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Assessment of direct knowledge of the human olfactory system.

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Introduction

The olfactory system is highly conserved across mammalian species (Ache and Young, 2005; Gelperin, 1999; Hildebrand and Shepherd, 1997; Laurent, 2002). In particular, the human and rodent olfactory systems share numerous common traits, including the basic organization of the olfactory central nervous system, aspects of odor guided behaviors, the nature of odorant receptor proteins, and processing at the molecular and synaptic levels (Fig. 1). These shared characteristics make rodents an excellent model for use in understanding the human olfactory system and has led to widespread use of rodents in olfactory studies. As a result, knowledge of the rodent olfactory system is expansive, and has been the primary guide to human olfactory research for decades. Though the olfactory systems of the two species are highly similar (Ache and Young, 2005), some differences are apparent (Mainland et al., 2014; Maresh et al., 2008; McGann, 2017; Trimmer et al., 2019), and direct data from humans is lacking. Our current understanding of the human olfactory system relies substantially on inferences from direct knowledge obtained in rodents. Inferring from rodents is well justified, and has moved the field of human olfaction forward. However, within the growing human olfaction literature, it is often unclear which statements are inferred from rodent work, and which are directly from human data. In a field dominated by rodent studies, and in order to avoid confusion and compounded misstatements, there arises a periodic need to assess the state of direct knowledge of the human olfactory system. Our goal here is to provide a thorough review of olfactory literature in order to assess and clarify our current direct knowledge of the human olfactory system, as compared to the rodent olfactory system.

In particular, direct knowledge of the rodent olfactory system has far out-paced direct knowledge of the human olfactory system, leaving large gaps in our relative knowledge of the human olfactory system. By identifying these deficits in human olfactory knowledge, we hope to provide some guidance for future work that will help close these gaps. Here, we argue this point by providing a review of the current knowledge of the rodent and human olfactory systems, highlighting similarities and differences across species, and particularly highlighting unknowns in the human system. A critical examination of confirmed versus

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inferred features of the human olfactory system will help identify particularly large gaps in this knowledge.

We also emphasize the clinical importance of obtaining direct knowledge of the human olfactory system. Olfaction is profoundly involved in a broad range of neuropathology, but our understanding of the mechanisms of this involvement is poor.

Neurodegenerative diseases often present with early olfactory symptoms in humans (Albers et al., 2006; Barresi et al., 2012; Doty, 2012; Godoy et al., 2015; Hawkes, 2003; Mesholam et al., 1998; Ross et al., 2008), and olfactory loss is a strong predictor of life expectancy (Devanand et al., 2015; Ekström et al., 2017; Pinto et al., 2014; Schubert et al., 2016). Both human and rodent work has implicated olfactory structures in Parkinson's disease (Doty, 2012; Ubeda-Bañon et al., 2014; Westermann et al., 2008), and there is also significant research from both species suggesting that olfactory cortical structures may be involved in seizure generation for some forms of epilepsy (Espinosa-Jovel et al., 2019; Galovic et al., 2019; Laufs et al., 2011; Menassa et al., 2017; Vaughan and Jackson, 2014; Vismer et al., 2015; Young et al., 2018).

In this article, we will review the current state of direct knowledge about each cortical structure of the human olfactory system. To maintain distinctions between the human and rodent systems, we will review each olfactory structure separately for each species, followed by a brief comparison of the two in order to elucidate how well the structure corresponds across species. We include a particularly thorough discussion of piriform cortex, which is the largest subregion of primary olfactory cortex, and the olfactory area most implicated in epilepsy.

Olfactory Bulb

The olfactory bulb is the first site of olfactory processing and refinement. It receives projections from olfactory sensory neurons in the olfactory epithelium located inside the nasal cavity, whose axons project into glomeruli—spheroid units which are the site of synapses between the terminals of olfactory sensory neurons and dendrites of olfactory bulb cells, including mitral, tufted and periglomerular cells—in the bulb.

Rodent: The rodent olfactory bulb has been studied extensively. It has a clear laminar organization (Inaki et al., 2004; Macrides and Schneider, 1982; Nagayama et al., 2014), and contains a distinct layer of glomeruli situated in a regular layer that spans the entire circumference of the bulb. Each olfactory sensory neuron innervates a single glomerulus (or two) per half-bulb (Mombaerts, 2004), and each glomerulus is innervated only by sensory neurons expressing the same type of receptor (Firestein, 2001; Mombaerts, 1999), enabling a powerful convergence of input. In line with this organization, the total number of glomeruli in the bulb is about twice the number of receptor types found in the epithelium.

Numerous studies suggest that the rodent bulb forms odor representations through a spatiotemporal combinatorial pattern of activated glomeruli that is unique for each odor (Bathellier et al., 2008; Buck, 2004; Firestein, 2001; Fletcher et al., 2009; Haddad et al., 2013; Johnson et al., 1998; Kauer and White, 2001; Leon and Johnson, 2003; Mombaerts, 1999; Mori et al., 1999; Rubin and Katz, 1999; Spors et al., 2006; Spors and Grinvald, 2002; Xu et al., 2003; Youngentob et al., 2006). Another salient feature of the rodent bulb, on which there is extensive literature, is the presence of regular local field potential oscillations in several frequency bands. These oscillations have been associated with specific sensory, motor, and behavioral events (Beshel et al., 2007; Buonviso et al., 2003; Chery et al., 2014; Galán et al., 2006; Gray and Skinner, 1988; Kay, 2003; Kay et al., 2009; Lledo et al., 2004; Manabe and Mori, 2013; Martin et al., 2004; Ravel et al., 2003). The most prominent olfactory bulb oscillatory rhythm is the respiratory rhythm, which shapes the bulbar odor response (Fontanini et al., 2003; Fontanini and Bower, 2006, 2005; Schoppa and Westbrook, 2001; Spors and Grinvald, 2002; Tort et al., 2018; Tristan et al., 2009). There is also mounting evidence that olfactory bulb responses are modulated by noradrenergic (Doucette et al., 2007; McLean et al., 1989; Shea et al., 2008; Shipley et al., 1985), cholinergic (Ichikawa and Hirata, 1986; Liu et al., 2015; Nunez-Parra et al., 2013; Ojima et al., 1988; Rothermel et al., 2014) and serotonergic input (Brunert et al., 2016; Kapoor et al., 2016; Petzold et al., 2009), from the locus coeruleus, the basal forebrain and the Raphe, respectively. Thus output of the rodent olfactory bulb is impacted by both contextual cues and internal states (Doucette et al., 2007; Pager, 1974).

Throughout the lifespan, the olfactory system is a major site of neurogenesis in the rodent brain, with both sensory neurons and bulbar interneurons replaced at a rate of thousands per day (Alvarez-Buylla et al., 2001; Brann and Firestein, 2014; G. A. Graziadei and Graziadei, 1979; P. P. Graziadei and Graziadei, 1979; Lois and Alvarez-Buylla, 1994; Loo et al., 1996; Ming and Song, 2005). Neuroblasts move within cerebrospinal fluid, from the stem cell production sites in the subventricular zone to the olfactory bulb. Stem cells in the olfactory epithelium generate new sensory neurons. It has been suggested that this is due in part to the fact that olfactory sensory neurons are exposed and experience significant environmental stress (Sammeta and McClintock, 2010).

