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Olfaction in Parkinson's disease and related disorders

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Abstract

Olfactory dysfunction is an early 'pre-clinical' sign of Parkinson's disease (PD). The present review is a comprehensive and up-to-date assessment of such dysfunction in PD and related disorders. The olfactory bulb is implicated in the dysfunction, since only those syndromes with olfactory bulb pathology exhibit significant smell loss. The role of dopamine in the production of olfactory system pathology is enigmatic, as overexpression of dopaminergic cells within the bulb's glomerular layer is a common feature of PD and most animal models of PD. Damage to cholinergic, serotonergic, and noradrenergic systems is likely involved, since such damage is most marked in those diseases with the most smell loss. When compromised, these systems, which regulate microglial activity, can influence the induction of localized brain inflammation, oxidative damage, and cytosolic disruption of cellular processes. In monogenetic forms of PD, olfactory dysfunction is rarely observed in asymptomatic gene carriers, but is present in many of those that exhibit the motor phenotype. This suggests that such gene-related influences on olfaction, when present, take time to develop and depend upon additional factors, such as those from aging, other genes, formation of α-synuclein- and tau-related pathology,or lowered thresholds to oxidative stress from toxic insults. The limited data available suggest that the physiological determinants of the early changes in PD-related olfactory function are likely multifactorial and may include the same determinants as those responsible for a number of other non-motor symptoms of PD, such as dysautonomia and sleep disturbances.

Keywords

Parkinson's disease; Neurodegenerative diseases; Olfaction; Genetics; Lewy body disease; Aging; Dopamine; Acetylcholine; Norepinephrine; Serotonin; Psychophysics; Electrophysiology; Functional imaging; Dystonia

Introduction

Since its description by James Parkinson in 1817, Parkinson's disease (PD) has been classically viewed as a movement disorder characterized by bradykinesia, rigidity, rest tremor, and postural instability. However it is now recognized that PD is one of a spectrum of α-synuclein- and tau-related disorders that are accompanied by such non-motor features as altered smell, taste, vision, cardiovascular function, sleep, gastric and bowel function, salivation, sebaceous gland activity, mood, and cognition (Halliday et al., 2011). Among the most salient non-motor features of PD is smell dysfunction, which occurs in at least 90% of cases (Doty et al., 1988a) and often appears years prior to the motor disturbance (Ross et al., 2008). This prevalence is much higher than that of the cardinal sign of rest tremor (~75%) and rivals or exceeds that of the other cardinal motor signs (Alves et al., 2008). Had this

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been known at an earlier time, PD may well have been classified as a primary olfactory disorder with secondary motor accompaniments.

In addition to the myopic focus on motor disability, two factors are responsible for the historical failure to recognize smell dysfunction as a key feature of PD. First, over 80% of patients with PD have less-than-total smell loss and fail to appreciate the dysfunction until tested (Doty et al., 1988a). This lack of awareness of olfactory loss is also seen in Alzheimer's disease (AD) (Devanand et al., 2000; Doty et al., 1987), in the Parkinson-Dementia Complex of Guam (PDG) (Doty et al., 1991a), and in the general population (Wehling et al., 2011). Second, practical and well-validated quantitative clinical olfactory tests were not available until the mid-1980s. Following the development of the University of Pennsylvania Smell Identification Test (UPSIT) in 1984 (Fig. 1), nearly a hundred studies have been published in the peer-reviewed literature demonstrating olfactory dysfunction in patients with PD. Indeed, an explosion of interest in olfaction by neurologists and neuroscientists occurred after this test became generally available (Fig. 2). This interest was fueled by findings that smell tests can differentiate PD from progressive supranuclear palsy (Doty et al., 1993), essential tremor (Busenbark et al., 1992; Shah et al., 2008), and parkinsonism induced by the proneurotoxin 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP) (Doty et al., 1992a). Interest was further stimulated by a series of landmark neuropathology studies implicating the olfactory bulb as one of two brain regions where PD pathology seems to first appear (Braak et al., 2003a, 2004; Del Tredici et al., 2002). Other important milestones that have driven interest in olfaction by neurologists are the pioneering discovery in 1997 of smell loss in some members of families with inherited forms of PD (Markopoulou et al., 1997) and evidence from longitudinal studies that smell testing predicts future development of PD in a sizable number of asymptomatic first degree relatives, as well as in at-risk members of the population at large (Ponsen et al., 2004, 2010; Ross et al., 2008).

The present review is an up-to-date description of the anatomical and functional olfactory abnormalities found in PD and related disorders. The relatively recent discoveries of olfactory dysfunction in genetic forms of PD are reviewed in detail, as are environmental risk factors associated with olfactory loss. As will be shown, multiple factors likely contribute to the development of PD-related olfactory dysfunction. Damage to cholinergic, serotonergic, and noradrenergic systems appear to be as important, if not more important, than damage to the dopaminergic system. Such damage is intertwined with a number of factors, including excessive microglial activation and inflammation, development of α-synuclein- and tau-related neuropathology, and cytosolic disruption of cellular processes such as those involved in monoamine storage and transport.

Basic anatomy and physiology of the olfactory system

To better understand factors potentially responsible for PD's influence on olfactory processing, a brief review of basic aspects of olfactory anatomy and physiology is in order. As will be clear from this section, there are multiple sectors of the olfactory system where PD-related pathology can potentially disrupt odor perception. Because of the complexity of the olfactory system, the reader is referred elsewhere for more detailed and thorough accounts of its anatomy and physiology (Cleland, 2010; DeMaria and Ngai, 2010; Glatz and Bailey-Hill, 2011; Hawkes and Doty, 2009; Menco and Morrison, 2003; O'Connor and Jacob, 2008; Shepherd et al., 2004; Shipley and Ennis, 1996; Su et al., 2009; Wilson and Stevenson, 2003, 2006).

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Olfactory epithelium and receptors

An estimated 6,000,000 bipolar olfactory receptor cells, which are derived from the olfactory placode and thus are of central nervous system origin, are embedded within the human olfactory neuroepithelium (Moran et al., 1982). This pseudostratified columnar epithelium lines, within each side of the nose, the cribriform plate and sectors of the superior septum, the superior turbinate and, to a lesser degree, the middle turbinate (Leopold et al., 2000). A given receptor cell sends 10–30 receptor bearing cilia from its dendrite into the olfactory mucus (Fig. 3) and extends a long unmyelinated axon through the epithelium and cribriform plate to the olfactory bulb, a structure described in detail in the next section. Numerous types of cells are found within this neuroepithelium (Fig. 4), including sustentacular (supporting) cells that, among other functions, insulate the receptor cells from one another (Menco and Morrison, 2003). Poorly understood microvillar cells are present in a ratio of 1 per 10 receptor cells (Fig. 4) (Rowley et al., 1989). Like the supporting cells, these cells project short microvillae into the mucus. All cells within the epithelium arise from basal stem cells located near the basement membrane (Huard et al., 1998).

To reach the receptors, odorants must first traverse the mucus that covers the epithelial surface. This is achieved either by diffusion or by the aid of ‘odorant binding’ proteins that shepherd hydrophobic molecules through aqueous environments (Pevsner and Snyder, 1990). Unlike the surrounding respiratory epithelium, whose secretions come from seromucous glands and goblet cells, the mucus of the olfactory area is mainly derived from specialized Bowman's glands. This unique mucus contains dozens of biotransformation enzymes that play an important role in not only odorant clearance, but in the destruction of bacteria, degradation of pro-inflammatory peptides, viral inactivation, and toxicant metabolism (Ding and Dahl, 2003). Recent studies suggest that enzymatic conversion of odorants is fast enough within the mucosa to influence their perception (Nagashima and Touhara, 2010).

Nearly 400 different functional olfactory receptors, members of the heptahelical G-protein-coupled receptor (GPCR) superfamily, are expressed in the ciliary membranes of human olfactory receptor cells (Rouquier et al., 2000). In mammals, this gene family is extremely large. Rodents have over 1200 odor-related genes, about a third of which are pseudogenes, whereas humans have around 850 such genes, with slightly more than half being pseudogenes (Mombaerts, 2004; Hasin et al., 2008). The genes that express the olfactory receptors are distributed on all but two chromosomes, with the majority being on chromosome 11 and most of the remainder on chromosomes 1, 6 and 9 (Glusman et al., 2001). Odorants adhere to receptor pockets bound by receptor transmembrane domains 3, 5, and 6 (Saito et al., 2009). The bond is a loose one, explaining why odorant dwell times are less than a millisecond (Bhandawat et al., 2005). An occupied receptor activates a GTP-binding protein, most likely G_{olf}, enriched in the cilia of the receptor cells. This in turn activates type III adenylyl cyclase, catalyzing the production of 3′,5′-cyclic monophosphate (cAMP). cAMP induces the opening of a cyclic nucleotide-gated channel, producing an influx of sodium and calcium ions and depolarization of the receptor neuron (Breer, 1994) (Fig. 5).[1] Subsequent activation of calcium-activated chloride channels further amplifies this initial depolarization and efflux of Cl^- from the cell (Stephan et al., 2009). Interestingly, only one type of receptor is expressed on a given receptor cell, although each receptor cell is responsive to a range of odorants (Holley et al., 1974; Sicard and Holley, 1984). Thus, the ‘olfactory code’ for a given odorant molecule reflects the activation of combinations of

[1]Another class of receptors has been identified in the olfactory epithelium which includes members of the trace amine-associated receptor (TAAR) family (Liberles and Buck, 2006). They have high agonist promiscuity, are highly diverse among species, and may have different functions in different species, although their function has not been demonstrated (Staubert et al., 2010).

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receptor cells that overlap with those of other odorant molecules, producing unique spatial maps within both the epithelium and the olfactory bulbs (Johnson and Leon, 2007).

After incurring damage, the olfactory receptor cells and other elements of the epithelium have a propensity for regeneration from the basal cells, although the degree of regeneration depends upon the extent to which the basal cell layer has been compromised (Bergman et al., 2002). Thirty years ago it was believed that the olfactory receptor cells died and were replaced at regular intervals, but it is now known that cell turnover is more complicated, being modulated by numerous environmental and genetic factors. Cells living for up to a year have been found within the rat epithelium (Hinds et al., 1984) and the rate of basal cell mitosis differs as a function of epithelial thickness and other factors (Mackay-Sim, 2003; Mackay-Sim and Patel, 1984).

Before projecting centrally through the cribriform plate, the axons of the unmyelinated receptor cells coalesce within the lamina propria into bundles of about 200 axons, each of which becomes surrounded by olfactory ensheathing cells (OECs) with features similar to those of astrocytes and Schwann cell mesaxons (Fig. 6). These axonal bundles are further encapsulated by olfactory nerve fibroblasts (ONFs) which define the olfactory nerve (CN I) fascicles that enter into the cribriform plate. A distinct population of microglia and macrophages is found between the OECs (Smithson and Kawaja, 2010). These cells serve to thwart the spread of viruses and other xenobiotics into the brain through the olfactory fascicles. As discussed in more detail later in this review, the direct projection of the receptor cells from the nasal cavity into the brain creates a passageway for xenobiotic invasion into the central nervous system (CNS) that effectively bypasses the blood brain barrier (Doty, 2008; Jackson et al., 1979).

Olfactory bulbs

The olfactory bulbs are a key element of the olfactory system where much of the pathology responsible for PD-related olfactory dysfunction likely resides. These paired structures, which are located at the base of the brain directly over the cribriform plate, are relatively complex. Although often viewed as simple relay stations, they are much more than that, performing complex neural computations similar to those of the primary cortices of other sensory systems (Cleland and Linster, 2005). In addition to having been compared to the retina in terms of its neural processing (Ghatpande, 2009), the olfactory bulb has been viewed as the “olfactory thalamus” given that it performs the final stage of sensory processing before information is sent to the cortex (Kay and Sherman, 2007).

As shown schematically in Fig. 7, several layers of the bulb can be anatomically defined on the basis of cell type and composition. The *olfactory nerve layer* is made up of interweaving axonal bundles of the incoming receptor cell axons. These axons selectively penetrate and ramify inside spherical glomeruli located in the next layer of the bulb, the *glomerular layer.*[2] The olfactory receptor cells that express the same receptor protein project to a common glomerulus, making each glomerulus, in effect, a functional unit (Mombaerts et al., 1996). The primary dendrites of the major output neurons of the bulb, the mitral and tufted cells, synapse with the receptor cell axons within the glomeruli. The cell bodies of the mitral cells make up the bulb's *mitral cell* layer. Situated between the glomerular and mitral cell layers is the large *external plexiform layer*. Each mitral/tufted cell extends secondary dendrites into this layer where they synapse with local interneurons, including axonless juxtaglomerular,

[2]The glomeruli decrease in number with age and are nearly absent in persons over the age of 80 years (Smith, 1942), being dependent upon trophic influences from the receptor cells. The receptor cells undergo age-related damage, either from environmental xenobiotics (Nakashima et al., 1984), from the pinching of their axons by oppositional bone growth within the cribriform plate (Kalmey et al., 1998), or possibly from age-related pathology like that documented in more central brain regions (Wilson et al., 2007, 2011).

