns of olfactory bulb activity (electrical odors) during posttraining slow-wave sleep enhances subsequent memory for those patterns (Barnes and Wilson, 2014). The identical replay imposed during waking, in contrast, induces memory extinction. Disrupting piriform cortical association fiber synapses during this posttraining period with the GABAB receptor agonist baclofen impairs the accuracy of the memory, which again is consistent with the hypothesis that posttraining slow-wave sleep allows strengthening of cortical ensembles representing the learned odor (Barnes and Wilson, 2014).

The features of piriform cortical function described here (i.e., dependence on afferent and local spike timing, synaptic plasticity and sleep for acquisition, consolidation and expression of odor object perception and memory) suggest a vulnerability in odor perception to disruption of any of these processes. For example, spike rate and timing, as well as synaptic plasticity, are strongly influenced by local inhibitory interneurons (Bekkers and Suzuki, 2013) and neuromodulatory tone (Chapuis and Wilson, 2013; Linster et al., 1999). This issue will be revisited in section 3 on olfactory cortex and pathology.

2.2 Entorhinal Cortex

The entorhinal cortex is the gateway for information entering and leaving the hippocampal formation. The entorhinal cortex is a component of the medial temporal lobe memory system, although it is increasingly believed to have a perceptual function (Baxter, 2009; Suzuki, 2009). Neuroanatomically, the entorhinal cortex is transitional between paleocortex and neocortex. For example, similar to piriform cortex but different from neocortex, the entorhinal cortex receives extensive afferent input to Layer I. Similar to neocortex but different from piriform cortex, the entorhinal cortex is organized into six layers, each with differing local and network connections. In addition to connections with the hippocampus, the entorhinal cortex also receives dense input from the perirhinal cortex, amygdala, thalamus, and modulatory areas like the cholinergic medial septum (Canto et al., 2008). The entorhinal cortex also displays intrinsic memory functions, for example, maintaining stimulus-specific neural activity during delay periods (working memory). Finally, the entorhinal cortex appears uniquely sensitive to a number of disorders including Alzheimer's disease (Braak and Braak, 1992), with Layer II neurons particularly vulnerable (Stranahan and Mattson, 2010), suggesting a possible role for this entorhinal cortex–piriform cortex feedback pathway in neurodegenerative olfactory deficits.

In terms of olfaction, the entorhinal cortex (primarily, the lateral entorhinal cortex) receives input from both the main olfactory bulb and piriform cortex, and projects directly back to both areas (Agster and Burwell, 2009; Chapuis et al., 2013; Cleland and Linster, 2003; Haberly and Price, 1978). In fact in rodents, afferent fibers from olfactory areas are the dominant input to lateral entorhinal cortex (Kerr et al., 2007). This input terminates in Layer I on the apical dendrites of Layer II/III pyramidal and stellate cells (Burwell and Amaral, 1998; Luskin and Price, 1983). These Layer II/III neurons are also the main class of output neurons to both the hippocampal formation and back to olfactory areas (Agster and Burwell, 2009). Entorhinal cortex output to other, nonolfactory areas is predominantly from Layer V pyramidal neurons. The back projection from entorhinal cortex to the olfactory bulb is strongest to the piriform cortex, with weaker projections to the olfactory bulb (Chapuis et al., 2013). Interestingly, there is also a very weak crossed projection to the contralateral piriform cortex (Chapuis et al., 2013).

The lateral entorhinal cortex is responsive to [perhaps odorous] objects in an open field (single units, Deshmukh and Knierim, 2011) and to odors (assessed with LFPs, Boeijinga and Lopes da Silva, 1989; Chabaud et al., 2000; Eeckman and Freeman, 1990; Kay and Freeman, 1998; and single units, Xu and Wilson, 2012). Single-unit odor receptive fields (i.e., the precision with which individual neurons code for different odors) are more narrow in the entorhinal cortex than in anterior piriform cortex, and entorhinal units are far less likely to be entrained to respiration (Xu and Wilson, 2012). As in more peripheral regions of the olfactory pathway, the nature of the entorhinal cortical odor responses is sensitive to internal state (e.g., hunger; Chabaud et al., 2000). In fact, in tasks where animals expect an odor that signals reward to occur at a certain time, the entorhinal cortex is activated (beta band oscillations) prior to the olfactory bulb odor response (Kay and Freeman, 1998), potentially providing anticipatory top-down modulation of the olfactory bulb/piriform cortex by the entorhinal cortex.