Human: The human olfactory bulb has not been as well characterized as its rodent counterpart. Similar to rodents, it has a laminar organization (Burmeister et al., 2012; Maresh et al., 2008; Zapiec et al., 2017). However, unlike rodents, the distinction between layers is not rigorous, and varies across individuals (Maresh et al., 2008). The spatial distribution of glomeruli in the human olfactory bulb is irregular and complex. The glomerular layer does not extend around the full circumference of the bulb (Hoogland et al., 2003; Maresh et al., 2008; Zapiec et al., 2017), and glomeruli are sometimes found at deep locations that invade other layers (Hoogland et al., 2003; Maresh et al., 2008; Zapiec et al., 2017). Human glomeruli also have highly variable volumes and shapes (Hoogland et al., 2003; Maresh et al., 2008; Zapiec et al., 2017).

It is still unknown how human olfactory sensory neurons map onto the bulb, and therefore we lack a basic understanding of what a human glomerulus represents (Zapiec et al., 2017). A topic of much interest is the total number of glomeruli contained in the human olfactory bulb. Due to their irregular shapes and sizes, it is difficult to unambiguously identify distinct glomeruli in sections or in 3D reconstructions (Zapiec et al., 2017). Due to these considerations, a definitive, exact count of glomeruli in the human bulb is still lacking. It appears likely, however, that it contains a surprisingly large number of glomeruli, especially in relation to the number of olfactory sensory neurons, with estimates averaging above 5,500, and ranges in number to above 10,000 (Maresh et al., 2008; Zapiec et al., 2017). Since there are around 400 olfactory sensory neuron types in the human genome, the ratio of 2–3 glomeruli per olfactory receptor type, which has been established in rodents, may not apply in humans. This suggests that there may be a fundamentally different organization of human glomeruli compared to rodent counterparts. Despite these possible differences in overall organization of glomeruli, odor processing appears to be identical at the molecular and synaptic levels in the bulb across species (Maresh et al., 2008). No studies have examined spatial activation patterns in the human bulb. Very few studies have examined oscillatory dynamics of local field potentials in the human bulb (Hughes et al., 1970; Iravani et al., 2019; Sem-Jacobsen et al., 1953), with just a handful of studies reporting odor-evoked oscillations in the theta (Hughes et al., 1970), beta (Hughes et al., 1970) and gamma (Iravani et al., 2019) ranges, similar to rodents. Moreover, the relationship between these local field potential dynamics and sniff cycles is not yet clear.

It is a matter of significant controversy whether neurogenesis takes place in the human olfactory bulb, with high-profile publications reporting contradictory results (Curtis et al., 2007; Sanai et al., 2004). It is generally agreed that human glomeruli degrade over the human life span, leading to reduced olfactory perceptual function (Doty and Kamath, 2014; Smith, 1942). Loss of olfactory function has also been observed in early stages of numerous degenerative diseases (Adams et al., 2018; Del Tredici et al., 2002; Demarquay et al., 2007; Doty, 2017; Godoy et al., 2015; Hüttenbrink et al., 2013; Pinto et al., 2014; Whitcroft et al., 2017; Wilson et al., 2011), and has been linked to life expectancy (Devanand et al., 2015; Ekström et al., 2017; Pinto et al., 2014; Schubert et al., 2016). However, with so few studies measuring the integrity of the human glomerular layer, it is not clear whether loss of olfactory function relates to degradation of the glomerular layer in the human bulb. Notably, a careful review of an early pioneering study by Carlton G. Smith (Smith, 1942), which quantified the degree of glomerular degradation in more than 200 human olfactory bulbs, found that some humans across a broad age range—including above the age of 80—showed absolutely no loss of glomeruli. [Footnote: See also Liss and Gomez (1958), in which bulbs from a patient over 100 years showed only mild neuronal loss, and no correlation between bulbar degeneration and age was found; and Bhatnagar et al. (1987), where the volume of a 102-year-old’s glomerular layers was found to be among the largest of all ages examined.] This finding may have been somewhat lost within the field, as the published paper broadly concluded that human glomeruli degrade with age at an average rate of about 1% a year. Though this general conclusion is true, closer inspection of the original data (Fig. 2) revealed a number of aged bulbs showing no glomerular loss, including some over the age of 80 (Fig. 2, **red box**). Put another way, some 80-year-olds have glomeruli that are indistinguishable from those of a 15-year old. We can think of two possible explanations for this. One is that the glomeruli in the olfactory bulbs of these individuals do not degrade, for either environmental or genetic reasons. The other is that olfactory neurogenesis occurs over the lifetime of these individuals, but not (or lesser so) in those whose glomeruli show degeneration. The finding that glomerular layer integrity is preserved in some individuals deserves reconsideration within the olfactory community, and the mechanisms behind it investigated, as it may have profound clinical implications.

Comparison—The rodent and human olfactory bulbs both receive projections from sensory neurons in the olfactory epithelium inside the nasal cavity, through the cribriform plate. Both human and rodent bulbs exhibit an overall laminar organization, but the layers are less rigorous and lacking in symmetry in humans compared to rodents. Both the human and rodent bulbs exhibit glomerular compartmentalization, indicating similar organization and features of glomerular synapses across species (Maresh et al., 2008). Aside from these similarities, there are indications of potentially dramatic differences between rodents and humans in the overall organization and number of glomeruli. Human glomeruli are patchy, variable in size and shape, and intrude into deep layers of the bulb. In stark contrast, rodent glomeruli are highly regular and symmetrically positioned around the entire bulb circumference (Hoogland et al., 2003; Maresh et al., 2008; Zapiec et al., 2017). There also appear to be a surprisingly large number of glomeruli in the human bulb relative to the number of distinct olfactory receptor types found in the epithelium, perhaps on the order of a ten times higher ratio than is found in rodents. This suggests likely differences in the organization of axon convergence from the epithelium to the bulb across species. The human bulb also exhibits wide variations in morphology that do not correlate with age on autopsy (Bhatnagar et al., 1987; Hoogland et al., 2003; Maresh et al., 2008; Smith, 1942; Zapiec et al., 2017), and a recent study found normal olfactory abilities in humans with no observable olfactory bulbs on MRI scans (Weiss et al., 2020), suggesting wide individual variation in the overall shape of the human olfactory bulb. Given these differences in the spatial organization of the glomerular layer, and number of glomeruli across species, we suggest caution in inferring rodent findings of odor-evoked spatial patterns and electrophysiological signatures to humans. It is possible that the human bulb may exhibit very different odor-evoked responses, in both their spatial and oscillatory characteristics. Notably, it is worth mentioning that environmental differences between laboratory animals and naturally behaving animals, including humans, may also contribute to the stark observed differences. Specifically, rodents in the lab come from particular strains, and are housed in ventilated, climate-controlled, pathogen-free environments with highly consistent olfactory exposures (Zapiec et al., 2017). By contrast, humans experience a much broader range of olfactory exposures, toxins, viruses, and aging. The extent to which these living conditions may drive observed differences across species is unknown. Therefore, these differences should be considered when drawing conclusions from existing studies.

Olfactory cortex:

Mitral and tufted cells in the olfactory bulb project monosynaptically, without relaying through the thalamus, onto a number of brain regions which have been collectively defined as primary olfactory cortex (Carmichael et al., 1994; Price, 2009, 1990). Olfactory cortical targets of mitral and tufted cells appear to differ in rodents (Ghosh et al., 2011; Nagayama et al., 2010; Shipley et al., 2004). The extent to which the cortical targets of mitral and tufted cells differ in humans is unknown. In general, olfactory cortical regions are better defined in rodents compared to humans, in both their structures and functions. However, we do not have a complete understanding of the functional role that each of these cortical areas plays in olfactory processing in either species. Here we will discuss the major primary olfactory cortical structures present in both rodents and humans, including the anterior olfactory nucleus, the olfactory tubercle, amygdala, entorhinal cortex and piriform cortex.