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periglomerular, and granule cells. The GABAergic granule cells are the most numerous cells in the olfactory bulb, with their soma positioned within the bulb's deepest layer, the *granule cell layer*. About 80% of the synaptic contacts with granule cells are organized as reciprocal pairs, with the mitral/tufted-to-granule synapse being excitatory and the granule-to-mitral/tufted synapse being inhibitory (Shepherd et al., 2004).

Glutamate is the primary neurotransmitter of the olfactory receptor cells, activating AMPA and NMDA receptorsinthe apical dendriteofmitral and tufted cells within the glomeruli. Dopamine (DA) and GABA receptors are present on the receptor cell axonal arbors, allowing for presynapatic modulation of the glutamate output by the juxtaglomerular or periglomerular cells (Berkowicz et al., 1994; Gutierrez-Mecinas et al., 2005). The dendrites of these local interneurons ramify within multiple glomeruli (usually two) and extend axonal processes across several glomeruli, contacting other local interneurons and modifying activity within neighboring glomeruli. In accord with the receptors found on the olfactory receptor cell axonal arbors, the major neurotransmitters of these cells are DA and GABA (Aroniadou-Anderjaska et al., 2000; Halasz et al., 1977). In some cases, both DA and GABA are present in the same cell (Betarbet et al., 1996; Maher and Westbrook, 2008). Some periglomerular cells are neither dopaminergic nor GABAergic, containing either calretinin or calbindin (Kosaka and Kosaka, 2011). It is noteworthy that both the initiation and maintenance of dopamine expression in the periglomerular cells depends upon the input and integrity of the olfactory receptor cells and that dopamine expression markedly increases throughout life (McLean and Shipley, 1988).

Like the receptor cells, the primary transmitter of mitral and tufted cells is glutamate, although some tufted cells employ dopamine (Halasz et al., 1978). Numerous transmitters and neuromodulators are involved in bulbar cell interactions at the level of the glomerulus (Fig. 8) and within the external plexiform layer (Fig. 9).

Centrifugal fibers enter the bulb from higher brain structures and modulate bulbar activity via their terminations within all layers of the bulb, save the nerve cell layer (Kratskin and Belluzzi, 2003). The influences of the centrifugal processes on olfactory bulb function are significant and wide-spread. Indeed, the neural projections entering the bulb may outnumber those exiting the bulb. Many of these projections come from pyramidal cells within the anterior olfactory nucleus (AON), a multi-component structure with a major segment located within the posterior olfactory bulb.

Cholinergic fibers enter the bulb from the ipsilateral nucleus of the horizontal limb of the diagonal band via the medial forebrain bundle (Kasa et al., 1997; Woolf, 1991). The highest density of these fibers is within the glomerular layer (Ojima et al., 1988), where they modulate the activity of dopaminergic periglomerular cells largely through nicotinic receptors (Pignatelli and Belluzzi, 2008). Cholinergic fibers also project into the external plexiform layer, where they influence mitral cell activity via nicotinic receptors, as well as into the granule cell layer, where their influence is mainly via muscarinic receptors (Castillo et al., 1999). A rich centrifugal innervation into the glomerular layer of the bulb is also made by serotonergic fibers from the dorsal and median raphe nuclei, although all bulbar layers, save the olfactory nerve layer, contain some serotonergic fibers. Serotonin (5-hydroxytriptoline or 5-HT) polarizes juxtaglomerular cells and indirectly hyperpolarizes mitral cells (Petzold et al., 2009). Noradrenergic fibers enter the bulb from the locus coeruleus (LC) via the medial forebrain bundle (Kratskin and Belluzzi, 2003). This paired pigmented nucleus, which is estimated to contain up to 60,000 neurons in the young adult (Baker et al., 1989), is located in the rostral pons near the lateral floor of the fourth ventricle (Gesi et al., 2000). The LC is the primary source of norepinephrine (NE) in the brain and projects its axons to all brain regions save the basal ganglia. In the rat, at least 40% of the

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~1600 LC neurons on each side of the brain project to the olfactory bulb, reflecting a projection nearly 10 times as great as that to any other part of their cerebral cortex (Shipley et al., 1985). The fibers are most dense within the granule and internal plexiform layers.

Like the olfactory epithelium, the olfactory bulb exhibits considerable plasticity, with many of its cells undergoing replacement over time (Altman, 1969). Precursor cells originate in the anterior subventricular zone of the brain and generate large numbers of neuroblasts (Cayre et al., 2009; Gheusi et al., 2000). Some of these neuroblasts undergo restricted chain migration along the rostral migratory stream, a pathway that extends from the subventricular region to the core of the olfactory bulb (Lois et al., 1996; Rousselot et al., 1995). The migrating neuroblasts express a unique polysialylated-neural cell adhesion molecule (PSA-NCAM) that aids their migration (Rousselot et al., 1995). When they reach the bulb, the neuroblasts differentiate and migrate outward along glial processes, repopulating periglomerular and granule cells. Such replacement is facilitated by odorant stimulation and other factors (Rochefort et al., 2002). Nerve growth factor (NGF) and epidermal growth factor (EGF) increase the synthesis of choline acetyltransferase within the subventricular zone (Tirassa et al., 2003). PSA-NCAM-positive immature cells in the olfactory bulb express multiple acetylcholine (ACh) receptor subunits and are contacted by cholinergic fibers (Kaneko et al., 2006). Although ACh promotes survival of newborn neurons within the bulb, it does not increase proliferation of the subventricular neuronal progenitor cells (Kaneko et al., 2006). Interestingly, 6-hydroxydopamine damage to dopaminergic neurons within the substantia nigra and ventral tegmental area reduces the number of subventricular proliferating neural precursors by about 40% in rats, but not mice, implying that these dopaminergic projections may be a key regulator of neurogenesis in the adult forebrain of some species (Baker et al., 2004, 2005).

A frequently overlooked element of olfactory bulb anatomy which may relate to the olfactory loss seen in PD is its atypically generous endowment with microglia and other glial cells (Lawson et al., 1990). Glial cells far outnumber neurons, accounting for around 90% of all cells in the brain (Fellner et al., 2011). Under normal circumstances, microglial cells – glial cells of mesodermal origin and primary effectors of innate immune responses – exist in the ‘resting’ state. However, when injury occurs, such as from ischemia, trauma, or xenobiotic exposure, they become activated, change into a macrophage-like cellular morphology, and proliferate. Some brain microglia are derived from peripheral bone-marrow-derived cells that cross the blood–brain barrier (Rodriguez et al., 2007). Upon activation, microglia express genes related to inflammation, including cytokines, enzymes, adhesion molecules, and free radicals which serve to eliminate pathogens (Lehnardt, 2010). Under normal circumstances, inflammatory responses are tightly regulated since too much or two little can result in pathology (Minghetti, 2005). Neurons, in fact, regulate microglial activity via CD200 receptors on the microglia (Wang et al., 2011c). If not kept in check, however, severe pathology can be induced. For example, endogenous ‘danger signals’ from injured or necrotic cells can activate Toll-like-receptors (TLRs) with pro-inflammatory and pro-apoptotic capabilities that can induce oligodendrocyte and neuronal injury (Lehnardt et al., 2007; Tang et al., 2007; Ziegler et al., 2007).

Germane to the present review, Lalancette-Hebert et al. (2009) have shown that ischemic injury to the brain actives microglia not only at the site of ischemic insult, but in the olfactory bulb, a point far from the locus of the injury. Such bulbar activation was found to occur several hours before microglial activation in tissues near the site of attack and lasted months after the attack. Based on these and other observations, these authors proposed that olfactory bulb microglia serve as sensors of brain inflammation in general. They point out that such microglia are functionally unique in being pre-set to a permanent ‘alert’ position, reflecting in part the dynamic renewal/apoptosis processes within the bulb and bulbar

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responses to xenobiotics. In light of such observations, the olfactory bulb is very likely to be vulnerable to microglial-related pathology.

The projections from the olfactory bulb to more central structures are unique, in that they go directly and ipsilaterally to cortical regions without first synapsing within the thalamus. However, as noted later in this review, some thalamic connections exist between these cortical regions and regions of the orbitofrontal cortex. Moreover, there is evidence that a thalamic relay is involved in the selective attention to odorants (Plailly et al., 2008). Importantly, lesions within the thalamus appear to disrupt, at least to some degree, the ability to identify odors (Sela et al., 2009).

The olfactory cortex is defined as those brain regions that receive the mitral and tufted cell projections from the olfactory bulb. Since the olfactory bulb itself can be viewed as a cortical structure, these regions are often termed secondary olfactory structures (Cleland and Linster, 2003). In humans and most mammals, they include the AON, the olfactory tubercle, the anterior and posterior piriform cortices, the lateral entorhinal cortex, the periamygdaloid cortex, and the anterior cortical nucleus of the amygdala (Cleland and Linster, 2003). The largest of these structures is the pear-shaped piriform cortex (PC). The outermost layer of this 3-layered allocortex receives most of the bulb's mitral and tufted cell axons, where they synapse with dendrites of pyramidal cells. Its middle-most layer contains the majority of the pyramidal cell soma, although some soma are located in its deepest layer. As with the olfactory bulb, piriform neural activity is modulated by intrinsic and extrinsic sources. The PC is richly endowed with NE, 5-HT, and DA receptors and receives substantial projections from the ventral tegmental area, substantia nigra, and LC (Datiche and Cattarelli, 1996). It is reciprocally connected with such brain regions as the orbitofrontal cortex, insular cortex, the hypothalamus, the hippocampus, and the mediodorsal nucleus of the thalamus — structures that are also interconnected with one another (Cleland and Linster, 2003). The cells of the PC rapidly habituate to familiar odors, but not unfamiliar ones, suggesting it is tuned to changes in the odorous environment and is involved in sharpening the contrast between different odors. The anterior PC likely encodes information about the molecular structure of odors, whereas the posterior PC appears to encode odor quality (Gottfried et al., 2006; Howard et al., 2009).

The orbitofrontal cortex (OFC), which traditionally has been viewed as secondary olfactory cortex, plays a critical role in establishing the reward value of odorants. For example, neurons in this region decrease their responses to the odor of food after satiety occurs (Critchley and Rolls, 1996). Moreover, lesions in the OFC impair the ability to learn contingencies of reinforcement. For example, in a go/no go discrimination task, OFC lesions compromise the ability to respond to a rewarded stimulus and to inhibit responses to a non-rewarded stimulus (Butter et al., 1969; Iversen and Mishkin, 1970). It is within the OFC where the convergence and interaction of information from multiple sensory systems occurs. For example, some neurons respond to both gustatory and olfactory stimuli, while other neurons respond only to olfactory stimuli or only to taste stimuli (Rolls and Baylis, 1994). Such representations change as a result of learning; i.e., the reward value of each stimulus is consistently updated within the OFC by experience (Rolls, 2000).

Quantifying the function and integrity of the human olfactory system

Numerous functional and structural approaches are available for assessing the integrity of the olfactory system in PD, although only a few have been widely used. These can be divided into psychophysical, electrophysiological, psychophysiological, and imaging procedures.

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Psychophysical Tests

Psychophysical tests – tests in which subjects provide a volitional response of some sort to the presentation of stimuli—are the most widely employed tests for quantifying olfactory system function (for reviews, see Doty, 2007; Doty and Laing, 2003). Such tests directly relate to an individual's perceptual experience. Olfactory psychophysical tests include tests of odor sensitivity (e.g., threshold tests), identification, discrimination, memory, and hedonics, as well as tests of the perceptual build-up of odor intensity across odorant concentration gradients (e.g., rating scales and tests using magnitude estimation). The majority of studies assessing olfaction in PD have employed odor identification tests, most notably the UPSIT, although a few have used other tests, including tests of odor detection, discrimination, and memory (Doty, 2003).

Despite the widespread availability of seemingly different psycho-physical olfactory tests, it should be stressed that making simple distinctions among – or neurological or psychological inferences from – such tests is problematic. Most nominally distinct olfactory tests are strongly correlated with one another (Doty et al., 1994), although they differ on a number of dimensions which confound their comparisons. Thus, they typically employ different odorants (Doty et al., 1995b), have differing cognitive demands (Hedner et al., 2010), and vary in reliability and sensitivity (Doty et al., 1995b). Reliability and sensitivity depend upon a number of factors, including test length (e.g., the number of items or trials) (Doty et al., 1995b). Importantly, the terms used to describe the operational nature of such tests are not isomorphic with independent physiological or psychological processes. For example, odors cannot be identified if they cannot be detected or discriminated from one another. Most detection paradigms require remembering an odor and comparing it to a blank, so memory is involved even in what seems to be a simple detection task. Without first encoding a percept, identification, discrimination, and memory cannot be performed. Hence, reported differences among nominally distinct tests need not reflect differences in functions implied by their names and should not be literally interpreted.

Misconceptions related to such issues are rampant in the literature. Perhaps the most poignant are claims that olfactory thresholds are solely a measure of peripheral, i.e., epithelial, olfactory function. The origin of this myth seems to have come from the fact that auditory and visual thresholds are primarily indices of peripheral sensory function (e.g., Borus and Rintelmann, 1971), as well as from early studies in the AD literature claiming this distinction (Koss et al., 1987, 1988). The latter studies, which employed small sample sizes (≤ 10), reported that while an UPSIT deficit was seen in AD patients relative to controls, a threshold deficit was not. Although they used a reliable identification test (test–retest $r>0.90$), the single ascending series threshold test they utilized is very unreliable ($r<0.40$) (Doty et al., 1995b). Hence, the difference noted between the two tests was confounded by test sensitivity. Subsequent threshold studies using more sensitive threshold procedures and larger sample sizes have uniformly observed significant threshold deficits in AD, as well as in PD (Mesholam et al., 1998).