Aspiration lesions of the entorhinal cortex have novel effects on odor discrimination memory. Depending on the task, odor discrimination memory can be impaired (Staubli et al., 1984, 1986) or enhanced (Ferry et al., 1996; Wirth et al., 1998). These prior studies have in part interpreted their findings in the context of entorhinal cortex as the major afferent of the hippocampal formation, and odor quality differences were not closely controlled. However, as described above, the entorhinal cortex is also a major feedback afferent to the olfactory system (Canto et al., 2008; Haberly and Price, 1978) and robustly modulates odor-evoked activity in the piriform cortex (Bernabeu et al., 2006; Chapuis et al., 2013; Kay et al., 1996; Mouly and Di Scala, 2006), which could contribute importantly to these effects. For example, recent work using reversible silencing of the entorhinal cortex with muscimol infusions demonstrates that loss of entorhinal feedback enhances piriform cortical single-unit activity and odor-evoked LFP oscillations. This suggests an important targeting of inhibitory interneurons by top-down inputs to the piriform (Luna and Morozov, 2012). Diverse inhibitory interneurons are spatially allocated to specific layers of both the anterior and posterior piriform cortex, as identified by canonical subpopulation markers (Bekkers and Suzuki, 2013; Young and Sun, 2009). This arrangement provides complementing patterns of regulatory activity from each interneuron subpopulation in response to piriform inputs. This results in dynamic modes of phasic inhibition and thus effective information transfer. Hyperexcitability in the piriform is thus associated with impairment in very fine behavioral odor discrimination ability—with no impact on discrimination of more distinct odors (Chapuis et al., 2013). This impairment in odor perception is reminiscent of the olfactory impairments in early stages of Alzheimer's disease, which is also associated with entorhinal neuropathology (Braak et al., 2011).

2.3 Thalamocortical Olfaction

In most sensory systems, attention and conscious sensory perception is mediated by thalamocortical circuits. In humans, the same may be true for olfaction (Plailly et al., 2008), with an important role specifically for the MDT and OFC. Damage to the MDT can impair several aspects of odor perception and memory in humans and nonhuman animals. The OFC, which is highly multisensory, plays a critical role in perhaps the single most conscious olfactory experience humans have—flavor perception. The role of MDT in odor sensory processing has received relatively little attention compared to its neocortical target, the OFC.

2.3.1 Mediodorsal Nucleus of the Thalamus—The MDT receives input from several different olfactory structures: the piriform cortex, the cortical nucleus of the amygdala, the olfactory tubercle, and the lateral entorhinal cortex (Bay and Cavdar, 2013; Cornwall and Phillipson, 1988; Heimer, 1968; Krettek and Price, 1977b; Kuroda and Price, 1991; Powell et al., 1963; Price, 1985; Price and Slotnick, 1983). More specifically, the MDT can be divided into three different subregions: medial, central, and lateral, with the first two areas receiving the majority of olfactory inputs. The medial region receives projections from the caudal piriform cortex, the ventral endopiriform nucleus, the basolateral and central nucleus of the amygdala, and the lateral entorhinal cortex (Bay and Cavdar, 2013; Cornwall and Phillipson, 1988; Krettek and Price, 1974; Price, 1985; Ray and Price, 1992); the central part receives projections from the deep layers of the rostral piriform cortex and the olfactory tubercle (Cornwall and Phillipson, 1988; Krettek and Price, 1974; Price, 1985; Price and

Slotnick, 1983). The MDT projects to the OFC (Krettek and Price, 1977a) which has direct reciprocal connections with the piriform cortex (Illig, 2005; Schoenbaum and Eichenbaum, 1995). Functionally, MDT units have been shown to respond to lateral olfactory tract stimulation and to various odorant categories including biological, monomolecular, and mixtures odorants (Benjamin and Jackson, 1974; Courtiol and Wilson, 2014; Imamura et al., 1984; Jackson and Benjamin, 1974; Price, 1985; Price and Slotnick, 1983; Takagi, 1986; Yarita et al., 1980). Our lab has also demonstrated in anesthetized rats that MDT units display narrowly tuned odor response characteristics with a majority of units responding to only one odor within our odor set (Courtiol and Wilson, 2014). At the network level, we demonstrated that MDT and piriform cortex activities are closely related: odor stimuli induce a conjoint emergence of beta frequency oscillations in both the MDT and the piriform cortex, and some MDT units fire in phase with piriform cortex-beta frequency oscillations (Courtiol and Wilson, 2014). Beside this odor responsiveness, the precise role of the MDT in olfaction remains to be determined. Interestingly, lesion studies in both humans and animal models suggest a role for the MDT in olfactory perception, discrimination, learning, and attention (for a more detailed review, see Tham et al., 2009).