Olfactory cortex: Anterior olfactory nucleus

The lateral olfactory tract—the bundle of nerves containing mitral and tufted cell axons—projects first to the anterior olfactory nucleus (AON), which is the anterior/rostral-most cortical olfactory structure, in both rodents and humans. It is a complex structure that has not been well characterized in either species, and its function in olfactory processing is not well understood. It is generally agreed that the AON is in fact a cortical structure, despite its name (Allison, 1954; Haberly, 2001; Haberly and Price, 1978; Rose, 1926; Scott and Harrison, 1987; Shipley and Ennis, 1996), and therefore the term "anterior olfactory nucleus" has been challenged (Brunjes et al., 2005; Haberly, 2001).

Rodent: In rodents, the AON is divided into two main zones based on Nissl staining, the pars externa and the pars principalis. The pars externa is a thin, dense ring of cells at the rostral end of the AON, and the pars principalis encompasses the rest of the structure (Brunjes et al., 2005; Valverde et al., 1989). The pars principalis has been further subdivided into dorsal, ventral, medial and lateral divisions, but their exact borders are variable and somewhat arbitrary across studies (Davis and Macrides, 1981; de Olmos et al., 1978; Haberly and Price, 1978; Herrick, 1948, 1924; Price, 1973; Valverde et al., 1989; Young, 1936). There is considerable heterogeneity within the AON, in terms of anatomical and functional subdivisions, cell morphology and neurochemical phenotypes (Brunjes et al., 2005; Illig and Eudy, 2009). This suggests the region likely has a complex role in olfactory processing (Brunjes et al., 2005), though it has historically been assumed to function as a simple intermediate relay between the bulb and cortical areas (Lledo et al., 2005). Studies suggest there are topographically defined projections from the bulb to the pars externa (Lledo et al., 2005; Scott et al., 1985), but these do not appear to be maintained in the remainder of the AON (Kay et al., 2011; Miyamichi et al., 2011). However, the entire AON does appear to maintain the dorsal-ventral topography of the bulb (Miyamichi et al., 2011). Rodent studies suggest the pars externa is involved in odor localization (Esquivelzeta Rabell et al., 2017; Kikuta et al., 2010), and it forms symmetrical mirrored connections between the two bulbs (Grobman et al., 2018; Yan et al., 2008). The medial aspect of the pars principalis could be involved in top-down modulation of bulbar responses (Aqrabawi et al., 2016). More broadly, rodent studies suggest a role for the anterior olfactory nucleus in the initial formation of representations of odor objects—complex odor stimuli processed as unique percepts (Haberly, 2001; Lei et al., 2006; Thomas-Danguin et al., 2014)— allowing higher cortical structures to perform more associative functions, relating information about odor objects to movement and behavior.

Human: The human AON has been only scarcely studied. Broadly, the anatomy of the human AON does not appear to closely correspond to the rodent AON. Early anatomical studies reported that the human AON does not include a pars externa (Crosby and Humphrey, 1941; Crosby and Humphrey, 1939). It has been divided into retrobulbar, cortical anterior and cortical posterior subdivisions (Mai et al., 2015; Öngür et al., 2003; Ubeda-Bañon et al., 2017). Like the rodent AON, the human AON is a true cortical structure (Zilles and Amunts, 2012). The topography of bulb projections into the human AON is still unknown, and its cell morphology has not been thoroughly characterized (Allison, 1954; Crosby and Humphrey, 1939). Though no studies have specifically examined the olfactory function of the human AON, a recent study found unique functional connectivity between the AON and brain areas involved in object recognition (Zhou et al., 2019a), in accordance with earlier suggestions that the AON is involved in olfactory object formation in rodents (Haberly, 2001; Lei et al., 2006).

Though the specific function of this region in human olfactory processing is not known, several studies have implicated the human anterior olfactory nucleus as a key early site of pathological changes in neurological diseases, including Parkinson’s Disease and Alzheimer’s disease (Del Tredici et al., 2002; Marin et al., 2018; Pearce et al., 1995; Saiz-Sanchez et al., 2010; Ubeda-Bañon et al., 2017, 2014), emphasizing the potential clinical importance of future studies of the AON in humans.

Comparison: There is a strong need for more studies on both rodent and human AON. With so little data on the human AON in particular, it is difficult to draw meaningful comparisons of this structure across species. It is possible that the pars principalis is functionally similar across species, but the apparent lack of a pars externa in humans suggests significant differences in functionality of this region. The pars externa is thought to be involved in olfactory lateralization in rodents (Esquivelzeta Rabell et al., 2017; Kikuta et al., 2010). Its absence in humans may account for poor human performance in lateralizing olfactory stimuli with no trigeminal component (Frasnelli et al., 2010, 2008; Kobal and Hummel, 1992; Moessnang et al., 2011; Porter et al., 2005; Radil and Wysocki, 1998; Sorokowski et al., 2019; Wysocki et al., 2003). Rodent studies suggest a potential role for the AON in odor object formation (Aqrabawi and Kim, 2018; Haberly, 2001), and human resting functional connectivity data support this hypothesis (Zhou et al., 2019a).

Olfactory cortex: Olfactory tubercle:

The olfactory tubercle is a recipient of direct bulbar input, and along with the nucleus accumbens, constitutes the ventral striatum. As such, the majority of research on the olfactory tubercle has been conducted in the context of reward, rather than olfaction (Ikemoto, 2007). Thus the role of the olfactory tubercle in olfactory processing is not well understood.

Rodent: In rodents, the olfactory tubercle occupies a relatively large aspect of the basal forebrain (Giessel and Datta, 2014; Millhouse and Heimer, 1984; Wesson and Wilson, 2010). The tubercle is a cortical structure, though unlike other olfactory cortical areas, it does not possess an association fiber system (Haberly and Price, 1978). It can be divided into two main components: a cortical zone and a cap/hilus zone (Wesson and Wilson, 2010; Millhouse and Heimer, 1984). Projections from the olfactory bulb to the tubercle consist mainly of tufted, as opposed to mitral, cells (Giessel and Datta, 2014; Wesson and Wilson, 2011). Since tufted cells show enhanced odor sensitivity, enhanced respiratory entrainment and broader receptive fields compared to mitral cells (Mori and Shepherd, 1994; Shepherd et al., 2004), the olfactory tubercle may be important for olfactory tasks requiring high sensitivity. Indeed, rodent studies suggest potential roles for the tubercle in odor discrimination (Murakami et al., 2005; Wesson and Wilson, 2010), olfactory multisensory integration (Wesson and Wilson, 2010) and state-dependent modulation of olfactory bulb activity (Gervais, 1979). Studies also suggest a role for the rodent olfactory tubercle in sensory hedonics and social behavior (Gervais, 1979; Hitt et al., 1973). These data suggest the olfactory tubercle is an integral structure for processing olfactory information.

Human: The human olfactory tubercle is a relatively small structure that has not been well defined either anatomically or functionally. In general, its broad characteristics are similar to the rodent tubercle (Allison, 1954). On the surface of the brain it shows two distinct parts: one, adjacent to the olfactory tract, is smooth and rounded; the other is perforated by many small blood vessels. These likely correspond to the cortical and cap/hilus zones in the rodent. The characteristic lamination is most conspicuous in the anterolateral part, and this breaks up more medially (Allison, 1954). It is not known whether the human tubercle receives more tufted, as opposed to mitral, cell projections from the bulb. Few human studies have examined the function of the tubercle in olfactory processing, though it may be involved in odor reward value coding (Howard et al., 2016), olfactory attention (Zelano et al., 2005) and determination of the source of olfactory information (trigeminal versus olfactory) (Zelano et al., 2007). Resting-state functional magnetic resonance imaging (fMRI) data suggest unique functional connectivity between the olfactory tubercle and brain areas that are involved in emotional processing, depression, and social cognition, including anterior paracingulate cortex, left frontal pole and the left fusiform gyrus (Zhou et al., 2019a), consistent with early rodent data suggesting a role for the tubercle in hedonics and social cognition.