Electrophysiological measures

The odor event-related potential (OERP) is the most widely employed human electrophysiological measure of smell function (Kobal, 2003). Operationally, pulses of odorants are embedded in a humidified and temperature-controlled stream of air flowed through the nose. Such pulses synchronously activate a large number of neurons. With enough trials, the temporal pattern of the firing of these neurons can be discerned from the other brain activity through computer averaging of signals received by electrodes on the scalp, resulting in electrical responses whose waveforms can be measured. Unlike auditory brain stem event-related potentials, the OERP has not been found to be a reliable indicator

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of the location of the pathology within the olfactory pathway. Its dependence upon complex and expensive equipment has limited its general clinical use. In PD its initial wave-form latencies and amplitudes, when able to be observed, generally correlate with psychophysical and central functional imaging measures (Deeb et al., 2010; Welge-Lussen et al., 2009).

Another electrophysiological measure used in olfactory studies is termed the electro-olfactogram (EOG) (Hummel et al., 1996; Scott and Scott-Johnson, 2002). This measure of summated potentials is obtained from electrodes placed inside the nose on the surface of the olfactory epithelium. Like the OERP, the EOG has received little attention in studies of PD, despite its potential use in determining the integrity of the function of the receptor cells. In general, the intensity of odorants is positively correlated with the magnitude of the EOG (Doty et al., 1990). The general clinical practicality of the EOG is limited in that many persons cannot tolerate electrodes placed in their noses without anesthesia and the responses from a given electrode location may not be representative of the entire epithelium. Moreover, bulbar pathology may influence EOG magnitudes by reducing presynaptic inhibitory activity on the olfactory receptor cells, thereby confounding its interpretation. Since the EOG, at least in those species where it has been measured, can be recorded for some period after death (Scott and Brierley, 1999), a normal EOG need not be an index of normal odor perception.

Psychophysiological tests

A number of tests have measured autonomic and other psycho-physiological responses to odors, most notably changes in heart rate, respiration, and blood pressure (for review, see Doty et al., 2004). Such tests have not been widely employed, given their variability and sensitivity to stimulation from free nerve endings from the trigeminal nerve (CN V). Recently a unique test, termed the sniff magnitude test, has become commercially available that quantifies the decrease in inhalation that typically occurs upon the presentation of an odorant that is perceived as noxious (Frank et al., 2003). In effect, when such an odor is unexpectedly encountered during a sniff, a subject with a normal sense of smell immediately terminates the sniff. A person with no smell continues to produce a normal sniff. The degree to which inhalation is inhibited has been found to correlate with other olfactory test measures (Tourbier and Doty, 2007). This test is sensitive to PD-related deficits, although less so than other measures (unpublished data). Because of its lack of reliance on the conscious reporting of a perceptual experience, it may be of particular value in assessing olfaction in PD patients with dementia, given that it only requires a subject to initiate a sniff. It does, however, rely on affective perception, i.e., the subject's ability to experience pleasantness and unpleasantness.

Neuroimaging

Structural imaging paradigms allow for quantification of the volume of specific brain structures, including the olfactory bulbs and tracts. While the results of MRI volumetric assessments of the olfactory bulbs are reliable (Yousem et al., 1997), they are variable (Yousem et al., 1998). In the case of PD, for example, some laboratories report smaller bulbs in PD patients than controls (Wang et al., 2011b), whereas other do not (Möller et al., 2005). Although Wang et al. found moderate but significant correlations between odor recognition thresholds and olfactory bulb volumes in both their PD ($r=-0.42$, $p<0.05$) and control ($r=-0.45$, $p<0.0001$) subjects, the effects of age were not statistically removed from the correlations. When this is done in normal cohorts, correlations between olfactory bulb volumes and olfactory test measures are markedly attenuated (Buschhuter et al., 2008).

Functional imaging studies examining brain metabolism in resting, i.e., non-stimulated, conditions have generally noted mild metabolic reduction in PD patients within the caudate

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nucleus, the piriform cortex, the cingulate cortex, the medial prefrontal cortex, the dorsolateral prefrontal cortex, the medial occipital cortex, and the lateral parieto-temporo-occipital area (Baba et al., 2011). Although greater metabolic reductions within these regions is seen in persons with the most olfactory dysfunction (Baba et al., 2011), it is not clear whether this association is specific to olfaction.

Perhaps a more promising approach for understanding the basis of PD-related olfactory deficits stems from the development of neurotransmitter-specific ligands for use in single photon emission tomography (SPECT) and positron emission tomography (PET) protocols. These paradigms allow for the determination of correlations between olfactory test findings and neurotransmitter receptor deficiencies in a number of brain regions (e.g., Bohnen et al., 2010). As described later in this review, this approach may provide new insights into the physiological bases of PD-related olfactory dysfunction.

Another promising imaging approach to quantifying olfactory pathology is diffusion tensor imaging (DTI). DTI makes it possible to visualize the location, orientation, and anisotropy of the white matter tracts of the brain. In essence, the diffusion of the water molecules orients along nerve bundles as a result of their axonal architecture and myelin sheathing. By applying diffusion MRI gradients in multiple noncollinear directions, it is possible to quantify the anisotropy and diffusivity. Significant decreases in diffusivity have been found in the region of the olfactory tracts of PD patients (Rolheiser et al., 2011; Scherfler et al., 2006).

The olfactory phenotype of sporadic Parkinson's disease

Since 1975 nearly 100 peer-reviewed studies have compared the olfactory function of so-called sporadic or idiopathic PD patients to that of normal controls. Essentially in all cases statistically significant differences between these two groups have been observed, regardless of the type of test employed, reiterating the likelihood that most such tests sample a common sensory domain (Doty et al., 1994).

A number of generalizations can be made from this literature regarding the nature of the olfactory dysfunction of PD. First, the dysfunction is *bilateral and robust*, being present in 90% or more of sporadic PD cases (Hawkes and Doty, 2009). Indeed, olfactory tests differentiate PD patients from controls better than clinical motor tests (Bohnen et al., 2008b). In one meta-analysis that compared olfactory test scores of PD patients to those of controls, Cohen effect sizes larger than 3 were found (effect sizes>0.80 are considered “enormous”) (Mesholam et al., 1998). Second, *women with PD tend to outperform their male counterparts* (Stern et al., 1994), a sex difference seen not only in the general population (Doty et al., 1984a), but in diseases ranging from AD (Doty et al., 1987) to schizophrenia (Good et al., 2007; Seidman et al., 1997). Third, *anosmia is not the norm*. In one study, only 38% of 81 PD patients had UPSIT scores suggestive of anosmia and 87% of 38 patients could reliably detect the highest stimulus concentration presented in an odor detection threshold test (Doty et al., 1988a). In another study, all but one of 41 PD patients reported that 35 or more of the 40 UPSIT items had some type of odor, even though the perceived sensation did not correspond to any of the response alternatives (Doty et al., 1992b). Fourth, *the olfactory deficit seems unrelated to specific odorants*. Despite the fact that a number of studies have suggested that some odorants differentiate PD from controls better than other odorants, little consistency has been found among studies and the relative influences of culture, odorant intensity, odorant type, and specific response alternatives on the tests are unknown and likely complicate the issue (Boesveldt et al., 2007; Bohnen et al., 2007; Daum et al., 2000; Double et al., 2003; Hawkes et al., 1997; Silveira-Moriyama et al., 2005). The focus on psychological odor qualities is misleading, since odorants activate

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multiple receptors and most, such as those in the UPSIT, are comprised of dozens of chemicals. Fifth, *the average olfactory dysfunction of PD is equivalent to that observed in early stage AD and in a number of other neurological diseases*. For example, patients with early stage AD, PD, and the Parkinson-Dementia Complex of Guam (PDG) exhibit mean UPSIT scores around 20 (Doty et al., 1991a, 1991b; Mesholam et al., 1998). Sixth, *olfactory testing can be useful in differential diagnosis*, such as discerning PD from progressive supra-nuclear palsy (PSP), MPTP-induced parkinsonism (MPTP-P), multiple system atrophy (MSA), and essential tremor (ET), disorders with little or no olfactory dysfunction (Busenbark et al., 1992; Doty et al., 1993, 1995a; Ondo and Lai, 2005; Shah et al., 2008; Wenning et al., 1995). Seventh, *medications used to control the motor dysfunction of PD have no influence on the smell deficit* (e.g., L-DOPA, DA agonists, anticholinergic compounds). Thus, the smell loss is as severe in non-or never-medicated patients as in medicated ones (Doty et al., 1992b; Quinn et al., 1987; Roth et al., 1998). Eighth, the olfactory dysfunction of well-established PD is *relatively stable over time and is unrelated to disease stage or duration* (Barz et al., 1997; Doty et al., 1988a, 1989, 1992b; Hawkes et al., 1997), although this generalization may not apply to all patients or to patients in the earliest stages of the disease (Berendse et al., 2011; Herting et al., 2008; Siderowf et al., 2005; Tissingh et al., 2001). Ninth, particularly in later PD stages, *suboptimal sniffing behavior may contribute to the olfactory problem*. However, the degree of the contribution is small (Sobel et al., 2001). Tenth, *losses in both olfaction and cardiac sympathetic function are closely related* in PD, as evidenced by strong correlations between olfactory test scores and cardiac ^{123}I-metaiodobenzylguanidine (MIBG) uptake. This association is independent of disease duration and clinical ratings of motor function (Lee et al., 2006). Eleventh, although strong relationships between olfactory and cognitive test scores are lacking in PD cohorts (Doty et al., 1989), there is evidence that *olfactory test scores are weakly correlated with some cognitive measures* in PD, most notably ones involving verbal memory and executive performance (Bohnen et al., 2010; Morley et al., 2011). Twelfth, *longitudintal studies demonstrate that the olfactory deficit precedes the classical clinical PD motor signs by several years*, serving as a ‘pre-clinical’ or ‘pre-motor’ marker (Haehner et al., 2007; Ponsen et al., 2004; Ross et al., 2005). Thirteenth, *olfactory testing is sensitive to risk factors associated with future development of PD*. Among such risk factors are age (Doty et al., 1984a), head trauma (Doty et al., 1997), and lifetime intake of caffeinated beverages (Siderowf et al., 2007). Fourteenth, *some asymptomatic first-degree relatives of patients with sporadic forms of PD exhibit olfactory dysfunction that predicts future development of PD* (Berendse et al., 2001; Montgomery et al., 1999, 2000; Ponsen et al., 2004). In one study, olfaction was tested in 361 asymptomatic relatives of PD patients (Ponsen et al., 2004). Those with test scores in the top and bottom 10% of the group underwent [^{123}I]β-CIT labeled DA transporter functional imaging within the striatum, a measure of PD-related pathology. At the 2-year follow-up, 4 of the 40 relatives with olfactory test scores in the bottom 10%, all of whom exhibited substantial reduction in transporter uptake at baseline, had developed clinically defined PD, while none of the 38 relatives with test scores in the top 10% did so. The remaining individuals in the bottom 10%, while not yet exhibiting motor signs of PD, exhibited significant declines in transporter uptake across the two test sessions, implying PD was developing.

The olfactory phenotypes of monogenetic forms of Parkinson's disease

It has been known for over a quarter century that individuals with a mutation in the P450 cytochrome CYP2D6-debrisoquine hydroxylase gene are at increased risk for developing PD (Elbaz et al., 2004; Smith et al., 1992). The activity of similar detoxification enzymes are, in some cases, higher in the olfactory mucosa and olfactory bulb than in the liver, raising the possibility that their compromise could facilitate xenobiotic penetration into the

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brain via the nasal route (Ding et al., 1992; Iscan et al., 1990; Xie et al., 2010; Zhang et al., 2005).

More recently monogenic forms of PD have been discovered, although in a few cases the identification of such forms may have been premature (Table 1). In some unique populations, such as the Arab-Berbers of North Africa, over 40% of cases of familial PD have a well-documented mutation, namely the leucine-rich repeat kinase 2 gene (LRRK2) mutation (Lesage et al., 2005). Most cases of PD, however, are viewed as sporadic, with familial monogenetic forms accounting for only a small percentage of cases. For example, only about 1% of sporadic cases of PD in North America carry the LRRK2 gene (Correia et al., 2010).

Since the pioneering work of Markopoulou et al. (1997), which identified anosmia and hyposmia in some individuals from families with inherited parkinsonism, olfactory dysfunction has been tested in a number of patients with monogenetic forms of PD. As described below, heterogeneity exists in terms of the olfactory dysfunction observed in genetic forms of PD, although in many instances the olfactory test scores are very similar to those observed in sporadic PD.