Animals with MDT lesion are not anosmic; however, MDT lesions lead to deficits in both olfactory perception and learning. Relative to perception, Sapolsky and Eichenbaum (1980) have shown that lesions of the MDT alter odor preference in the hamster leading to inappropriate reproductive behaviors. Linked to this distortion of odor preference, studies of patients with damage in the MDT following cerebral hemorrhage, ischemic infarctions, or abscess provide similar evidence. In fact, olfactory hedonic judgments were found to be altered in single-case patient studies (Asai et al., 2008; Rousseaux et al., 1996) as well as in a larger set of patients with thalamic lesions (Sela et al., 2009). Relative to discrimination and learning, Eichenbaum et al. (1980) were the first to report that rats with MDT lesions do not have olfactory detection deficits but require more trials to reach the performance criterion in a difficult discrimination task (stimuli similarity, novelty, or reversal; Eichenbaum et al., 1980; Staubli et al., 1987). Similarly, it has been found that rats with MDT lesions were impaired in odor set and reversal learning (Slotnick and Kaneko, 1981; Slotnick and Risser, 1990) and have deficits in an olfactory continuous delayed nonmatching-to-sample task (Koger and Mair, 1994). The effect of MDT lesions on olfactory learning is further supported by the study of Kawagoe et al. (2007) who showed that MDT units in behaving rats may support associative learning by encoding the reward value of the olfactory cue. Finally, as in smaller animals, humans with thalamic damage present deficits in both odor discrimination and odor identification but not in odor detection (Potter and Butters, 1980; Sela et al., 2009; Tham et al., 2011b). Interestingly, attention deficits may also underlie the problems of MDT-lesioned rodents and humans in performing difficult discrimination tasks given the role of MDT in modulating attention in olfaction (Olofsson et al., 2013; Spence et al., 2001; Tham et al., 2009, 2011a,b; Zelano et al., 2011).

Plailly et al. (2008) were the first to test the hypothesis that the MDT could be involved in odor attention processing. In humans, they designed a specific olfactory attention task and looked for the connectivity among the piriform cortex–MDT–OFC trans-thalamic pathway using functional magnetic resonance imaging (fMRI). They showed that attending to odors specifically increased the functional connectivity between the piriform cortex and MDT and

between the MDT and OFC. These results were corroborated by a recent fMRI study by Veldhuizen and Small (2011) who showed significant activation of the MDT when attending to odors. These results in healthy humans are further supported by the observation that humans with thalamic damages have deficits in olfactory attention-related tasks (Tham et al., 2011a,b). These studies point out the possible contribution of the MDT in olfactory attention but have to be put in perspective of the recent report by Keller (2011). Due to the modest amount of fibers from the piriform cortex to the MDT, Keller proposed that the MDT by itself could not support the attention to odors; rather, Keller suggests that the MDT may be involved in the coordination of attentional shift between olfactory and other sensory modalities.

Finally, MDT has been proposed to be involved in neurological disorders including schizophrenia (Hazlett et al., 2004; Pakkenberg, 1990), bipolar disorder and depression (Anand et al., 2009). This is particularly interesting given that olfactory deficits are common among these neurological disorders (schizophrenia, bipolar disorder, or depression; Cumming et al., 2011; Pause et al., 2001; Rupp, 2010, respectively).

2.3.2 Orbitofrontal Cortex—The OFC, which is actually composed of several regions (Price, 1985), receives direct input from the MDT and the anterior piriform cortex, and thus shows a strong olfactory-induced activation in both humans and nonhuman animals (Gottfried and Zelano, 2011; Rolls, 2004; Schoenbaum et al., 2009; Zatorre et al., 1992). The OFC, however, is also strongly multisensory, with single units capable of responding to gustatory, visual, and somatosensory stimuli (Rolls et al., 2003). One perceptual outcome of such convergence is flavor, with gustatory, retronasal olfactory, and mouth feel combining with visual information about the consumed food to shape the unitary flavor percept (Small and Prescott, 2005).

OFC single units in rodents can respond differentially based on odor quality, but also based on acquired odor-reward value (Alvarez and Eichenbaum, 2002; Ramus and Eichenbaum, 2000; Schoenbaum et al., 1999). Reversing the reward value of an odor can reverse some cells' differential response to that odor, while other cells respond selectively to the odorant quality regardless of the association. Given the sensitivity of many OFC single units to odor-reward associations, responses can also be modulated by changes in reward value, for example, by satiating the animal to a particular reward (Rolls, 2001). In what may be the only study to date comparing odor selectivity in the OFC to earlier stages of the olfactory pathway, Tanabe et al. (1975) found that OFC single units were more odor selective than OB or piriform cortical single units.