Comparison: Broadly speaking, the rodent and human olfactory tubercle appears similar, with both containing two distinct zones. However, with so little data collected from the human tubercle, we do not know how well these zones correspond across species. While the rodent tubercle receives exclusively tufted cell projections from the bulb, we do not know if this is the case in humans. We are also lacking electrophysiological data from the human olfactory tubercle, and there have only been a handful of descriptive, early anatomical studies that describe it. Interestingly, human studies found functional connectivity between the olfactory tubercle and brain regions that exhibit known tubercle-connectivity in rodents, including the mediodorsal thalamus, the nucleus accumbens and the raphe nuclei in the brainstem (Zhou et al., 2019a). This suggests similar functional profiles across rodent and human olfactory tubercle, however more research is needed on the human tubercle to confirm these similarities.

Olfactory cortex: Amygdala:

The amygdala is comprised of numerous subregions, a subset of which receive direct input from the olfactory bulb. The amygdala has been studied extensively as a region critical for emotional processing and learning, and threat detection. Its role in olfactory processing is less understood, despite the fact that several of its subregions are considered part of primary olfactory cortex.

Rodent: In rodents, the olfactory bulb sends projections to several amygdalar subregions, including the posterolateral cortical amygdala, the anterior cortical amygdala, the medial nucleus of the amygdala, the periamygdaloid cortex and the nucleus of the lateral olfactory tract (de Olmos et al., 1978; Devor, 1976; Ennis et al., 2014; Iurilli and Datta, 2017; Martinez-Marcos and Halpern, 2006; Miyamichi et al., 2011; Pro-Sistiaga et al., 2007; Scalia and Winans, 1975; Skeen and Hall, 1977; Sosulski et al., 2011; Ubeda-Bañon et al., 2007). The posterolateral cortical amygdala receives the most projections from the bulb (Iurilli and Datta, 2017), with significantly fewer connections reaching the other subregions. The amygdala also receives input from the accessory olfactory bulb, which is important for innate social and olfactory guided behaviors in rodents (Edwards, 1974; Feierstein et al., 2010; Luo et al., 2003; Murphy and Schneider, 1970; Wilson et al., 1987). Accessory olfactory information mainly reaches the medial nucleus of the amygdala and the posteromedial cortical amygdala (Dulac and Wagner, 2006; Guthman and Vera, 2016; Keshavarzi et al., 2015; Pardo-Bellver et al., 2017; Raisman, 1972). The majority of rodent studies on olfactory amygdala subregions have focused on the accessory olfactory system. These studies suggest that the medial amygdala represents olfactory social information (Ying Li et al., 2017), and plays a key role in predator-odor-induced innate fear behaviors (Takahashi, 2014). Studies have also shown that medial amygdala is involved in innate approach and avoidance behaviors, through divergent projections that regulate each behavior (Miller et al., 2019). Amygdala studies focusing on the main olfactory system are fewer in number, and have focused mainly on the cortical amygdala. These studies suggest the cortical amygdala also participates in innate, odor-driven behaviors (Root et al., 2014), potentially through a preserved bulb-to-amygdala topographical map (Sosulski et al., 2011). However, a more recent study concluded that the cortical amygdala exhibits a distributive odor coding mechanism (Iurilli and Datta, 2017). Very little is known about the periamygdaloid cortex, and it has inconsistent naming conventions across studies and species. Finally, the nucleus of the lateral olfactory tract is the smallest of the cortical olfactory amygdala areas, and recent studies suggest that it may be required for normal olfaction and that it undergoes neuroplastic changes during chronic stress (Vaz et al., 2017).

Human: In humans, direct evidence has shown that the olfactory bulb sends monosynaptic projections to the anterior cortical amygdala, the medial amygdala, the periamygdaloid cortex (Allison, 1954; Crosby and Humphrey, 1941; Gonçalves Pereira et al., 2005). In addition, descriptive evidence from humans and indirect evidence from monkeys strongly suggests that the nucleus of the lateral olfactory tract receives direct projections as well (Allison, 1954; Crosby and Humphrey, 1941), though this remains to be shown directly. It has been suggested that the human nucleus of the lateral olfactory tract may be divided into rostral and caudal nuclei (Crosby and Humphrey, 1941), which has been observed in monkeys, rabbits and bats (Meyer and Allison, 1949). The central nucleus and the bed nucleus of the stria terminalis likely receive bulb projections in monkeys (Meyer and Allison, 1949); though unknown, it is possible that this is also the case in humans. Notably, these areas have not been well-defined in humans, and the precise location and extent of bulbar projections into these areas has not been quantified. Though olfactory involvement in the amygdala as a whole has been investigated, few human studies have considered the olfactory subregions separately, and therefore we know very little about the specific functions of these areas in human olfaction. Functional neuroimaging studies suggest the amygdala may represent odor intensity and valence (Anderson et al., 2003; Jin et al., 2015; Winston et al., 2005), though in these studies, fMRI signals were combined across subregions. Intracranial EEG (iEEG) studies suggest that the amygdala is involved in odor coding (Hudry et al., 2003; Jiang et al., 2017), and iEEG and electrical stimulation studies suggest a role in nasal respiratory control mechanisms (Zelano et al. 2016; Nobis et al. 2018; Nobis et al 2019).

Comparison: The projections from the olfactory bulb to the amygdala may constitute some of the biggest differences between rodents and humans in the central organization of the olfactory system. This is not only because the rodent bulb projects to a larger number of subregions, but also because the rodent amygdala receives heavy input from the accessory olfactory system, which humans lack (Meredith, 2001). Additionally, the olfactory amygdala subregion receiving the most bulbar projections in rodents is the posterolateral cortical amygdala, whereas in humans, it is the anterior cortical amygdala. Despite these differences, there are indications of potential similarities across species. For example, human studies have found valence and intensity coding in the amygdala, and a potential role in nasal respiratory control, which, taken together, may be analogous to rodent amygdala roles in approach-avoid behaviors. There is a need for more human studies aimed at quantifying the number and location of olfactory projections into the amygdala, and for more human studies aimed at deciphering the unique role that each subregion plays in olfactory processing.

In clinical terms, olfactory amygdala subregions have been implicated in respiratory control; rodent studies have established anatomical connections between respiratory centers in the brainstem and the amygdala (Hopkins, 1975). Human studies have found that electrical stimulation of human amygdala disrupts nasal breathing (Dlouhy et al., 2015; Lacuey et al., 2017; Nobis et al., 2019, 2018). A deeper understanding of the role of amygdalar subregions in human respiration has particular importance to patients with epilepsy, given its potential relevance to sudden unexpected death in epilepsy (SUDEP), a leading cause of death in epilepsy (Bateman et al., 2010; Dlouhy et al., 2015; Ryvlin et al., 2013).

Entorhinal cortex: The entorhinal cortex, a multi-sensory area, is the main interface between the neocortex and the hippocampus, and is important for memory, navigation and the perception of time (Fyhn et al., 2004; Jessen et al., 2006; Suzuki et al., 1997) The entorhinal cortex is engaged at an earlier stage of processing in the olfactory system compared to other sensory systems, because it receives direct input from the olfactory bulb.