PARK1/PARK4 locus mutations (α-synuclein)

Most patients with PARK1/PARK4 – an autosomal-dominant form of PD – exhibit the motor phenotype early in life, usually in their ′30s and ′40s, although later onset may occur in some with the A30P mutation (Kruger et al., 1998). The encoded protein is α-synuclein. Bostantjopoulou et al. (2001) reported that 2 of 8 Greek PD patients carrying the G209A PARK1 mutation were anosmic, whereas the other five were normal. Tijero et al. (2010) tested an *asymptomatic* carrier of the E46K substitution in the α-synuclein gene and found no evidence of smell loss.

PARK2 locus mutations (Parkin gene)

The most common form of *early-onset* parkinsonism carries the autosomal recessive Parkin gene (PARK2). The Parkin protein co-localizes with actin filaments andis largely expressed incytoplasm and neuronal processes. One mechanism by which Parkin induces cell death is by autophagocytosis of mitrochondria (Narendra et al., 2009). Khan et al. (2005) found none of 27 PARK2 patients had abnormal UPSIT scores. A PARK2 negative PD group and a sporadic PD patient group evidenced the expected deficits. Normal UPSIT scores were reported by Alcalay et al. (2011) for compound PARK2 heterozygotes — i.e., individuals who had PARK2 mutations on both the paternal and material alleles (Alcalay et al., 2011). PD patients who did not carry the PARK2 gene and non-compound heterozygotes had UPSIT scores in the range expected in sporadic PD.

PARK6 locus mutations (Pink-1 gene)

The clinical features of PARK6 PD are similar to those of PARK2 PD. This autosomal-recessive disorder is caused by mutations of the PTEN-induced putative kinase 1 (PINK1) gene. Several lines of evidence suggest that this gene exerts a neuroprotective effect by inhibiting the formation of reactive oxygen species (Wang et al., 2011a). Ferraris et al. (2009) administered tests of odor identification, detection, and discrimination to 7 patients with homozygous PARK6 PD and 6 patients with heterozygous PARK6 PD. Detection thresholds were said to be more preserved and discrimination more impaired in the PARK6 PD patients than in 19 sporadic PD cases, who exhibited odor identification deficits. In contrast, Eggers et al. (2010) reported that none of four homozygous PARK6PDpatients they tested had UPSIT scores outside of the 10th percentile of age- and sex-matched normal controls. Although 4 of 10 heterozygotes did so, only one was at or below the 5th percentile,

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suggesting to these authors that PARK6 mutations have only modest influences on smell function.

PARK 8 locus mutations (LRRK2 gene)

Mutations in the leucine-rich repeat kinase 2 gene (LRRK2/ Dardarin) are associated with the most common form of dominantly inherited PD. In general, homozygotes and heterozygotes have the same clinical features, implying the absence of a gene dose effect (Ishihara et al., 2006). Penetrance ofthe most common LRRK2 mutation (G2019S on exon 41) is incomplete and age-dependent, suggesting the mutation by itself does not induce pathology and that additional genetic or environmental factors contribute to disease risk (Lesage et al., 2007).

As shown in Table 2, a number of studies have administered olfactory tests to patients with PARK8 mutations, with most studies testing patients with the G2019S mutation. In general, the observed scores and their distributions are similar to those expected for sporadic cases of PD, although one study of 31 G2019S PD mutation carriers reported UPSIT scores that were slightly but significantly ($p<0.001$) higher than those of a group of non-mutation carrying PD patients [mean (SD)=24.8 (7.08) vs. 18.8 (8.05]. Both groups had test scores that were far below those of controls [33.6 (3.82)] and 28 non-manifesting mutation carriers [30.1 (7.55)] (Saunders-Pullman et al., 2011). An observation of somewhat higher test scores in the PARK8 cases relative to what is generally see in sporadic PD was similarly noted a year earlier in 14 G2019S mutation carriers by Silveira-Moriymama et al. (2010) using Sniffin' Sticks (Hummel et al., 1997), as well as contemporaneously by Ruiz-Martinez et al. (2011) using a briefer version of the UPSIT (B-SIT; Doty et al., 1996). As apparent from Table 2, smell test scores of patients with non-G2019S PARK6 mutations are variable but generally fall within the range expected for individuals with sporadic PD (Berg et al., 2005; Kertelge et al., 2010; Khan et al., 2005; Lin et al., 2008).

It is noteworthy that several of the aforementioned studies reported that *asymptomatic* LRRK2 mutation carriers had no smell dysfunction (Silveira-Moriyama et al., 2008; Saunders-Pullman et al., 2011). This observation is in accord with a study by Johansen et al. (2011) in which the B-SIT was administered to 47 *non-symptomatic* family members of LRRK2 PD patients, 32 positive and 15 negative for either the G2019S or the N1437H mutation. Unlike measures of urinary and sleep dysfunction, the B-SIT scores were normal in both groups and did not differ significantly from one another [respective means (SD) = 9.1 (2.0) & 8.7 (1.5)]. In light of such findings, it is tempting to conclude that at least some asymptomatic PARK8 gene carriers are similar to asymptomatic Huntington's disease (HD) gene carriers, who do not exhibit smell loss until sometime near the expression of the clinical phenotype (Bylsma et al., 1997; Moberg and Doty, 1997). It is not yet known as to when the loss appears relative to the onset of motor dysfunction in either HD or PD, although one HD study suggests that the loss may occur 5–10 years before symptom onset (Paulsen et al., 2008).In most sporadic cases ofPD in the United States, this average period is likely less than 10 years, although exceptions are apparent (Marras et al., 2005; Ross et al., 2008; Tanner et al., 2007). The possibility exists that age is associated with gene penetrance, although other factors may be involved as well.

Glucocerebrosidase-related parkinsonism

Glucocerebrosidase (GBA) is a gene implicated in parkinsonism that causes Gaucher's disease (GD), the most prevalent autosomal recessive lysosomal disorder. While the most prominent features of GD are related to bone, hematologic, and pulmonary features, parkinsonism is common and, in some cases, a presenting feature of the disease (Saunders-Pullman et al., 2010).

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Two studies have tested olfaction in parkinsonian patients carrying the GBA mutation. Goker-Alpan et al. (2008) tested 6 such patients. Three were anosmic, 2 severely microsmic, and 1 moderately microsmic. The mean UPSIT score was within the range expected for patients with sporadic PD [17.66 (6.47)]. Saunders-Pullman et al. (2010) tested two GBA-related PD cases, both of whom proved to be anosmic (UPSIT scores=13 & 10). In one of these cases – a male tested at the age of 54 years – the initial PD sign, a right-hand rest tremor, appeared at 48 years of age, soon followed by such symptoms as anxiety, depression, orthostasis, urinary urgency, and medication sensitivity. Interestingly, this patient reported that the smell dysfunction had appeared when he was a teenager. Assuming the accuracy of this recollection, the olfactory dysfunction in this case preceded the other symptoms by more than 30 years.

Olfactory phenotypes of other neurodegenerative disorders associated with parkinsonian signs

As mentioned in the introduction, PD falls along a continuum of disorders associated with motor dysfunction and, in many cases, similar neuropathology. Among these and other neurodegenerative disorders are amyotrophic lateral sclerosis, corticobasal degeneration, drug induced parkinsonism, Lewy body disease, multiple system atrophy, the parkinson-dementia complex of Guam, progressive supranuclear palsy, pure autonomic failure, vascular parkinsonism, and X-linked dystonia parkinsonism (‘Lubag’). Since some of these disorders are spared significant olfactory dysfunction, comparisons of their pathologies to those of disorders where such dysfunction is present, including PD, may aid in isolating the involved underlying pathological processes. Of particular interest, as described later in this review, are neurotransmitter anomalies common to several disorders.

Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS), popularly known as Lou Gehrig's disease, is the most common form of motor neuron disease. Its primary pathology is degeneration of neurons within the anterior horn of the spinal cord and cortical neurons with which they interact. The A4V mutation of the superoxide dismutase SOD1 gene along with FUS positive basophilic inclusions have recently been described in early onset forms of ALS, but most forms are considered sporadic (Aksoy et al., 2003; Baumer et al., 2010; Juneja et al., 1997). Only one study has histologically evaluated the olfactory bulbs from ALS patients, finding in 8 cases accumulation of lipofuscin in cells within the principal neurons of the bulb and AON (Hawkes et al., 1998).

Elian (1991) was the first to assess olfactory function in ALS. The UPSIT scores of 15 British ALS patients (8 with severe bulbar involvement; 8 with confinement to wheel chairs) were significantly lower than those of 15 age- and sex-matched controls [respective means (SDs)=25.2 (7.25) and 35.15 (4.97); $p<0.005$]. Subsequently, Sajjadian et al. (1994) administered the UPSIT to 20 male and 17 female American ALS patients, also finding modest but significant decrements in smell function, with the test scores of the men being lower than those of the women [respective male & female ALS means (SD)=28.00 (8.94) and 32.29 (7.24), $p<0.001$]. Separate testing of each side of the nose of an additional 7 male and 7 female ALS patients found no evidence of lateralized differences. In a third study on this topic, Hawkes et al. (1998) administered the UPSIT to 34 ALS patients and 135 controls. A modest but significant ($p<0.0001$) decrement analogous to those seen in the earlier studies was observed [respective ALS and control means (SDs)=30.2 (5.0) & 33.8 (4.3)].

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Corticobasal degeneration

In corticobasal degeneration (CBD), parkinsonian features are observed along with limb dystonia, ideomotor apraxia, myoclonus and ultimately, cognitive decline. This disorder is associated with the accumulation of tau protein mainly in the fronto-parietal cortex and basal ganglia. The temporal cortex and the olfactory bulbs appear to have little or no tau pathology (Tsuboi et al., 2003).

In one study of 7 patients with clinically suspected CBD, UPSIT scores did not differ significantly from those of age-matched controls (Wenning et al., 1995). A similar conclusion was reported in a more recent study of 7 patients with clinically defined CBD for odor discrimination, although mild deficits in odor naming and odor picture matching were noted (Luzzi et al., 2007).

Drug-induced parkinsonism

Drug-induced parkinsonism (DIP) is most commonly caused by neuroleptic drugs, such as trifluoperazine (Stelazine), flupentixol (Dopixol), and haloperidol (Serenace) that act by non-selectively blocking both D_1 and D_2 dopamine receptors. The prevalence of DIP is lower today than twenty five years ago, reflecting the introduction of selective D_2 DA receptor antagonists for treating psychotic disorders (e.g., quetiapine; clozapine). The influences of DIP on smell function are not entirely clear, as the range of involved drugs is large and only a few studies with relatively small sample sizes have addressed this topic in detail.

Hensiek et al.(2000) tested 10patients whose DIP had been induced by phenothiazine preparations administered for at least 2 weeks. Five of the patients had abnormal UPSIT scores and failed to make a complete recovery from DIP even after the medication was changed or stopped. Of the remaining five, all but one had normal UPSIT scores and all regained normal motor function after medication adjustment. Bovi et al. (2010) administered odor identification and detection tests to sixteen DIP patients (7 Haloperidol, 5 Amisulpride, 2 Perphenazine, 1 Fluphenazine, 1 Clomipramine), 13 PD patients, and 19 age- and sex-matched normal controls. The DIP patients were divided based on normal (n=9) and abnormal (n=7) putamen DA transporter binding as determined from ^{123}I-FP-CIT SPECT imaging. Only those DIP patients with a pathological putamen uptake had abnormal olfactory test scores — scores which, like those for PD, correlated with putamen uptake values. These findings suggested that olfactory loss of DIP patients, when present, is more closely associated with central DA damage than with drug-induced DA receptor blockade.

In contrast to these findings are those of Lee et al. (2007). These investigators administered the B-SIT to 15 DIP and 15 matched normal controls. The DIP had been induced by Levosulpiride, Haloperi-done, Flunarizine, Perphenazine, Metoclopramide, or Risperidone. The B-SIT scores of the DIP patients did not differ from those of 15 controls and were significantly higher than those of 24 patients with sporadic PD (6.9 vs. 4.4; $p<0.001$).

A special case of drug-induced parkinsonism appeared in young drug addicts in northern California in the early 1980s which reflected an error in the synthesis of a heroin-like substance. The agent resulting from the error in synthesis, MPTP, is metabolically converted within the brain, mainly in glial cells, to the toxic ion 1-methyl-4-phenyl-piperidinium (MPP^+) by monoamine oxidase B. MPP^+ selectively damages striatal DA neurons by interfering with complex 1 of the electron transport chain. Unlike MPTP, MPP^+ crosses biological membranes freely, has a high binding affinity to the dopamine transporter, and readily enters dopaminergic terminals. Mice that lack this transporter are protected from MPTP toxicity (Bezard et al., 1999).

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In the only human study on this topic, six of the original young MPTP-induced parkinsonism patients (MPTP-P) were administered the UPSIT and a phenyl ethyl alcohol detection threshold test (Doty et al., 1992a). Comparison groups consisted of 13 young PD patients and ten normal subjects. The UPSIT and threshold scores of the MPTP-P patients did not differ significantly from normal controls, although there was a trend in that direction. The young PD patients, on the other hand, had marked olfactory dysfunction.