In humans, the OFC is activated by odor stimulation as assessed with fMRI and positron emission tomograph (PET) (Jones-Gotman and Zatorre, 1993; Li et al., 2010b; Zatorre et al., 1992), with an apparent bias toward the right OFC. In healthy subjects, OFC thickness correlates with odor performance with greater cortical thickness associated with improved odor perception (Frasnelli et al., 2010; Seubert et al., 2013). Lesions of the OFC, again especially the right OFC, are associated with problems of odor discrimination and identification, though not of detection (Jones-Gotman and Zatorre, 1988; Zatorre and Jones-Gotman, 1991). The differences between the left and right OFC appear to be some of the

more robust lateralization effects observed in olfactory structure–function (Royet and Plailly, 2004). Finally, as noted above, in addition to odor perception, the MDT–OFC pathway may also be involved in attention to odors (Plailly et al., 2008).

Beyond this basic sensory physiology, the OFC plays very important roles in a variety of higher-order functions (Gottfried and Zelano, 2011; Mainen and Kepecs, 2009; Rolls, 2004; Schoenbaum et al., 2009). In fact, although extensive work on OFC function has utilized odors as important cues in behavioral tasks, most of this work has not addressed odor coding *per se*, but instead has focused on other aspects of the task. The OFC appears critically involved in expectation and behavioral flexibility (Schoenbaum et al., 2009). Thus, in addition to responding to odors in an odor-guided task, OFC single units also respond to the expectation of reward and to cues signaling upcoming rewards (Schoenbaum and Eichenbaum, 1995; Zelano et al., 2011). Lesions of the OFC impair reversal learning, perhaps due to an impairment in the ability to update expected outcomes (Schoenbaum et al., 2009).

It is interesting to emphasize that this higher-order prefrontal cortex has robust direct reciprocal connections with such an early stage of the olfactory processing stream in the anterior piriform cortex. It has been suggested that one mechanism used by the OFC in promoting behavioral flexibility is to update distributed brain regions on changing stimulus associations (Schoenbaum et al., 2009). Single units in the piriform cortex, like the OFC, encode information about odor associations (Chen et al., 2011; Gire et al., 2013b; Schoenbaum and Eichenbaum, 1995), in addition to odorant physicochemical quality. Thus, as odors acquire or change associative value through experience or training, the OFC may provide top-down feedback on stimulus-predicted outcomes. In fact, recent evidence has demonstrated that as animals learn difficult odor discriminations, there is a concomitant plasticity of OFC–piriform cortex top-down synaptic input, with a depression of left OFC input to left piriform cortex (Cohen et al., 2013). Once the discrimination is well learned, the strength of this connection returns to baseline levels. Interestingly, in contrast to this depression in the left hemisphere, the synaptic input from the right OFC to the right piriform cortex is enhanced after initial learning (Cohen et al., 2008). Thus, not only can the OFC dynamically modulate the piriform cortex in a task-dependent manner, but also the tonic effectiveness of this input is also plastic. How loss of this top-down input following OFC damage contributes to the observed olfactory perceptual deficits is not known.

3 OLFACTORY CORTEX AND PATHOLOGY

Olfactory perceptions, including detection, discrimination, recognition, identification, and hedonics, are highly sensitive to a wide range of disorders. Olfactory dysfunction can be due to a variety of peripheral problems, including nasal obstruction, toxin-induced damage to the olfactory sensory epithelium, and closed-head injury which can sever the olfactory nerve as it projects through the cribriform plate into the olfactory bulb. However, the olfactory perceptual problems associated with disorders such as AD, Parkinson’s disease, schizophrenia, and depression are not generally associated with peripheral causes but rather appear to be primarily central in origin. In many cases, these olfactory disorders emerge

early in the onset of the disease and occur in the absence of deficits in other sensory systems.

Lesion work in rodent models has demonstrated that basic olfactory perception, that is, detection and simple discrimination, is very robust in the face of large-scale structural damage (McBride and Slotnick, 2006; Slotnick, 1985; Slotnick and Berman, 1980; Slotnick and Risser, 1990). However, local changes in circuit function, for example, through manipulations of local inhibition (Abraham et al., 2010; Lepousez and Lledo, 2013; Nusser et al., 2001), changes in neuromodulatory tone (Chapuis et al., 2013; Doucette et al., 2007; Hellier et al., 2010; Mandairon et al., 2006), or changes in top-down signaling (Chapuis et al., 2013) can impact fine odor discrimination.