Rodents: In rodents, the olfactory bulb sends projections that cover the entire extent of entorhinal cortex (Insausti et al., 2002). Each of the entorhinal cortical subfields projects in a topographical manner onto the hippocampus. Relatively few studies have focused specifically on the role of entorhinal cortex in olfactory processing, though it appears that the medial and lateral entorhinal cortices may have distinct functions. While the medial entorhinal cortex is critical for spatial navigation, with a prominent role in grid cell coding (Doeller et al., 2010; Hafting et al., 2005; Stensola et al., 2012; Zhang et al., 2013), the lateral entorhinal cortex encodes other stimulus features, including olfactory information, with importance in olfactory memory, discrimination and associative learning (Chapuis et al., 2013; Igarashi et al., 2014; Leitner et al., 2016; Xu and Wilson, 2012; Young et al., 1997). It was recently demonstrated that the direct, lateral entorhinal cortex-to-hippocampal

CA1 pathway is required for olfactory associative learning, highlighting a key role for this region in olfactory associative learning (Yiding Li et al., 2017).

Human: Very few studies have focused on the human olfactory entorhinal cortex (Beall and Lewis, 1992; Krimer et al., 1997). Experimental evidence for a direct human bulb-entorhinal connection is still lacking, though strong but indirect evidence exists, in the identification of a distinct rostromedial subfield that shows similarities with the olfactory entorhinal area in monkeys (Insausti et al., 1995) (also see EO in Mai et al. 2015). Unlike rodents, the human olfactory bulb projections into entorhinal cortex likely do not cover the entire region, but appear to focus on a small subregion comprising approximately 15% of the entorhinal cortex. Aside from a small collection of functional neuroimaging studies that have identified odor-responsiveness in the entorhinal cortex (Bensafi et al., 2008; Gottfried et al., 2002a; Levy et al., 1997; Poellinger et al., 2001; Wang et al., 2005; Zald and Pardo, 2000; Zelano et al., 2007), few studies have directly examined its role in olfactory processing. That said, a recent study found grid-like representations in entorhinal cortex during olfactory spatial navigation (Bao et al., 2019), though this study was not focused on the olfactory entorhinal area. Still, this recent exciting finding indicates similarity in the function of the entorhinal cortex across species.

Comparison: With very little data on human entorhinal cortex, it is difficult to draw meaningful comparisons across species. However, the apparent large difference in the extent of bulbar projections into rodent and human entorhinal cortices may suggest significant differences in olfactory processing within this region across species.

Olfactory cortex: Piriform Cortex:

Piriform cortex is the largest recipient of olfactory bulbar input, and is by far the most studied of all central olfactory areas. Piriform cortex has a phylogenetically preserved three-layered paleocortical structure (Vaughan and Jackson, 2014). It is often referred to as primary olfactory cortex.

Rodent: Piriform cortex is a relatively large structure within the rodent brain, occupying up to 10% of the total cortical volume (Illig and Wilson, 2009). It can be divided into three main subdivisions: anterior, ventral-anterior, and posterior (Illig and Wilson, 2009), though is also commonly divided into only anterior (APC) and posterior (PPC) subdivisions (Calu et al., 2007; Grau-Perales et al., 2019; Haberly and Price, 1978; Stettler and Axel, 2009; Yang et al., 2017). These subregions have been defined based on their distinct bulbar inputs, distinct intrinsic architecture, and distinct outputs. Anterior piriform receives the heaviest output from the bulb, with much lighter bulbar input into posterior piriform. Ventral-anterior piriform is likely the only part of piriform that receives input from tufted cells, with dorsal-anterior piriform receiving mitral cell projections and little or no tufted cell input; whereas posterior piriform receives only mitral cell input (Igarashi et al., 2012; Illig and Wilson, 2009; Mori et al., 2013). Furthermore, anterior piriform has a thicker layer Ia, whereas posterior piriform has a thicker layer Ib, reflecting its much heavier associative input compared to anterior piriform (Wilson et al., 2006). In line with these anatomical differences, studies suggest functional differences across the piriform subregions as well

(Litaudon et al., 2003; Wilson, 1998; Zhang et al., 2006). Generally, studies have found that odor-evoked responses in anterior piriform are more closely tied to physical features of the stimulus, whereas responses in posterior piriform reflect more associative information (Calu et al., 2007; Kadohisa and Wilson, 2006; Roesch et al., 2006).

It has consistently been shown that projections from the bulb to piriform cortex are spatially distributed, with no preservation of the topography of the olfactory bulb (Ghosh et al., 2011; Iurilli and Datta, 2017; Miyamichi et al., 2011), and that information about odor identity can be extracted from the spatiotemporal dynamics of these ensemble patterns and from firing rates (Haddad et al., 2013; Illig and Haberly, 2003; Miura et al., 2012; Poo and Isaacson, 2009; Rennaker et al., 2007; Stettler and Axel, 2009; Sugai et al., 2005; Zhan and Luo, 2010). Information about odor intensity may be represented through different features of piriform responses, including response latency (Bolding and Franks, 2017). At the same time, numerous studies suggest that the function of piriform cortex goes beyond simple odor-identity coding and is strongly impacted by its regional connectivity with other cortical areas (Cleland and Linster, 2003; Sadrian and Wilson, 2015). Posterior piriform cortex has been implicated in associative functions such as odor learning and memory (Calu et al., 2007; Chen et al., 2014; Choi et al., 2011; Gire et al., 2013; Johnson et al., 2000; Martin et al., 2006; Roesch et al., 2006; Sacco and Sacchetti, 2010; Schoenbaum and Eichenbaum, 1995), and the region may mediate learned olfactory responses and behaviors (Choi et al., 2011). Moreover, the strength and composition of piriform networks has also been shown to depend on experience and on the state of the organism (Chapuis et al., 2013; Cohen et al., 2015, 2008; Hasselmo and Barkai, 1995; Kay and Freeman, 1998; Linster and Hasselmo, 2001; Wilson and Sullivan, 2011).

The connectivity patterns of the different rodent piriform subregions also differ. For example, one of the major output targets of rodent piriform is the mediodorsal thalamus (Courtiol and Wilson, 2015). The posterior piriform cortex (along with AON and cortical amygdala) projects more medially in the mediodorsal thalamus while the anterior piriform cortex (along with the olfactory tubercle) projects mainly to the central region of the mediodorsal thalamus (Bay and Çavdar, 2013; Inagaki et al., 1983; Krettek and Price, 1974; Price, 1985; Price and Slotnick, 1983; Ray and Price, 1992). As another example, ventral-anterior piriform output is almost exclusively to anterior piriform and orbitofrontal cortex, which projects back to the ventral-anterior piriform (Illig and Wilson, 2009). Anterior and posterior piriform have relatively similar projection patterns to regions outside of primary olfactory cortex, with just a few key differences. Both subregions project to ventral agranular insula and infralimbic areas, but only anterior piriform projects to ventrolateral orbitofrontal cortex, and only posterior piriform projects to posterior agranular insula and perirhinal cortex (Luskin and Price, 1983).