It is possible that olfactory dysfunction would have been detected in these individuals if greater MPTP exposure had occurred, either via higher doses or more frequent exposures, or if testing had been performed sooner after their MPTP exposure. Olfactory bulbs from MPTP-treated mice exhibit inflammatory microgliosis and increased expression of cytokines associated with apoptosis such as interleukin-1α (IL-1α) and IL-1β (Vroon et al., 2007). MPTP-treated marmoset monkeys will eat bananas tainted with the bad-smelling odorants, unlike controls or before MPTP treatment (Miwa et al., 2004). The olfactory dysfunction of mice who receive intranasal MPTP recovers over time (Prediger et al., 2006),as does at least one non-motor measure of MPTP-treated monkeys which correlates with olfactory dysfunction in humans (i.e., cardiac denervation) (Elsworth et al., 2000; Goldstein et al., 2003).

Essential tremor

Essential tremor (ET) is sometimes mistaken for PD, even though it differs clinically from PD in a number of ways. For example, the tremor is an action tremor, not a resting tremor, and, unlike PD, ET is not associated with stooped posture, slow movement, or a shuffling gait. There is a family history of tremor in around 50% of cases, unlike PD where there is no more than 5%. The tremor of ET is more likely to involve legs, hands, voice and the head, unlike PD tremors that are most common in the hands when they are at rest. However, this disorder is heterogeneous on a number of grounds and persons with ET are more at risk than those in the general population for developing AD and PD in the future (Laroia and Louis, 2011; Louis, 2009). While damaged cerebellar Purkinje cells are an element of the disease (Axelrad et al., 2008), it is debatable whether they are the pathological basis of the disorder (Louis et al., 2011; Rajput and Rajput, 2011). To my knowledge, no studies have uniformly found neuropathology of any sort within the olfactory bulbs or higher olfactory structures of ET patients.

In contrast to PD, patients with ET have no meaningful olfactory dysfunction. As early as 1992, Busenbark et al. (1992) reported that 15 ET patients scored normally on the UPSIT. Although a later study claimed that a number of ET patients had mild impairment on the UPSIT (Louis et al., 2002), all subsequent studies have found normal UPSIT scores in ET patients (Djaldetti et al., 2008; Shah et al., 2005, 2008). Shah et al. (2008), for example, compared UPSIT scores of 59 ET patients to those of 64 tremor-dominant PD patients. Nearly complete separation of the two groups was made on the basis of UPSIT scores and to lesser degree on measures from OERPs. Surprisingly, when ET subjects were separated by family history of tremor in a first degree relative, this group scored significantly *better* than age-and gender-matched controls, a finding that begs replication.

Lewy body disease

Lewy body disease (LBD) is defined pathologically as a neurodegenerative disorder in which Lewy bodies are heavily distributed throughout the brain. Lewy bodies are intracellular cytoplasmic inclusions, typically of a spherical shape, that form within cell bodies. Lewy neurites, which can extend for considerable distances, are also present in axons and dendrites, and, like Lewy bodies, are mainly comprised of misfolded α-synuclein. PD is generally considered to be a form of Lewy body disease given its wide-spread Lewy

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body pathology. LBD is associated with dementia. If the dementia appears after the onset of the motor symptoms by a year or more, the disorder is called *Parkinson Disease Dementia*. If the dementia occurs before, during, or within a year of the motor symptoms, the syndrome is termed *Dementia with Lewy bodies* (McKeith, 2006).

The few studies that have tested olfactory function in patients with LBD find an olfactory phenotype similar that of PD (Liberini et al., 2000; McShane et al., 2001; Olichney et al., 2005; Wilson et al., 2011). In the largest of these studies, 26 persons with LBD were identified from a sample of 201 autopsied brains of older persons (Wilson et al., 2011). None had PD prior to death and all had been previously administered the B-SIT. Those without Lewy bodies performed at the level expected for someone of their age [mean (SD) age at time of death=88.0 (6.54) yrs], whereas those with Lewy bodies exhibited test scores similar to those expected from older patients with PD (Aden et al., 2011). Importantly, after adjusting for age, sex, education, and time from testing to death, those with Lewy bodies located within limbic or cortical regions exhibited decreased smell function, whereas those with Lewy bodies confined to the substantia nigra showed no significant olfactory deficit. Although these authors did not examine the olfactory bulbs for Lewy pathology, other studies have found such pathology, as well as neurofibrillary tangles and tau pathology, in the bulbs of patients with LBD as well as PD (Mundinano et al., 2011; Tsuboi et al., 2003).

Multiple system atrophy

Multiple system atrophy (MSA), a relatively rapid evolving form of parkinsonism, is accompanied by dysautonomia that affects orthostatic blood pressure, digestion, and the bladder. Dysarthria, stridor, contractures, dystonia, sexual dysfunction, and rapid eye movement (REM) sleep behavior disorder are typical clinical features (Kaufmann and Biaggioni, 2003). In its early stages, it is often misdiagnosed as PD. In 1989, glial cytoplasmic inclusions (GCLs) were discovered in MSA brains (Papp et al., 1989). This discovery confirmed that striatonigral degeneration, sporadic olivopontocerebellary atrophy, and the Shy-Drager syndrome are, in fact, MSA with different clinical expressions. Its most common form associated with PD (MSA-P) accounts for ~80% of all cases and is largely defined by akinesia and rigidity. Cerebellar ataxia is dominant in its other form (MSA-C). In both forms, pathology appears in the basal ganglia, cortex and spinal cord, but peripheral autonomic neurons are spared. Kovacs et al. (2003b) have reported pathological changes in the olfactory bulbs of MSA patients that mainly reflect cytoplasmic inclusions in oligodendrocytes.

In the pioneering study on this topic, 29 patients with a clinical diagnosis of MSA were administered the UPSIT, along with 123 controls (Wenning et al., 1995). Moderate impairment was noted, with a mean UPSIT score of 26.7 compared to the control mean score of 33.5 ($p<0.001$). There were no differences between the MSA-P and MSA-C types. Subsequent investigations have reported similar findings (Abele et al., 2003; Garland et al., 2011; Goldstein et al., 2008; Müller et al., 2002a; Nee et al., 1993). Unlike PD, no meaningful correlation has been found between odor identification test scores and measures of cardiac ^{123}I-metaiodobenzylguanidine (MIBG) uptake (Lee et al., 2006).

Parkinsonism Dementia Complex of Guam

The Parkinsonism Dementia Complex of Guam (PDC), also known as the ALS/parkinsonism-dementia Complex of Guam (ALS/PDC), is a progressive taupathy that has the features and pathology, in variable combinations, of atypical parkinsonism, dementia, and ALS. It is largely confined to the residents of Guam (where it is known by the Chamorros as lytico-bodig disease), the Mariana islands, the Kii peninsula of Japan, and the coastal plain of West New Guinea (McGeer and Steele, 2011). In the past, this disease was

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very common in Guam, accounting for at least 15% of adult deaths in the Chamorro population between 1957 and 1965 (Reed and Brody, 1975; Reed et al., 1966). However, its prevalence has declined markedly in recent years and by 1999 the ALS component was no longer evident (Plato et al., 2003). This suggests the possible involvement of environmental toxins, such as those found in *Cycas micronesica*, a plant previously used to make flour for tortillas and other food products (Ly et al., 2007). Consumption of washed cycad flour pellets by Sprague–Dawley male rats induces a progressive parkinsonian syndrome (Shen et al., 2010).

Significant olfactory bulb pathology is present in PDC, with nearly complete loss of the cells within the AON (Perl and Doty, unpublished data). A retinopathy with an appearance similar to a larval migration has been noted in a significant number of these patients (Cox et al., 1989; Kato et al., 1992), as well as in ALS/PDC Japanese patients from the Kii peninsula (Kokubo et al., 2006). This unique retinopathy has not been found in any other part of the world or in any other neurodegenerative disease

In the first of two published studies, the UPSIT was administered to 24 PDC patients (Doty et al., 1991a). The UPSIT scores of the PDC group were depressed, being equivalent to those from 24 AD and 24 PD North American patients matched on smoking behavior, gender, and age. Prior to testing, the patients were generally *unaware* of their deficit, with 87% of the PDC patients reporting that they had no smell problems. An abbreviated version of the UPSIT was administered in the second of these studies to 9 Guamanians with symptoms of ALS, 9 with symptoms of pure parkinsonism, 11 patients with pure dementia, and 31 patients with PDC, as well as to 53 neurologically normal Guamanians and 25 neurologically normal North American controls (Ahlskog et al., 1998). The UPSIT scores were markedly depressed in the four disease groups relative to the controls, and did not differentiate among the four groups.

Progressive supranuclear palsy

Progressive supranuclear palsy (PSP) is characterized by an inability to voluntarily look up or down, as well as a rapid progression of motor dysfunction, imbalance, and cognitive decline. This disorder is commonly misdiagnosed as PD. Like PD, PSP is associated with widespread accumulation of tau protein in degenerating nerves, although the olfactory bulbs appear to be spared (Tsuboi et al., 2003). In accord with such sparing, Doty et al. (1993) found no significant differences between the UPSIT scores of 21 PSP patients and 21 matched normal controls; however, there was a trend towards higher threshold values in the PSP group ($p=0.085$). Similar UPSIT findings were found in a subsequent study of 15 cases of PSP by Wenning et al. (1995). However, subsequently Silveira-Moriyama et al. (2010) found that PSP patients, while not exhibiting the same degree of smell loss as PD, scored significantly lower than normal controls on the UPSIT. In another study, 23 relatives of PSP patients exhibited lower UPSIT scores than 23 matched controls (Baker and Montgomery, 2001), although both sets of scores were within the normal range.

Pure autonomic failure

Pure autonomic failure (PAF) is a slowly progressing degenerative disease in which failure of the autonomic nervous system is the sole clinical finding (Hague et al., 1997). Lewy bodies are present in the brain stem and pre- and postganglionic autonomic neurons, as well as in the peripheral sympathetic and parasympathetic nerves (Hague et al., 1997). It is conceivable that this disorder is a precursor to PD, but given its slow progression most patients die before significant PD-related CNS involvement becomes evident (Kaufmann and Biaggioni, 2003). Patients with PAF exhibit UPSIT scores essentially equivalent or only

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slightly above those of patients with PD (Garland et al., 2011; Goldstein and Sewell, 2009; Silveira-Moriyama et al., 2009b).

Vascular parkinsonism

Vascular parkinsonism (VP) occurs in patients with extensive cerebrovascular disease involving the basal ganglia, particularly the putamen and striatum. This disorder is often difficult to differentiate from PD. However, it has no resting tremor, is variably responsive to L-DOPA, and exhibits no DA transporter deficits on SPECT or PET imaging. In one study, acute onset cases were found to disproportionately have lesions in the subcortical gray nuclei (striatum, globus pallidus and thalamus), whereas those with insidious onset tended to have more diffusely distributed lesions (Zijlmans et al., 1995).

Katzenschlager et al. (2004) compared the UPSIT scores of 14 VP patients to those of 18 PD patients and 27 normal controls of similar age. The UPSIT scores of the VP patients did not differ significantly from those of the controls (respective mean UPSIT scores = 26.1 and 27.6), whereas the PD patients scored significantly lower than both of these groups (mean UPSIT=17.1; ps<0.0001). These findings imply that olfactory testing may be helpful in differentiating VP from PD.

X-linked recessive dystonia-parkinsonism

X-linked recessive dystonia-parkinsonism, also termed ‘Lubag’, is found primarily among adult male Filipinos with maternal roots from the Philippine Island of Panay. The average age of onset is approximately 40 years. This disorder typically presents with parkinsonism but dystonia, mainly in the jaw, neck, trunk, and eyes, becomes the salient feature as the disease progresses. In some cases, the dystonia occurs the limbs, tongue, pharynx, and larynx, but this is less frequent. The disease can rapidly progress over the course of a few years, resulting in death from pneumonia or other infections.

In the sole study to assess olfactory function in this disease, Evidente et al. (2004) administered a culturally modified 25-item version of the UPSIT to 20 affected males and 20 controls. Slight dysfunction was observed relative to controls (respective means adjusted to 40-item UPSIT scale = 29 and 33, $p < 0.001$). This was observed in the earliest stages of the disease and was unrelated to disease duration, severity, and the degree of dystonia.

Sensitivity and specificity of olfactory testing in differentiating PD from non-PD

The sensitivity and specificity of olfactory testing in discriminating between “sporadic” PD patients and controls or some other forms of parkinsonism equals or exceeds that of other biomarkers, including SPECT and PET imaging of the DA transporter (Deeb et al., 2010). In one study of 180 PD patients and 612 non-PD controls, the sensitivity and specificity of the UPSIT in distinguishing between male PD patients and controls under the age of 61 years was 91% and 88%, respectively (Doty et al., 1995a). For women of the same age, the corresponding values were 79% and 85%. The sensitivity and specificity of this test for those 61 to 70 years of age were 81% and 82% for men and 80% and 88% for women. Katzenschlager et al. (2004) found the overall sensitivity and specificity of the UPSIT in distinguishing between PD (mean = 72.6 yrs) and vascular parkinsonism (mean = 74 yrs) to be 86% and 89%, respectively. When the data were divided into two age categories (65–75 and 76–88 yrs), the sensitivity and specificity values were 100% and 86% and 86% and 80%, respectively. Similar sensitivity and specificity estimates have been noted by others (Double et al., 2003; Möller et al., 2002b).