Here, we review work on two classes of pathology that have been associated with changes in odor perception and reflect different stages over the life-span. Developmental ethanol exposure can have profound, long-lasting effects on olfactory system anatomy and physiology (Sadrian et al., 2013), though the effects on odor perception can be relatively subtle (Youngentob and Glendinning, 2009). In contrast, AD is strongly associated with olfactory perceptual problems that emerge very early in disease onset, with concomitant changes in olfactory cortical function. One of the earliest problems to emerge in AD is in odor identification, the most cognitively demanding component of olfactory perception. Can this provide insight into cortical subregional contributions to different aspects of odor perception?

3.1 Developmental Ethanol Exposure

There are multiple developmental impairments directly linked to alcohol exposure during embryogenesis, clinically generalized as fetal alcohol spectrum disorders (FASDs). During maternal alcohol consumption, ethanol readily passes the placental barrier and blood–brain barrier, thereby leaving the embryonic brain vulnerable to cytotoxic insult. In an FASD mouse model of single-day binge exposure during early development, ethanol induces immediate apoptotic neurodegeneration (Ikonomidou et al., 2000). In fact, very early exposure to alcohol (gestational day 8 in the mouse) can result in complete loss of the olfactory bulbs (Parnell et al., 2009). This immediate wave of cell death is associated with long-lasting deficits in olfactory circuit anatomy, function, and behavior (Wilson et al., 2011b). These most recent developments are an expansion of a previously conceived vision for the olfactory system to serve as a model for the investigation of the fundamental mechanisms of early alcohol-induced neurobehavioral deficits (Kirstein et al., 1997). Binge-modeled alcohol exposure for a single day during early brain development is sufficient to cause long-lasting deficits in olfacto-hippocampal circuit function. These changes include odor-evoked hyperactivation of local field potentials in the piriform cortex and hippocampus, local feedback inhibition deficits, including decreases in parvalbumin-positive inhibitory interneurons, and elevated coherence between the piriform cortex and hippocampus (reviewed in Sadrian et al., 2013). Interestingly, no discrimination impairments were found in these animals when testing highly divergent monomolecular odorants, although hippocampal-dependent spatial memory impairments were observed. Although discrimination of dissimilar odors was intact, impaired discrimination was

observed in an odor-association task using highly similar odorant mixtures in adult rats that were treated with chronic alcohol exposure throughout pregnancy (Akers et al., 2011). Recent human studies have also shown olfactory impairment in children with gestational alcohol exposure (Bower et al., 2013). There are multiple studies on olfactory impairments in humans as a result of heavy alcohol consumption during adulthood or adolescence, yet the systematic dissection of fetal alcohol-related olfactory deficiency toward understanding and diagnosing human FASD is a promising source that remains unexploited.

There are additional considerations to be made for the effects of fetal alcohol on olfaction beyond odorant encoding. There is a substantial amount of evidence from both studies in animals and humans that developmental alcohol exposure results in significant alterations in behavioral responsiveness and even preference to alcohol odor later in life (Chotro and Molina, 1990; Eade et al., 2010; Faas et al., 2000; Spear and Molina, 2005; Youngentob and Glendinning, 2009). Fetal alcohol exposure in humans may therefore influence an individual's chemosensory preferences that promote impulsive drinking behavior to perpetuate the FASD life-cycle.

The long-term circuit deficits caused by binge-modeled alcohol exposure in mice carry multiple indications of synaptic excitation/inhibition imbalance in multiple brain regions, including the piriform cortex (Sadrian et al., 2013). This general condition is shared by other common neurobehavioral pathologies, such as autism (Ramamoorthi and Lin, 2011) and schizophrenia (Yizhar et al., 2011), as well as neurodegenerative diseases like AD (Verret et al., 2012). It is therefore intriguing that each of these conditions, including FASD, has commonly been characterized by sensory processing deficits (Baker et al., 2008; Carr et al., 2010; Wengel et al., 2011). Behavioral adaptation during infancy and early childhood is heavily reliant on sensory cues (Sullivan, 2012) and therefore integration of this information into appropriate behavioral outputs becomes complicated in cases of FASD (Jirikowic et al., 2008). It is likely that sensory processing deficits common in FASD are as much of a contributor to the maladaptive executive capacities by which the disorder is commonly characterized, as they are a comorbidity. Connecting back to a significance for circuit excitatory imbalance in FASD, sensory-evoked refinement of inhibitory networks has been shown to promote a return to cortical excitation/inhibition balance (Dorrn et al., 2010; Hensch, 2005). A cognitive remediation sensory panel may therefore be a valuable addition to occupational therapy regimens delivered to those suffering from FASD.