Human: Human piriform cortex is located at the junction of the frontal and temporal lobes, medial to the temporal stem (Mai et al., 2015). In humans, piriform cortex is subdivided anatomically into frontal- and temporal-lobe subdivisions (pirF and pirT, respectively). PirF and pirT occupy approximately 15% and 85% of the total piriform volume, respectively (Gonçalves Pereira et al., 2005). PirF is confined to a small triangular area on the lateral side of the olfactory tract. Medially, it is bound by the olfactory tubercle and lateral olfactory tract, and laterally, it merges into the insular cortex (Mai et al., 2015). PirF exhibits a typical laminar structure, including a plexiform layer containing olfactory tract fibers, a band of deeply staining pyramidal cells and a polymorphous cell layer with ill-defined internal limits (Allison, 1954). In earlier studies, pirF was considered part of the agranular insular cortex (Rose, 1928). PirT is much more extensive than pirF (Allison, 1954), beginning anteriorly at the limen insulae (which is the junction between the frontal and temporal lobes) and extending posteriorly to overlie the amygdaloid complex (Allison, 1954; Gonçalves Pereira et al., 2005). PirT progressively occupies a larger proportion of the gray matter in the caudal direction on the medial temporal lobe, up to 80% immediately anterior to the amygdala. Medially, pirT cortex merges into the perirhinal or entorhinal cortex, with its border marked by the sulcus semiannularis. Numerous olfactory tract fibers spread over pirT from their main point of termination at the angle between the frontal and temporal lobes. These fibers are present in the plexiform layer, and many turn inwards to terminate in relation to the dendrites of the pyramidal cells (Allison, 1954). In parts, pirT presents a typical lamination that is highly similar to monkeys or rabbits, but on the edges, the conspicuous pyramidal cell band breaks up to form small islets.

With so little knowledge about the human olfactory bulb and its cortical projections, we do not know whether bulbar input to human piriform cortex is spatially distributed, as in rodents. We also do not have a complete understanding of the distinct functions of human piriform subregions in olfactory processing. However, some progress has been made, with the vast majority of studies conducted using functional neuroimaging techniques. These studies have broadly corroborated rodent findings showing that ensemble spatial patterns in piriform cortex represent odor objects (Fournel et al., 2016; Gottfried, 2010; Howard et al., 2009; Li et al., 2010, 2008; Qu et al., 2016; Zelano et al., 2011). Notably, human studies have not always used the same procedure for defining piriform subregions, resulting in ambiguity in findings of heterogeneity across the human frontal and temporal subregions.

Though human neuroscience techniques are limited compared to those available to rodent researchers, working with human subjects does carry the advantage of allowing researchers to ask subjects to directly rate certain features of the odor stimulus. Several fMRI studies have reported greater BOLD signal magnitudes in piriform in response to unpleasant odors compared to pleasant odors (Bensafi et al., 2007; Gottfried and Dolan, 2003; Royet et al., 2003; Zelano et al., 2007), suggesting that odor pleasantness is represented in piriform cortex. Strikingly, all of these studies found that odor pleasantness was represented specifically in pirF, and not pirT, suggesting the possibility that these regions perform distinct olfactory functions. Interestingly, this effect was also present in the absence of odor stimulation, during imagined pleasant and unpleasant smells (Bensafi et al., 2007). The duration of BOLD signal increases may also play a role, with unpleasant odor responses being strong and short, and pleasant odor responses being longer and weaker (Gottfried et al., 2002b). Notably, some of these effects could be partly influenced by odor intensity, which must be very carefully controlled when studying odor hedonics (Anderson et al., 2003; Grabenhorst et al., 2007; Grabenhorst and Rolls, 2009; Rolls et al., 2008, 2003).

Also in agreement with rodent studies, numerous human studies have found that activity in human piriform cortex reflects higher-order associative functions, including working memory, odor imagination, odor learning and attention (Bensafi et al., 2007; Cerf-Ducastel and Murphy, 2006; Djordjevic et al., 2005; Gottfried et al., 2004, 2002a, 2002b; Gottfried and Dolan, 2003; Plailly et al., 2008; Royet et al., 2011; Zelano et al., 2009, 2005, 2011). More recently, iEEG techniques have been used to record local field potentials from human piriform cortex (Jiang et al., 2017; Noto et al., 2018; Zelano et al., 2016; Zhou et al., 2019b). These studies suggest a particular prevalence, relative to other frequency ranges, of theta oscillations in piriform cortex during odor detection and multisensory integration (Jiang et al., 2017; Zhou et al., 2019b). Thus the functional role of human piriform cortex is complex, with findings across studies indicating numerous potential aspects of odor processing represented in this region. While it is possible that different features of odors are represented as different features of piriform activity—oscillatory frequencies, temporal codes, spatial ensemble patterns, overall magnitude, etc.—these questions remain to be answered.

Recent fMRI data strongly suggest that human pirF and pirT have unique functional connectivity patterns (Zhou et al., 2019a) (Fig 3). Using data-driven k-means clustering techniques, pirF and pirT can be accurately parcellated based on their distinct whole-brain functional connectivity patterns. This distinction robustly survives across data sets, k values, and hemispheres. Interestingly, pirF exhibits connectivity with the mediodorsal thalamus whereas pirT does not. Furthermore, pirF exhibits strong functional connectivity with motor planning areas, including the caudate/putamen and the primary motor cortex, specifically at the face/nose/jaw section of the motor homunculus. In contrast, pirT exhibits connectivity with the brainstem raphe magnus and posterior insula, areas implicated in pain processing (Segerdahl et al., 2015; Woo et al., 2009) and respiratory modulations (Ackermann and Riecker, 2010; Evans et al., 2009), as well as the core language network (Ardila et al., 2014; Wible et al., 2005).

Comparison: Based on the limited knowledge we have about human piriform cortex, there are likely important differences in this region between species. Rodent and human piriform cortices are generally similar in their laminar structures (Allison, 1954), however our knowledge of human piriform cortex is much less detailed compared to rodent piriform. There is a great need for more studies on the anatomy and histology of human piriform cortex. In rodents, piriform cortex is divided into two main subregions—APC and PPC—with recent work indicating that ventral APC may constitute an important third subdivision. In humans, piriform is divided into two subregions—pirF and pirT (Allison, 1954; Crosby and Humphrey, 1941, 1939; Gonçalves Pereira et al., 2005; Rose, 1928). It is unclear how the human subdivisions correspond to the rodent subdivisions. While it is possible that non-human primate frontal piriform corresponds to rodent anterior, and non-human primate temporal piriform corresponds to rodent posterior (Carmichael et al., 1994), the small of number of human studies do *not* suggest the same to be true in humans. Rodent APC is similar in size to PPC, and APC receives a significantly greater density of projections from the bulb than PPC. In contrast, human pirF is very small relative to pirT, occupying only approximately 15% of the total volume of piriform cortex, and does not receive proportionally greater density of projections from the bulb compared to pirT. In fact, based on data from the few human studies, it seems likely that pirT receives a larger number of projections from the bulb than pirF (Allison, 1954). Further evidence from functional connectivity studies suggests a lack of correspondence between human pirF/pirT and rodent APC/PPC, with pirF and pirT exhibit strikingly different patterns of functional connectivity in humans (Zhou et al., 2019a). In rodents, the functional connectivity profiles of APC and PPC are not well established, but structural studies suggest overall similar connectivity patterns with areas outside of olfactory cortex. (Luskin and Price, 1983). More studies are needed to determine the correspondence between rodent and human piriform subdivisions.

Understudied bulbar targets

In rodents, the olfactory bulb projects to several medial brain areas that have been neglected in human olfactory studies. As a result, while these areas have been found to receive direct projections from the main olfactory bulb in rodents, whether this is also the case in humans is unknown. These areas constitute a medial olfactory cortex (Shipley et al., 2004), including the ventral and dorsal tenia tecta, the indusium griseum and the supraoptic nucleus of the hypothalamus. We will briefly discuss these areas in this section, and propose that all of these areas should receive more attention in future studies across species, and human studies in particular, to determine whether they receive human bulbar projections, and if so, what role they play in olfaction.