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Very high sensitivity and specificity, i.e., 100% and 88%, in differentiating PD patients from controls was reported in a study of diffusion weighted imaging (DWI) of the olfactory tracts (Scherfler et al., 2006), a finding that has since been supported by others (Rolheiser et al., 2011). Scherfler et al. first employed statistical parameter mapping of neuronal diffusivity using Trace (D) as the diffusivity marker in 12 PD patients and 12 controls. Significant increases in diffusivity were found within the region of the olfactory tracts of the patients. Trace (D) cut-off values were then established and applied to a new group of 9 early-stage PD patients and 8 age-matched controls. All of the PD patients were correctly classified and only one normal subject was misclassified as having PD.

It is clear that olfactory testing, and possibly DWI, can be useful in differential diagnosis. One should keep in mind, however, the fact that specificity estimates based on comparisons of individuals selected to be normal can be inflated relative to estimates based upon subjects selected from the general population. This is because olfactory deficits are present within the general population in the age groups where PD is most likely, including healthy persons and persons with disorders other than PD, including pre-clinical AD.

Etiology of PD-related olfactory dysfunction

Despite being well characterized phenotypically, the causes of the olfactory dysfunction of PD and other neurodegenerative diseases are poorly understood. To what extent are deficiencies in specific neurotransmitters involved? Can the location of the classic neuropathology of PD, such as Lewy bodies, explain the olfactory losses? What environmental factors, if any, could induce or catalyze the olfactory dysfunction seen in PD? Can a comparative analysis of the olfactory losses across forms of parkinsonism provide insight into common underlying mechanisms?

These and other questions are addressed in this section of the review. An examination of the neurotransmitter deficits that may contribute to the olfactory dysfunction of PD is provided, followed by types of cells within the olfactory system proper that are likely most vulnerable to PD-related pathology. Since there is an inextricable association between neurotransmitter activity and neuropathology, these two topics are often two sides of the same coin.

Neurotransmitter alterations

Among the major neurotransmitters altered in PD and for which considerable olfactory behavioral information is available in other contexts are ACh, DA, 5-HT, and NE. Alterations in any one or combination of these major transmitters and neuromodulators could conceivably produce or contribute to the olfactory dysfunction observed in PD. Such alterations, however, are not mutually exclusive and are typically interrelated. For example, in the striatum both ACh and 5-HT regulate dopaminergic output through direct (e.g., receptors on dopaminergic cells) or indirect (e.g., receptors on glial cells) means.

Acetylcholine

ACh is widely distributed in the brain and targets not only neurons, but astrocytes and oligodendrocyte progenitors (Carnevale et al., 2007; Cui et al., 2006). Several observations support the hypothesis that cholinergic deficits may be responsible, at least in part, for the olfactory dysfunction of PD. *First*, the nucleus basalis – a major cholinergic nucleus with projections to olfaction-related brain regions – is significantly damaged in PD, with autopsy studies reporting decreases in cell numbers ranging from 54% to 77% (Arendt et al., 1983; Nakano and Hirano, 1984; Rogers et al., 1985). This nucleus is similarly compromised in AD, where olfactory dysfunction is equivalent to that seen in PD. Importantly, this nucleus is not affected in MSA and is minimally affected in PSP, disorders accompanied by little or no olfactory dysfunction. *Second*, the α4 and α7 nicotinic ACh receptor subunits are

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markedly depressed in the cerebral cortex of PD patients, as occurs in the cortex of AD patients (Burghaus et al., 2003). *Third*, short latency afferent inhibition, a measure of cholinergic cortical circuits, is significantly increased in PD and AD, but not in PSP, in accord with their relative olfactory losses (Nardone et al., 2005). *Fourth*, the muscarinic ACh receptor antagonist scopolamine impairs human odor detection ability, suggesting cholinergic involvement in human odor perception (Serby et al., 1989). *Fifth*, systemic injections of physostigmine, an acetycholinesterase (AChE) inhibitor, increases the ability of rats to detect low concentrations of butanol within a background of pentyl acetate (Doty et al., 1999) and tighten odor generalization gradients in mice (Mandairon et al., 2011). *Sixth*, chemical blockage of nicotinic receptors by infusion of mecamylamine into the olfactory bulb of rats abolishes spontaneous discrimination behavior to chemically similar odorants, whereas infusion of neostigmine enhances such behavior (Mandairon et al., 2006). *Seventh*, the activity of dopaminergic periglomerular cells is modulated, i.e., inhibited, by cholinergic agents *in vitro* (Pignatelli and Belluzzi, 2008). *Eighth*, mouse strains that differ in the expression of α7-nicotinic ACh receptors correspondingly differ in their ability to perform an odor detection/discrimination task (Hellier et al., 2010). *Finally*, an association between ACh and olfactory function in PD was found in a positron emission tomography (PET) study employing the [^{11}C] methyl-4-piperidinyl propionate acetycholinesterase ligand (Bohnen et al., 2010). This ligand provides a measure of the integrity of the forebrain cholinergic pathway. Relatively strong correlations were present between UPSIT scores and the *in vivo* activity of this ligand in 58 patients within the hippocampus, amygdala, and neocortex (respective rs=0.63, 0.55, and 0.57; all ps<0.001). Similar correlations with dopaminergic activity in the striatum, as measured by [^{11} C]dihydrotetrabenazine vasicular monoamine type 2 (VMAT2) binding, were non-significant following correction for misapplied data points.[3]

Despite the fact that acetycholinesterase (AChE) activity, measured post mortem, is markedly reduced in the cerebral cortex of *de novo* PD patients with no dementia, no further reduction occurs in non-demented patients with advanced PD (Shimada et al., 2009). This implies that the cholinergic deficits, like the olfactory deficits, probably do not progress significantly during the course of the disease unless, conceivably, dementia becomes more manifest.

It is important to recognize that ACh can tonically influence microglial activation. In fact, lack of cholinergic inputs to microglia could remove restraints on inflammatory mediators such as the cytokine tumor necrosis factor-alpha (TNF-α), thereby inducing inflammation and apoptotic cell death (De et al., 2005). While low levels of TNF-α are likely neuroprotective (Suzuki et al., 2004), this is not the case with high levels. There is considerable support for the concept that activated glial cells and local inflammatory processes may contribute to the development of PD-related pathology, as well as pathology associated with a number of other neurodegenerative diseases (Minghetti, 2005).

Dopamine

DA also appears be related to smell dysfunction in PD, although its association is not straight-forward. Degeneration of dopaminergic neurons clearly occurs within the pars compacta of the substantia nigra and within the melanin-containing cells of the ventral

[3]This study inadvertently included zero UPSIT scores for persons who were clearly anosmic on other grounds, but because the UPSIT is a 4-alternative 40-odorant forced-choice test, chance performance would be, on average, 10, not 0. The original cholinergic correlations with the UPSIT scores were 0.56 for the hippocampus, 0.50 for the amygdala, and 0.46 for the neocortex (all ps<0.001). Correlations reported for the association with episodic verbal memory and MMSE scores became nonsignificant after these corrections (Nicolaas Bohnen, personal communication, August 30, 2011). The correlations indicated in the text are after the UPSIT scores with zeros were omitted from the analysis.

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tegmentum, the major source of dopaminergic projections into the olfactory tubercle and other mesolimbic regions. Such degeneration is spared in non-melanized cells of the ventral tegmentum (Tong et al., 2000). While the mesocortical and mesolimbic dopaminergic systems are markedly damaged in PD, they are largely spared in PSP (Ruberg et al., 1985), a disorder which, as noted earlier, has normal or near-normal olfactory function (Doty et al., 1993).

If the olfactory dysfunction of PD is related to DA, it is independent of the synaptic levels of this transmitter, since DA repletion has no effect whatsoever on olfactory test scores (Doty et al., 1992b; Quinn et al., 1987; Roth et al., 1998). Although a key feature of PD and other diseases associated with smell loss is marked damage to the AON, it should be noted that even in normal persons tyrosine hydroxylase (TH), the rate-limiting enzyme involved in DA synthesis, is absent in this structure (Huisman et al., 2004). Moreover, DA is not decreased in the olfactory bulbs from PD patients examined postmortem. In fact, the expression of TH is *increased* in the periglomerular region of the olfactory bulbs of PD patients, particularly in those of women (Huisman et al., 2004, 2008). This increase is accompanied by a gain in the number of dopaminergic periglomerular cells (Huisman et al., 2004; Mundinano et al., 2011). Similar increases in TH expression have been found in patients with AD and frontotemporal dementia (Mundinano et al., 2011). This is also seen in the olfactory bulbs of transgenic rats with α-synuclean mutations (rats that exhibit olfactory dysfunction before motor dysfunction; Lelan et al., 2011), as well as in the olfactory bulbs of wild-type mice and Macaca monkeys injected with MPTP (Belzunegui et al., 2007; Yamada et al., 2004). The elevated bulbar DA likely reflects increased migration of DA-secreting cells from the subventricular zone along the rostral migratory stream into the olfactory bulb, compensating for the loss of a DA-responsive substrate (Bedard and Parent, 2004). Interestingly, in female mice a surge in dopamine occurs within the olfactory bulb after mating that seems to disrupt the perception of odors contained within male mouse urine (Serguera et al., 2008). This adds credence to the concept that too much bulbar dopamine may alter smell function.

Although some studies appear to support the concept that the greater olfactory dysfunction of PD compared to MSA could reflect PD-related damage to dopaminergic cells, as indexed by in vivo DA transporter binding (Swanson et al., 2005), these measurements have been confined tothe striatum. Hence, it is not clear whether such effects are present in olfactory eloquent areas. Moreover, many studies do not exhibit differences in such binding between PD and MSA even in the striatum, and in some cases the reverse finding has been observed, especially in the caudate (Brooks et al., 1990; Scherfler et al., 2006). That being said, significant correlations have been found between UPSIT scores and DA transporter activity within the dorsal striatum, amygdala, and hippocampus of PD patients (Berendse et al., 2011; Bohnen et al., 2007, 2008a; Deeb et al., 2010; Siderowf et al., 2005), as well as in older non-PD cohorts (Wong et al., 2010). Whether such correlations reflect causal associations remains to be determined. They could, for example, be surrogates for adverse influences on dopaminergic cells from some other source, such as ACh or NE.

Behavioral studies in animals are clearly in accord with the view that dopamine influences olfactory function. Thus, intraperitoneal administration of the dopamine D1 selective partial agonist SKF 38393 enhances the odor detection performance of rats (Doty et al., 1998), whereas the dopamine D2 agonist quinpirole depresses such performance (Doty and Risser, 1989). Similar effects are observed when the task is to discriminate subtle differences between two odorants (Yue et al., 2004). Odor discrimination deficits are also observed in mice lacking the dopamine transporter or the D2 dopamine receptor (Tillerson et al., 2006).

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Norepinephrine

NE is abundant within most forebrain limbic structures, including the amygdala, the nucleus accumbens, the bed nucleus of the stria terminalis, the medial septal area, and the nucleus of the diagonal band of Broca (Farley and Hornykiewicz, 1977). As described earlier in the anatomy and physiology section, the LCis the source of noradrenergic projections to the olfactory bulb and to forebrain regions associated with smell. This nucleus is markedly damaged in PD. Indeed, the loss of noradrenergic neurons in this structure is more severe than the loss of dopaminergic neurons within the substantia nigra and, in the case of AD, the loss of cholinergic neurons within the nucleus basalis (Zarow et al., 2003). Interestingly, experimentally-induced damage to the rat LC results in a 25–50% reduction in dopamine release within the caudate nucleus and nucleus accumbens, despite the compensatory abilities of the nigrostriatal pathway to denervation. Hence, experimental LC injury appears to be as disruptive to striatal dopamine release – and its postsynaptic consequences as severe – as the destruction of the nigrostriatal pathway itself (Marien et al., 2004).

Del Tredici et al. (2002) found that 61% (17 of 28) of PD brains they studied had α-synuclean immunostained Lewy bodiesorneurites within the LC. This was somewhat greater than the frequency of such inclusions within the available material of this cohort for the AON (40%; 10/ 25), the olfactory bulbs (47%; 9/19), and the olfactory tracts (58%, 15/ 26), although all of the brains exhibited such inclusions within the dorsomotor nucleus of the glossopharnygeal-vagus complex (DMC). In general, when the olfactory structures were involved so was the LC. Thus, 11 of the 15 cases (73%) involving the bulbs or tracts also involved the LC. Interestingly, of the 17 total cases in which LC involvement occurred, 14 also exhibited Lewy bodies or neurites within one or more of the serotonergic raphe nuclei, i.e., the nucleus raphes magnus, the nucleus raphes obscurus, or the nucleus raphes pallidus.

Although the role NE plays in PD is not clear, it should be noted that it not only modulates cognitive function in a number of species, but facilitates olfactory learning and sharpens the signal-to-noise ratio in several sensory systems (Brennan et al., 1998; Sara, 2009; Sullivan et al., 1994). There is evidence that NE activates, *in vitro*, α1-noradrenergic receptors on mitral cells, increasing their responses to weak stimuli (Hayar et al., 2001). Pharmacological blocking of α-and β-adrenergic receptors together, but not singly, disrupts learning of an odor discrimination task; however, once the task is learned, such disruption has no effect (Doucette et al., 2007). Similarly, bilateral injection of 6-hydroxydopamine (6-OHDA) into the olfactory bulbs of adult rats, which completely depletes bulbar NE, fails to disrupt their performance on an established odor detection operant task (Doty et al., 1988b). Interestingly, young Tg2576 mice, a widely employed model for AD, exhibit degeneration of the LC, a deficit in the number of newborn neurons in the bulb's granular cell layer, and subtle odor memory deficits (Guerin et al., 2009). It is not clear, however, whether the olfactory deficit relates to the LC degeneration or the expression of β-amyloid, or both. β-amyloid expression appears as early as 3 months in Tg2576 mice and has been associated with olfactory dysfunction (Wesson et al., 2010).