3.2 Aging and Dementia

Loss of sensory system acuity is a common occurrence in the elderly. Whether it be detection threshold deficits or memory-associated deficits, elderly individuals often complain of not being able to see, hear, or smell the way they used to. While vision and audition have received a fair share of attention in the past and present, the olfactory sense is of particular interest for its involvement in a number of age-related dementing diseases, most notably AD. Though olfactory degradation is a part of normal aging, there is a difference in phenotype and severity between the type of decline in olfactory function seen in benign aging and dementing diseases such as AD. In fact, major deficits in olfactory detection, discrimination, and identification have recently been used as a way to detect the

possible presence of AD and distinguish it from normal aging and mild cognitive impairment (Bahar-Fuchs et al., 2011; Murphy, 1999; Nordin and Murphy, 1998; Rahayel et al., 2012).

Research into olfactory degradation in AD has focused on the relationship between pathology, anatomy, and resulting behavioral deficits. In order to better understand the systematic degradation of the olfactory system and how it relates to AD progression, it is important not only to understand the basic pathologies involved in AD but also how and through what avenues this pathology spreads through the olfactory cortical pathway. Though recent advances in neural imaging techniques have allowed researchers to better study AD pathology in the human population (Li et al., 2010a), animal models of the disease offer the unique opportunity to track, manipulate, and control aspects of AD pathology and its cognitive consequences that would otherwise be impossible. Therefore, discussions on the pathology and consequences of the disease made here are in the context of the aforementioned transgenic animal models.

Since it was first described by Alois Alzheimer in the beginning of the twentieth century (Alzheimer et al., 1995), AD has been characterized as a disease with two main pathologies: neurofibrillary tau tangles (NFTs) and amyloid-beta (Aβ) oligomers and plaques (Braak and Braak, 1996; Braak et al., 1993). Tau has been shown to play a role in the structural integrity of microtubules which function in maintaining neuronal structure, function, and transport throughout the brain (Weingarten et al., 1975). In AD, tau becomes hyperphosphorylated, leading to a breakdown of microtubule structure and function and causing dystrophic neurons that aggregate abnormally into NFTs (Iqbal et al., 1994). Meanwhile, Aβ, a by-product of amyloid precursor protein (APP), is produced from the cleavage of APP by gamma and beta secretase to produce Aβ protein of varying lengths, of which Aβ40 and Aβ42 are the most common (Vassar et al., 1999). In the healthy, aging brain, the ratio of Aβ40 to Aβ42 is roughly 90/10 (Lewczuk et al., 2004). However, as research into various forms of early onset or familial AD (FAD) has revealed, through a variety of factors including mutations in presenillin-1 (PS1) (Group, 1995) and PS2 (role in gamma secretase) (Shen and Kelleher, 2007; Sherrington et al., 1996), in the AD brain, this ratio is shifted toward a higher percentage of Aβ 42, often considered to be the more pathological species (Goate et al., 1991; Levy-Lahad et al., 1995; Lewczuk et al., 2004; Sherrington et al., 1995). Following cleavage, monomeric Aβ can aggregate into soluble dimers, trimers, and oligomers (Kamenetz et al., 2003) as well as insoluble Aβ-cored plaques. While amyloid plaques were once thought to be the most pathological form of the protein, recent reports show that oligomers may be a better predictor of pathology (Lue et al., 1999; McLean et al., 1999). It should also be noted that another component of APP cleavage are intracellular C-terminal fragments (Flammang et al., 2012). These APP intracellular domains (AICDs) have potent apoptotic and neuropathologies inducing effects which may contribute to AD pathology (Kogel et al., 2012; Konietzko, 2012; Schettini et al., 2010).

Though both Aβ accumulation and NFTs are prominent pathologies implicated in AD (Braak and Braak, 1996; Duyckaerts et al., 2009), here, because of the wide-spread use of rodent models of AD that carry FAD transgenes involved in the abnormal production of Aβ (for reviews, see Ashe, 2001; Elder et al., 2010; Guenette and Tanzi, 1999), we concentrate

our discussion of AD pathology on Aβ and its spread through the olfactory pathway in rodent models.

While progression of Aβ pathology through the olfactory pathway can at times be dictated by the specific animal model in question, for the most part, Aβ accumulation appears earliest in OB, followed by deposition in more rostral cortical areas. Research in our lab employing the Tg2576 mouse has demonstrated, more specifically, that Aβ accumulation in the olfactory pathway begins in the olfactory nerve/glomerular cell layer of the OB and spreads to the external plexiform, mitral/tufted cell, and inner plexiform layers before finally appearing in the granular cell layer. Other cortical downstream targets of OB are also affected later on in disease development including OFC, all layers of the anterior and posterior piriform cortex, and entorhinal cortex (Wesson et al., 2010, 2011).