Tenia tecta—Also spelled taenia tecta, this structure is commonly divided into two subregions: the ventral tenia tecta (vTT) and the dorsal tenia tecta (dTT). The tenia tecta receives direct bulbar projections in rodents (Cleland and Linster, 2003; Haberly and Price, 1978). dTT is also referred to as the anterior hippocampal continuation (McNamara et al., 2004). The vTT contains predominantly pyramidal-type cells, while the dTT contains a more hippocampal-like cell structure (Haberly and Price, 1978).

In human olfactory studies, the tenia tecta is badly neglected. It is not known whether the human tenia tecta receives direct bulbar projections. In the human brain, the tenia tecta is a band of grey matter following a path analogous to the rodent along the inferior surface of the subcallosal gyrus, first described in 1712 by Lancisi (Di Ieva et al., 2007), with subsequent reports from Campbell (1905) and Rose (1927).

Indusium Griseum: Overlapping with or synonymous with the dorsal hippocampal continuation and the hippocampal rudiment, this thin band of grey matter is a continuation from the dTT moving along the supracollosal gyrus to the hippocampus. The indusium griseum receives direct projections from the rodent olfactory bulb (Wyss and Sripanidkulchai, 1983) and has a layered cellular structure which suggests analogues to the hippocampal formation. It is thought to be a continuation of the hippocampal formation (Wyss and Sripanidkulchai, 1983).

In humans, the indusium griseum also appears to be continuous with the tenia tecta, moving along the surface of the supracollosal gyrus to the hippocampus (Di Ieva et al., 2015). It is not known whether this region receives direct projections from the human olfactory bulb, and therefore whether it has any olfactory function in humans.

Supraoptic nucleus of the hypothalamus: In rodents, the supraoptic nucleus of the hypothalamus is situated at the base of the brain, adjacent to the optic chiasm. It receives direct projections from the olfactory bulb (Smithson et al., 1989), and is thought to be involved in post-partem bonding and water retention/regulation (Yang et al., 1995).

In humans, the supraoptic nucleus is situated medial to the olfactory tubercle and superior to the optic chiasm. It is not known whether this area receives any direct projections from the human olfactory bulb.

All of these areas lie medial to the lateral olfactory tract. Though it is now generally agreed that mammals have no medial olfactory tract, as all olfactory fibers moving medially arise from the lateral olfactory tract (Price, 1990), the pathway comprising the tenia tecta and the indusium griseum could constitute a medial olfactory pathway to the hippocampus, though this is highly speculative and has not been studied.

Clinical aspects of the olfactory system:

Olfactory dysfunction is a pervasive and early symptom across numerous neurodegenerative diseases, including Alzheimer’s disease, Parkinson’s disease, Lewey Body dementia, and others (Adams et al., 2018; Del Tredici et al., 2002; Demarquay et al., 2007; Doty, 2017; Godoy et al., 2015; Hüttenbrink et al., 2013; Pinto et al., 2014; Whitcroft et al., 2017; Wilson et al., 2011), highlighting the importance of furthering our understanding of human olfactory cortical areas. It is especially important, from a clinical perspective, to hash out the similarities and differences between the rodent and human olfactory systems, given the prevalence of rodent studies that have important clinical implications.

The reason that olfactory decline is so common in neurological disease is not fully understood, but there are several key differences between olfaction and other sensory modalities that could contribute. Anatomically, the olfactory system is unique in that its sensory neurons constitute the only part of the central nervous system that makes direct contact with the external environment. Sensory neurons in the nasal epithelium project from the olfactory mucosa, through the cribriform plate, and onto the olfactory bulb. The olfactory mucosa provides a potential location of pathogen entry in disease states where normal immune function could be compromised. The olfactory system is also unique in that projections from the periphery reach the cortex without relaying through the thalamus, meaning that olfactory information has privileged access to cortical and limbic brain areas and also may provide a potential pathway for pathology (Gottfried and Zald, 2005; Zald and Pardo, 1997).

Whether these unique aspects of the olfactory system play a role in the pervasive nature of olfactory deficits in cognitive decline is not clear. However, regardless of the reason, the frequency of olfactory deficits in neurodegenerative disease highlights the clinical importance of studying olfactory brain regions in patient populations. Abnormalities in olfactory cortical areas have been reported in several neurological disease types. It has been shown that different forms of cognitive impairment can be distinguished based on complex graph measures obtained from piriform cortex (Ebadi et al., 2017). Additionally, Parkinson’s disease and Lewy body dementia have both been shown to impact olfactory cortical areas (Ubeda-Bañon et al., 2017). Finally, another unique aspect of the olfactory system is that it constitutes one of the few areas in the brain where adult neurogenesis occurs (Lötsch et al., 2014; Whitman and Greer, 2009). Though speculative, it is tempting to consider the possibility that neurodegenerative disease could involve deficits in neurogenesis, thus leading to early olfactory degeneration. These data combine to show the clear clinical importance of understanding olfactory cortical structure and function and highlight olfactory pathways as key players in the progression of numerous neurodegenerative diseases. Future research is necessary and will be important in reaching full understanding of the known link between olfactory dysfunction and neurodegeneration.

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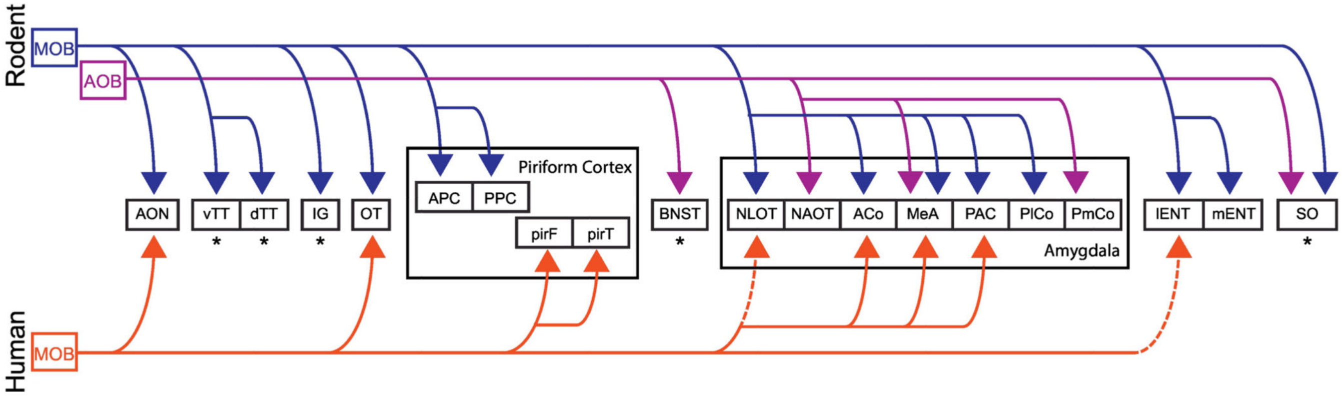

Figure 1:

Overview of the human and rodent olfactory systems. The major targets of olfactory bulb efferents are illustrated for humans (red) and rodents (blue and purple). MOB, main olfactory bulb; AOB, accessory olfactory bulb; AON, anterior olfactory nucleus; vTT, ventral taenia tecta; dTT, dorsal taenia tecta; IG, indusium griseum; OT, olfactory tubercle; APC, anterior piriform cortex; PPC, posterior piriform cortex; pirF, frontal piriform cortex; pirT, temporal piriform cortex; BNST, bed nucleus of stria terminalis; MeA, medial amygdala; PAC, periamygdaloid cortex; ACo, anterior cortical nucleus of the amygdala; PlCo, posterolateral cortical amygdala; PmCo, posteromedial cortical amygdala; NLOT, nucleus of the lateral olfactory tract; lENT, lateral entorhinal cortex; mENT, medial entorhinal cortex; SO, supraoptic nucleus. Dashed lines indicate that these projections have not been definitively shown in humans but are likely based on strong indirect evidence. *, it is not known whether this area receives direct projections from the main olfactory bulb in humans.