It is unlikely that NE deficiency alone causes the smell deficit of PD, since patients with dopamine β-hydroxylase deficiency, who do not synthesize NE, have normal smell function (Garland et al., 2011). If deficiencies in NE influence olfaction in PD, they may do so indirectly, such as via non-neural cells or other mechanisms. Both astrocytes and microglia express functional adrenergic receptors (Feinstein et al., 2002) and NE regulates transcription of inflammatory genes in these cells. Additionally, NE regulates the permeability of the blood– brain barrier (Kalinin et al., 2006). Hence, damage to the LC could, through such mechanisms, increase the vulnerability of the olfactory pathways to toxic xenobiotics, a concept that is supported by a number of animal studies. Thus, lesions of the LC in both primates and rodents increase nigrostriatal susceptibility to damage from

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MPTP, implying a protective role of the noradrenergic input into the striatum (Fornai et al., 1996, 1997; Mavridis et al., 1994; Wachowiak et al., 2005). The α2AR antagonist yohimbine exacerbates MPTP-induced DA neuronal damage in mice, whereas the α2AR agonist clonidine protects against such damage (Fornai et al., 1995). In transgenic mouse models of AD, NE, as well as the NE precursor L-threo-3,4-dihydroxyphenylserine (L-DOPS), reduces amyloid-related neuropathology (Kalinin et al., 2011; Madrigal et al., 2007).

Serotonin

5-HT is found throughout the CNS and plays a key role in arousal, emotion, feeding, sleep, and other basic functions (Fox et al., 2009). 5-HT can modulate the activity of other transmitters, including DA, glutamate, and GABA. For example, 5-HT circuits facilitate (e.g., via 5-HT_{1a}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_3, and $5HT_4$ receptors) or inhibit (e.g., via $5HT_{2c}$ receptors) DA release from nerve terminals (Di et al., 2008). In PD, 5-HT is markedly depleted in the caudate nucleus, cingulate cortex, entorhinal cortex, frontal cortex, hippocampus, and thalamus (Huot et al., 2011; Scatton et al., 1983). Lewy bodies are frequently found within the raphe nuclei, the origin of its projections (Braak et al., 2001).

As noted earlier, AD and PD exhibit marked smell loss, whereas PSP and MSA do not (Doty et al., 1993; Wenning et al., 1995). Interestingly, the limited data suggest that AD and PD exhibit a loss of 5-HT synthesizing neurons within the dorsal raphe nuclei, whereas PSP and MSA do not (Kovacs et al., 2003a). 5-HT is intimately associated with brain circuits related to smell function. For example, activation of brainstem serotonergic neurons reduces the amplitude of olfactory output within olfactory bulb glomeruli by activating subsets of periglomerular cells (Petzold et al., 2009). 5-HT fine-tunes glutaminergic neurons in the olfactory tubercle of the rat (Hadley and Halliwell, 2010). Interestingly, deafferentation of the 5-HT fibers ascending into the bulb by injection of the neurotoxin 5,7-dihydroxytryptamine produces anosmia in rats, with the anosmia appearing about 4 weeks after the injection but more than 3 weeks after the depletion of the serotonergic fibers (Moriizumi et al., 1994). Although NE fibers are spared in some such rats, this is not the case with dopaminergic neurons. Such neurons are decreased in the glomeruli and the bulbs are markedly shrunken, with atrophic granule, external, and internal plexiform layers and a reduction in olfactory receptor cells (Tsukatani et al., 1995).

Jovanovic et al. (2011) have recently demonstrated, in humans, that psychosocial stress induces widespread alterations in 5-HT within the limbic system and influences odor discrimination. In this PET study, 5-HT_{1A} receptor binding was assessed in 16 chronically stressed, but not hospitalized, subjects and 16 non-stressed controls during resting and odor activation periods. The chronically stressed subjects exhibited significantly less 5-HT_{1A} binding than the controls in the hippocampus, as well as in the anterior cingulate and insular cortices ($ps<0.001$). These subjects, unlike the controls, failed to show any meaningful odor-induced activation of the anterior cingulate cortex and performed significantly more poorly on an odor discrimination task.

PD-related pathology within the olfactory system

According to Braak and associates, neurons prone to PD-related pathology contain α-synuclein, the sine qua non criterion for defining PD pathology, as well as lipofuscin or neuromelanin granules (Braak and Del, 2009). These authors point out that those non-myelinated or sparsely myelinated projection neurons with disproportionately long and thin axons relative to their soma size are particularly susceptible to the abnormal aggregations and misfoldings of α-synuclein. They make the argument that less myelination places a greater metabolic burden on neurons to accomplish axonal transmission and increases their

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vulnerability to oxidative stressors associated with neurodegeneration. Additionally, they note that the more myelination, the greater the protection against pathogens and abnormal axonal sprouting.

While the olfactory receptor neurons seem to meet several of Braak's criteria (e.g., lack of myelination, presence of α-synuclein, long axons), abnormal α-synuclein deposits or Lewy bodies have not been observed in these cells. Although some dystrophic neurites and amyloid precursor proteins have been observed, similar changes are present in controls of the same age (Crino et al., 1995). Moreover, the expression of α-synuclein within the olfactory mucosa appears to be no different than that seen in AD, MSA, LBD, and healthy older controls (Duda et al., 1999). That being said, generalized α-synuclein pathology within the olfactory receptor cells could conceivably contribute to the PD-related smell loss since, with the exception of MSA, smell dysfunction occurs in all of these disorders and in older people generally (Doty et al., 1984a; Hawkes and Doty, 2009).

The main output projection cells of the olfactory bulb – the mitral and tufted cells – meet several of the criteria suggested by Braak et al. for susceptibility to PD pathology and, in fact, contain Lewy bodies and related pathology. For example, they are long projection neurons. However, their axons are typically myelinated and some of their primary dendrites may be myelinated as well (Tigges and Tigges, 1980). Lewy bodies and neurites are also found in the unmyelinated axon-less granule and periglomerular cells (Sengoku et al., 2008) and within the internal plexiform layer of the bulb (Fig. 10). Involvement of the AON is substantial, and the loss of neurons within the nucleus correlates with the number of Lewy bodies, as well as with disease duration (Daniel and Hawkes, 1992; Pearce et al., 1995). PD patients with the *LRRK2* genetic mutation also have Lewy bodies within the olfactory bulb (Khan et al., 2005; Ross et al., 2006).

Based upon a careful study of pathological material, Braak and his associates have proposed the hypothesis that PD-related pathology advances centrally in a predictable sequence, beginning in the olfactory bulb, the associated AON, and the DMC (Braak et al., 2003a, 2003b, 2004; Del Tredici et al., 2002) (Fig. 11). Recent work from other laboratories also supports the concept that Lewy pathology may progress along the olfactory pathways, with greater involvement of the bulbs and tracts (Hubbard et al., 2007). Although to a lesser degree than these structures, regions of the olfactory cortex of PD patients at some point display both AD- and PD-related pathology. Thus, Lewy bodies, as well as neurofibrillary tangles, are found within lamina II of the entorhinal cortex (Braak and Braak, 1990). In general, α-synuclein pathology is more severe in the temporal piriform cortex than in its frontal sectors or in the anterior portions of the entorhinal cortex (Silveira-Moriyama et al., 2009a). Interestingly, Lewy bodies have been found in the frontal, temporal, parietal, cingulate, and transentorhinal cortices of *LRRK2* PD patients who had olfactory deficits before death (Silveira-Moriyama et al., 2008), a distribution pattern seen in other *LRRK2* pathology studies (Ross et al., 2006).

A case for the direct involvement of Lewy bodies causing or contributingtothe olfactory lossof PD comes from the autopsy study of Wilson et al. (2011) that was part of the Rush Aging and Memory Project. These investigators found that non-PD cases with Lewy bodies within the limbic or nigral regions exhibited impaired olfaction prior to death, in contrast to the normal function of non-PD cases where such pathology was solely in the substantia nigra. Despite the fact that neuritic plaques and neurofibrillary tangles were also associated with smell loss, the Lewy body pathology accounted for more variance and remained significant after statistically controlling for such AD-related pathology. Unfortunately, pathology within olfactory eloquent structures such as the olfactory bulb and the AON was not assessed, although such pathology has been demonstrated by others (Mundinano et al.,

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2011; Tsuboi et al., 2003). Tsuboiet al. found that tau pathology within the AON was correlated with Lewy body pathology in the amygdala and cortex, suggesting that the olfactory deficits observed by Wilson et al. could be due to tau inclusions within this structure.

In their important paper, Tsuboi et al. (2003) found that those disorders for which olfactory loss is known to be present, i.e., AD, PD, and LBD, exhibit tau pathology within the bulbar component of the AON, whereas those for which olfactory loss is minimal or generally lacking, i.e., PSP and CBD, such tau pathology is absent. The tau protein plays an important role in stabilizing microtubules and, when hyperphosphorylated, results in the formation of paired helical filaments, known as neurofibrillary treads and tangles. In AD, tau pathology appears before β-amyloid deposition and is found in all segments of the bulb, with the highest level occurring in the AON (Smith et al., 1993). Olfactory deficits are seen in transgenic mice that over express human tau in their olfactory bulbs (Macknin et al., 2004).

There is recent evidence that olfactory dysfunction of PD is associated with gray and white matter volumes within the piriform and orbitofrontal cortices (Wattendorf et al., 2009; Wu et al., 2011). Thus, in one study early stage PD patients were found to have olfactory test scores that were inversely related to gray matter volume within the right piriform cortex (Wattendorf et al., 2009). In patients with somewhat more advanced PD, a similar correlation was noted between the gray matter volume ofthe right amygdala and their olfactory test measures. Whether such associations are secondary to olfactory bulb damage has yet to be determined, but they do suggest that pathology within higher order olfactory structures may contribute to the olfactory dysfunction observed in PD.

Associations with xenobiotics

Most cases of sporadic PD do not have a clearly established genetic basis. Twin studies find little evidence for heritability of PD in those populations that have been evaluated (Tanner et al., 1999; Ward et al., 1983). In the same manner, twin studies suggest that heritability of olfactory function is typically low, particularly in older age groups (Doty et al., 2011).

Exposures to a number of environmental agents, including those that can directly damage the olfactory system, are risk factors for PD. Among such agents are viruses, ionized metals, solvents, herbicides, and pesticides (for review, see Doty, in press). A clear-cut example comes from a recent multicenter case–control study that compared lifelong occupational and job task histories, including exposures to specific pesticides, of 519 PD cases to those of 511 controls (Tanner et al., 2009). The risk of having PD was associated with overall pesticide use (Odds Ratio, 1.90; 95% Confidence Interval, 1.12–3.21) and the use of any one of 8 pesticides known to induce PD-like syndromes in experimental animals (OR 2.20, CI 1.02–4.75). Three agents, the organochlorine 2,4-dichlorophenyoxy-acetic acid, the herbicide Paraquat, and the insecticide Permethrin, were associated with an approximately 3-fold increased risk of PD [respective ORs & CIs=2.59 (1.03–6.48), 2.80 (0.81–9.72) and 3.21 (0.65–15.80]. Analogous associations have been observed in other studies between not only pesticide use and PD (Elbaz et al., 2009), but between pesticide use and other neurodegenerative diseases such as AD and multiple sclerosis (Parron et al., 2011).

While genetic substrates likely interact with environmental factors to induce most forms of PD (Lin et al., 2011), genetic susceptibilities may be complex, involving yet-to-be identified combinations of genes idiosyncratic to individuals, aging, specific immune factors, and xenobiotics to which exposures have occurred. Moreover, multiple exposures to one or more offending xenobiotics may be associated with the induction of pathology, as has been observed in rodents (Thiruchelvam et al., 2002). Theoretically, xenobiotics could produce smell dysfunction by damaging olfaction-related neurons and glial cells as a result of

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penetration into the brain via the olfactory mucosa or other routes (Doty, 2008). In potential accord with this possibility is Braak et al. 's hypothesis of a peripheral to central advance of Lewy body-related pathology from the olfactory bulb, the associated AON, and the DMC (Braak et al., 2003a, 2003b, 2004; Del Tredici et al., 2002). Conceivably PD could be initiated or caused by pathogens that enter the brain via the olfactory nerves and/or vagal fibers from the enteric plexus, resulting in taste and smell dysfunction secondary to damage to the olfactory and DMC brain regions (Braak et al., 2006; Hawkes et al., 2007). More recently, Lerner and Bagic (2008) have made the argument, on the basis of known central neural connections, that the pattern of pathology proposed by Braak and colleagues could be explained solely on the basis of a pathogen entering the brain via the olfactory system.