Aβ deposition has been shown to disrupt targeting and connectivity of OSNs (Cao et al., 2012). Located in the olfactory epithelium, OSNs each express one out of about a thousand possible olfactory receptors (ORs) (Vassar et al., 1994). OSNs expressing the same OR normally innervate specific glomeruli in the OB. However, this targeting specificity is lost in the presence of Aβ. Cao et al. (2012) recently showed that OSNs in Tg2576 mice project to multiple glomeruli in OB as opposed to a specific glomerulus even in predepositing stages of development, which may be expected to dramatically impact odor coding even at this early stage of the pathway (Cheng et al., 2013).

In addition to mistargeting, Aβ pathology can also affect cell density and cell survival. Guerin et al. (2009) investigating predepositing Tg2576 found that the granule cell layer of the OB was thinner in these animals compared to WT and that this was due in part to a decrease in the rate of adult neurogenesis of granule cells coupled with an increase in the number of apoptotic cells in the area. Others have also reported thinner OB cell layers in other, more aggressive mouse models of AD (Cai et al., 2012).

Though research into the effects of Aβ pathology in the olfactory pathway has been highly focused on its effects in OB, Aβ pathology also affects more downstream regions of the olfactory pathway. Saiz-Sanchez et al., using the APP/PS1 mouse, found a decrease in the population of interneurons in olfactory tubercle, piriform cortex, and LEC that correlated with increasing Aβ and amyloid plaque pathology. More specifically, this group noticed a particular vulnerability of somatostatin and calretinin interneurons to Aβ, while parvalbumin expressing interneurons appeared more resistant to degradation (Saiz-Sanchez et al., 2012, 2013).

Recent research into the effects of Aβ on the morphology and cell populations of the different relays of the olfactory pathway demonstrate that, indeed, this protein has an adverse effect on neuronal survival and synaptic density and can certainly impact olfactory processing through this avenue. However, in addition to impacting neuronal structure, Aβ can also alter neuronal processing. Toward this end, electrophysiological research has uncovered a number of ways in which Aβ affects olfactory cortical information processing.

One of the most robust effects of early stages of Aβ deposition is neural circuit hyperexcitability. This hyperexcitability has been observed in both the hippocampal

formation (Busche et al., 2008, 2012; Palop et al., 2007) and the piriform cortex (Wesson et al., 2011) and can be expressed as both an increase in spontaneous single-unit activity (Xu and Wilson, 2012) and in enhanced or hypersynchronous local field potential oscillations (Wesson et al., 2011). Furthermore, in Tg2576 human APP mouse models, coherence of activity between the OB and piriform cortex is enhanced (Wesson et al., 2010, 2011), while coherence between bilateral OBs is disrupted (Liu et al., 2013). Importantly, reversal of Aβ deposition reverses olfactory system hyperexcitability (Wesson et al., 2011), strongly suggesting a causal link. It must be noted that the emergence of hyperexcitability within the olfactory system emerges before Aβ plaque formation, suggesting an important role for soluble Aβ oligomers or potentially AICD in this dysfunction. Finally, recall that loss of entorhinal cortical function also induces hyperexcitability in piriform cortex (Bernabeu et al., 2006; Chapuis et al., 2013). It is presently unclear how Aβ deposition within the entorhinal cortex may contribute to piriform cortical functional pathology. Aβ pathology in AD traditionally deposits first in the entorhinal cortex and has been shown to spread transsynaptically to connected areas (Braak et al., 1993; Harris et al., 2010), further suggesting the likely effect of pathology on the olfactory pathway.

While network function in the olfactory pathway seems to be disrupted, observations of single-unit olfactory processing in Tg2576 paint a different picture. Unpublished results from our lab (Xu and Wilson, 2012) demonstrate surprisingly that odor receptive field specificity of anterior piriform cortical single units remains unchanged in Tg2576 mice, even after extensive amyloid deposition and plaque formation. This would suggest limited effects of early stages of Aβ deposition on basic odor discrimination (Phillips et al., 2011).

Olfactory discrimination is the ability to distinguish whether one odor is different than another. The highest order of olfactory function and one which uniquely involves higher-order cognitive function is olfactory identification. Odor identification is the ability to assign a specific designation to a specific odorant stimulus. While all aspects of odor perception can be impaired in AD, a problem with odor identification is the earliest to emerge and can be present even in those simply predisposed to AD (Calhoun-Haney and Murphy, 2005; Murphy, 1999).