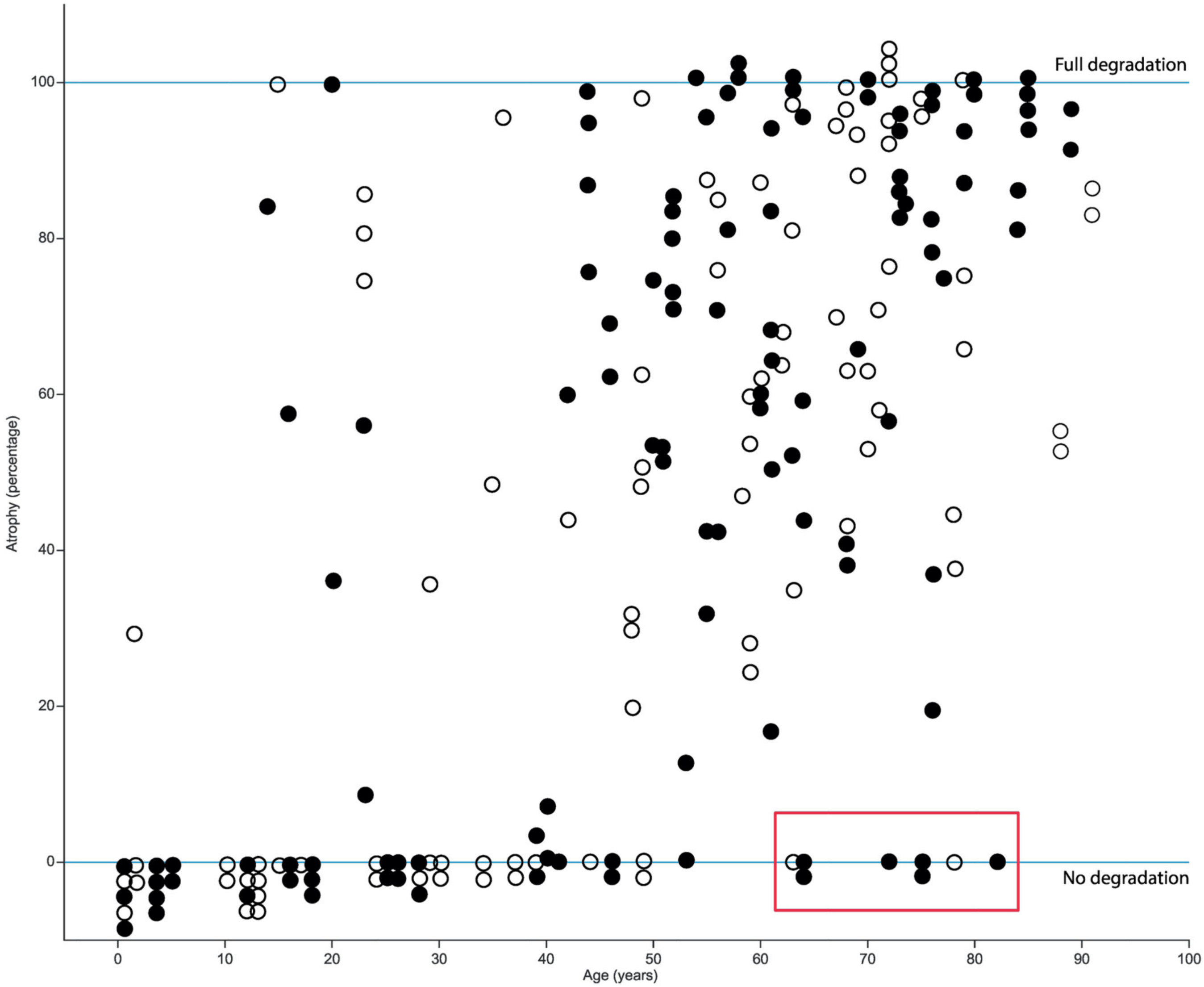

Figure 2:

Glomerular loss in over 200 olfactory bulbs, plotted by age. Notably, there is a subset of bulbs showing no glomerular loss over the broad range of ages. The red box highlights aged bulbs showing no glomerular loss in individuals over the age of 60. Points on or above the 100% line have lost all their olfactory nerve-fibers, and points on or below the 0% line have no glomerular loss. Dots and circles represent males and females, respectively. Figure adapted from and data taken from Smith (1942). To extract the data, the raw image was read into Matlab and binarized. The unweighted center of each marker, which was traced using Matlab's *bwboundaries* function, was retrieved and its age and atrophy values were calculated by interpolating the values of the x-axis and y-axis ticks.

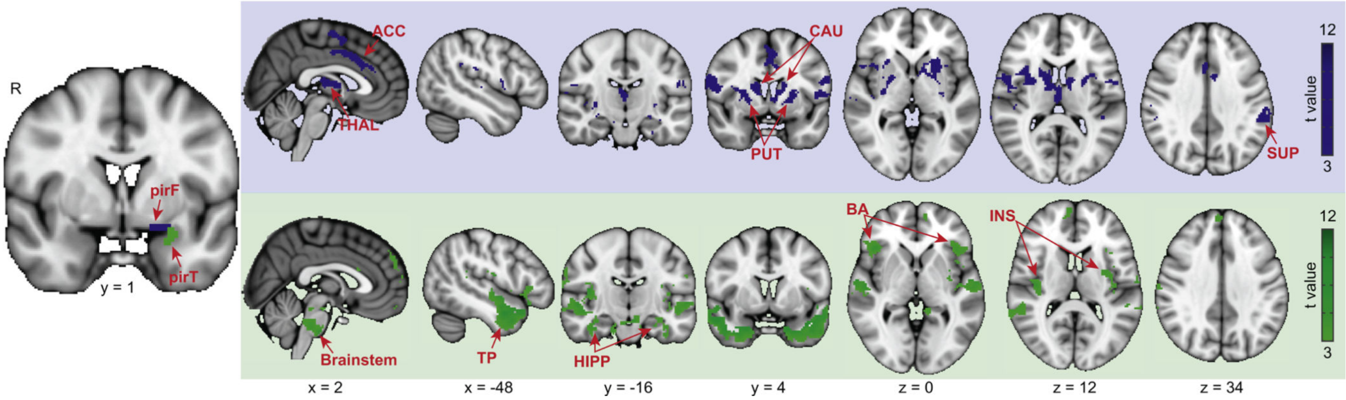

Figure 3:

Functional connectivity profiles of human pirF and pirT, adapted from (Zhou et al., 2019a). PirF and pirT show distinct whole-brain functional connectivity profiles. The t value maps show statistically significant (threshold-free cluster enhancement corrected $P < 0.001$) functional connectivity profiles unique to pirF (top row) and pirT (bottom row). R, right hemisphere; ACC, anterior cingulate cortex; THAL, thalamus; CAU, caudate; PUT, putamen; SUP, supramarginal gyrus; TP, temporal pole; HIPP, hippocampus; BA, Broca's area.