Given its importance as a possible early marker for AD (Bahar-Fuchs et al., 2011; Nordin and Murphy, 1998), startlingly little research has been conducted to investigate the effects of Aβ pathology on olfactory functioning in rodent models. What has been done has been spread across a number of different rodent models and at a number of different points in the development of AD pathology. Unsurprisingly, results have often been mixed with respect to the severity and type of olfactory dysfunction present. As mentioned above, Aβ or human APP expression in mouse OSNs, which can disrupt axon targeting of OB glomeruli, can impair odor discrimination (Cao et al., 2012; Cheng et al., 2013). This seems a reasonable consequence of damage to this peripheral in the sensory stream.

However, more centrally the effects are less clear. Cassano et al. (2011) reported impaired olfactory memory but intact discrimination in the 3×Tg mouse model assessed at 18 months of age. These animals demonstrated robust accumulation of Aβ as well as tau pathology in OFC, piriform cortex, and entorhinal cortex but not in OB (Billings et al., 2005; Oddo et al.,

2003a,b). Vloeberghs et al. (2008), investigating olfactory function in APP23 mice at 3–12 months of age, found no apparent dysfunction in odor detection. These animals demonstrate accumulation of Aβ in hippocampus, thalamus, and entorhinal cortex as well as a cerebrovascular Aβ phenotype (Kuo et al., 2001; Phinney et al., 1999). Guerin et al. (2009) using the often employed Tg2576 mouse found no apparent odor detection deficits but pronounced odor habituation changes at 7 months of age despite a lack of Aβ accumulation in any brain region. Our group using the same mouse model found similar results in odor habituation beginning at 6 months of age (Wesson et al., 2010, 2011, 2013). Preventing or reversing the Aβ accumulation restored normal odor habituation (Cramer et al., 2012; Morales-Corraliza et al., 2013; Wesson et al., 2011, 2013; Yang et al., 2011), while inducing damage to the locus coeruleus noradrenergic system exacerbated them (Rey et al., 2012). Finally, in a test of hippocampal-dependent odor memory, Young et al. (2009) found that as Tg2576 aged, they were able to remember fewer odors and made more errors in an odor span task designed to assess working memory for 12–22 odors.

Thus, central (nonolfactory sensory neuron) Aβ accumulation in mice appears to affect odor habituation and hippocampal odor memory, but has limited effects on odor discrimination *per se*. Unpublished longitudinal data from our lab examining discrimination of overlapping mixtures in Tg2576 mice support this view (Xu et al., 2013). The lack of impairment in behavioral odor discrimination aligns well with our preliminary observation of maintained piriform cortical single-unit odor receptive fields (Xu et al., 2013). But, then why is olfaction so strongly impaired in human AD? We propose that current assays of olfactory perception in rodents are not effective assays of human odor identification—the most sensitive indicator of aging-related pathology in humans (Albers et al., 2006; Doty, 2012; Murphy, 1999). Odor identification and naming in humans are remarkably complex processes involving a variety of cortical regions beyond the olfactory system (Olofsson et al., 2013). Thus, while mouse models will remain powerful tools for understanding mechanisms and potential treatments for AD-related neuropathology, better behavioral assays are required to bridge the gap between discrimination and identification.

4 SUMMARY

While events at the OR sheet and olfactory bulb are required for odor perception, the events that most closely drive odor-guided behavior and, in humans, conscious odor perception occur in the cortex. The olfactory system has not only unique, direct access to limbic and subcortical structures within 1–2 synapses from the OSNs but also similar immediate access to prefrontal cortex. There is emerging evidence that each of these divergent cortical regions may differentially contribute to the overall perception and quality of odors.

There are many unresolved issues regarding how cortex contributes to odor perception and memory. For example, several human imaging studies have identified lateralization in olfactory cortex (Royet and Plailly, 2004), with, for example, potential hemispheric specialization for odor memory and odor hedonics. Lateralization in nonhuman olfaction is largely unexplored. Similarly, mechanisms of odor attention and expectation on perception and cortical function are only recently receiving experimental attention in humans (Keller, 2011; Plailly et al., 2008; Tham et al., 2011b; Veldhuizen and Small, 2011; Zelano et al.,

2011) and to a lesser extent in nonhuman animals. The role of top-down inputs on odor coding in more peripheral regions will help identify mechanisms of these more complex cognitive issues (Chapuis et al., 2013; Markopoulos et al., 2012).

Perhaps most noteworthy of these unresolved issues is the dichotomy between a sensory system that is strongly resilient to central physical insult for basic odor detection and discrimination (McBride and Slotnick, 2006; Slotnick and Kaneko, 1981; Slotnick et al., 2004), yet is remarkably fragile in the face of a wide range of neurological disorders. We propose that much of this fragility reflects the tenuous nature of the link between odor quality perception and odor identification. Identifying adequate animal models of odor identification, which go beyond basic discrimination, will be essential for understanding how olfaction works, and what goes wrong when it does not.

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