There is considerable evidence that inhalation of some ionized metals can result in their incorporation into the olfactory mucosa and their transport into the brain to possibly induce or catalyze neurodegenerative disease (for reviews, see Doty, 2008; Tjalve and Hendriksson, 1999). In the case of manganese, where airborne exposure has been indirectly implicated with olfactory loss (Antunes et al., 2007), the divalent metal transporter-1 (DMT1) is likely involved. Such transport is enhanced by iron deficiency (Thompson et al., 2007). In accord with this concept is evidence that air pollution components, such as ultrafine particulate matter, may directly damage the human olfactory system and produce PD- and AD-related neuropathology within the olfactory bulbs (Block and Calderon-Garciduenas, 2009). Thus, post-mortem studies have identified, in the olfactory bulbs of both children and young adults who had lived in highly polluted areas of Mexico City, the accumulation of ultrafine (< 100 nm) particulate matter within the olfactory epithelium and bulbs. Evidence of up-regulation of cyclooxygenase-2 (COX2), interleukin 1 beta (IL1β), and the innate immunity receptor CD14 is present in these structures (Calderon-Garciduenas et al., 2004). Some of these individuals exhibit abnormal immunoreactivity to α-synuclein and β-amyloid (Aβ42) within the olfactory nerve ensheathing cells, mitral cells, and tufted cells (Calderon-Garciduenas et al., 2008). Importantly, subtle, but significant, decrements in smell function have been demonstrated in young residents from these polluted regions relative to those in less polluted cities such as Polotitlán (Calderon-Garciduenas et al., 2010).

As noted in the section on drug-induced PD, the best known xenobiotic directly tied to parkinsonism is MPTP. MPTP has a chemical structure similar to that of the herbicide paraquat, an agent that has also been associated with PD. Rodent studies have found that intranasal exposure to MPTP is generally more effective in producing PD-like behavioral and physiological motor symptoms than intraperitoneal exposure (for review, see Prediger etal., 2011). Such exposure induces smell loss and a pattern of sequential cognitive and motor changes similar to those of PD, as described by Braak et al., albeit on a shorter time scale (Prediger et al., 2010). In one set of studies, olfactory, cognitive, and motor changes were monitored in 3-month-old Wistar rats and 5-6 month-old C57BL/6 mice for weeks following exposure to a single nasal infusion of MPTP (0.1 or 1 mg in each nostril) (Prediger et al., 2006,2009,2010). Remarkably, the single intranasal administration of MPTP induced behavioral deficits accompanied by indicators of DA loss in the olfactory bulb, the pars compacta region of the substantia nigra, the striatum, and the prefrontal cortex. Decrements were also present in noradrenergic markers within the aforementioned structures, save the prefrontal cortex, as well as in the hippocampus. Interestingly, no decrement in 5-HT was seen in any of these structures. Cholinergic markers were apparently not assessed. Mitochondrial dysfunction, oxidative stress, activation of apoptotic cell death mechanisms, and glutamatergic excitotoxicity appear to be responsible for the observed changes (Franco et al., 2007; Moreira et al., 2010; Prediger et al., 2006, 2009, 2010). It should be noted that the marked decrement in DA within the olfactory bulb seems at odds with the evidence that the olfactory bulbs of PD patients and other MPTP-related models of

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PD, which uniformly show elevated bulbar DA. This conceivably reflects the intranasal application of the MPTP in these studies.

In light of the theory that xenobiotics may be responsible for the smell loss observed in PD, it is important to point out that viral upper respiratory infections are the most common cause of chronic, often *permanent*, smell loss in the general population (Deems et al., 1991) and that historically viruses were considered to be the primary cause of PD. Poser and colleagues (p. 213) proposed in 1969, for example, that "all parkinsonism results from a non-specific viral meningoencephalitis occurring at some time in life, often in a form so mild as to escape recognition or memory, but becoming clinically manifest later on, perhaps even many years later, as a result of additional injury to the central nervous system" (Poser et al., 1969). In 1977, Moore (1977) (p. 80) concluded that, "Most investigators agree that many if not most cases of Parkinson's disease are a result of viral infection." Such a unitary perspective is not widely held today following the discovery of genetic forms of PD and non-viral toxins like MPTP that can induce classic symptoms of PD.

Conclusions

It is apparent from the studies reviewed in this paper that individuals with PD or related disorders, including genetic forms of parkinsonism, exhibit varying degrees of olfactory dysfunction. While the basis of the dysfunction is likely multifactorial, particularly from the perspective of etiology, it is of considerable interest that those disorders with the most olfactory dysfunction are those with the most pathology not only within the olfactory bulbs, but within brain regions associated with cholinergic, serotonergic, and noradrenergic function. Since the latter systems appear to protect, in animal models, neurons from damage from such toxins as MPP^+, the loss of their regulatory influences on microglia and olfactory eloquent structures may set the stage for olfactory system damage from intrinsic or extrinsic insults. The role of microglia in this process is supported by a vast literature on this general topic, including evidence that pesticides are more toxic to mesencephalic dopaminergic neurons in culture when microglia are present than when they absent (Gao et al., 2003). Many neurons of the olfactory system, particularly those within the microglia-rich olfactory bulb, have high metabolic activity and reduced antioxidant capacity, making them susceptible to impairment of mitochondrial function, oxidative stress, and excitotoxicity. The observation that toxic damage to serotonergic neurons that enter the bulb produces anosmia and marked atrophy of all layers of the bulb strongly suggests that 5-HT input is essential for maintaining the integrity of the bulb and, in particular, dopaminergic neurons (Moriizumi et al., 1994; Tsukatani et al., 1995). Drugs that inhibit the 5-HT transporter are known to induce microglial activation and damage to dopaminergic neurons within the substantia nigra (Macgillivray et al., 2011).

It should not go unnoticed that most risk factors for olfactory loss are the same risk factors as those for the development of PD. Among such risks are age, sex, viral infections, head trauma, metal ion exposure, and pesticide exposure. The only major risk factor that seems to be inversely related to smell loss is cigarette smoking. Smoking adversely influences olfactory function, but nicotine has a protective effect on dopaminergic neurons, primarily through mitigation of microglial inflammatory responses (Park et al., 2007). However, smoking's effect on olfaction is largely reversible and not marked, with the olfactory function of most current smokers falling within the normal range (Frye et al., 1990). The finding that the olfactory function of relatives of individuals with PD who report high lifetime caffeine usage is better that that of relatives who report low lifetime caffeine use (Siderowf et al., 2007) is in accord with the general concept that olfaction and PD are interdependent and that a healthy cholinergic system, in the long run, protects against expression of both smell loss and the classic motor manifestations of PD. From this

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perspective, it is perhaps not surprising that organophosphate pesticides, whose major target is the cholinergic system, are a major risk factor for PD.

Although this review has focused primarily on the olfactory loss of PD and related disorders, it must be stressed that such loss is a major component of aging and is found, in varying degrees, in many other diseases, including other neurodegenerative diseases, neurodevelopmental disorders such as schizophrenia, and a vast array of diseases with cholinergic dysfunction, such as myasthenia gravis and Chagas disease (Leon-Sarmiento and Doty, unpublished). The increased numbers of dopaminergic periglomerular cells seen in the olfactory bulbs of PD patients also appear in the olfactory bulbs of AD patients and patients with frontotemporal dementia (Mundinano et al., 2011), disorders which exhibit olfactory losses similar to those observed in PD (Pardini et al., 2009; Rami et al., 2007). Lewy bodies – the classic defining neuropathological entity of PD – are found in 20-55% of autopsied AD brains. Conversely, neuritic plaques and neurofibrillary tangles, the defining pathological indices of AD, are found in the hippocampus or cerebral cortex of most patients with PD. As noted by Perl et al. (1998), “the concept that the neurofibrillary tangle and the Lewy body are specific and pathognomic features [respectively] of AD and PD does not hold true.”

A challenge for the future is to determine whether and to what degree common pathological substrates are involved in producing the olfactory losses that are present in numerous diseases. Like PD itself, it would seem reasonable to expect that a number of different pathophysiologic processes are involved, both among diseases and within individuals having the same disease — processes that ultimately reach the same endpoint of olfactory dysfunction. For example, the smell loss of some cases of PD may reflect epithelial or bulbar damage initiated by exposure to airborne environmental toxins. In other cases, such as in focal head trauma, microglial activation within the olfactory bulb may occur independently of direct exposure to toxins, as suggested by the work of Lalancette-Hebert et al. (2009). In some instances, damage to the cholinergic pathways via organophosphates could be involved. Importantly, research is needed to determine whether the olfactory dysfunction observed in PD and related disorders is truly dependent upon the formation of disease specific entities, such as Lewy bodies and tau-related neural inclusions and filaments. While correlations are present between olfactory test scores and these entities within the olfactory bulbs, it is yet to be determined whether such associations are obligatory or simply reflect easily measured endpoints of correlated processes. A common process, for example, could induce both the abnormal tau accumulations and the alterations in olfactory function.

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Fig. 1.

The University of Pennsylvania Smell Identification Test (known commercially as the Smell Identification Test) (Doty et al., 1984b). This test, developed in the early 1980s, is comprised of 40 microencapsulated odorants located next to forced-choice questions on each page of 10-page booklets. The vast majority of all olfactory studies of PD patients have used this test. Copyright © 2004, Sensonics, Inc., Haddon Heights, New Jersey.

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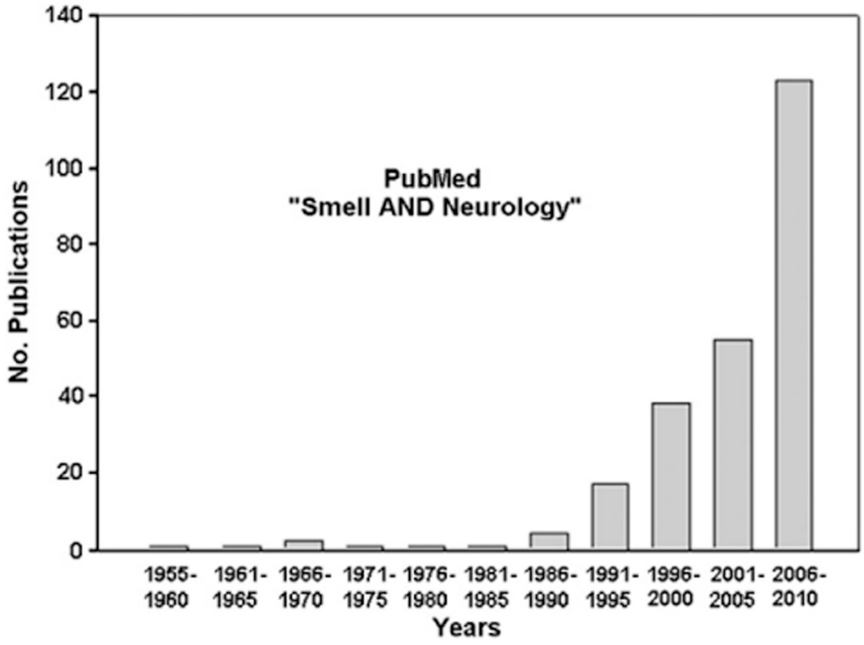

Fig. 2.

Number of publications appearing in PubMed for half-decades from 1955 to 2010 using search phrase “Smell AND Neurology”.

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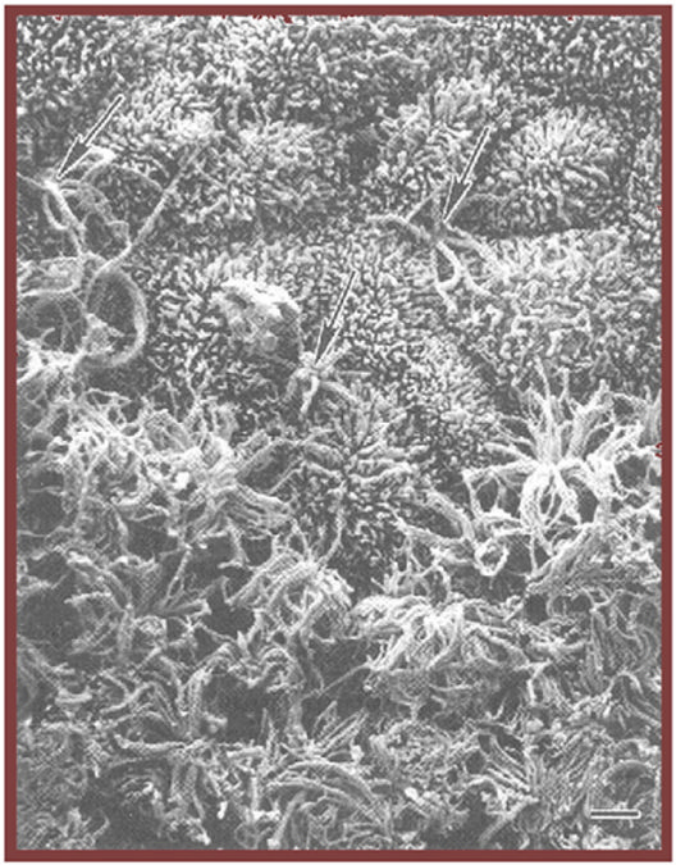

Fig. 3.

A transition zone between the human olfactory epithelium (bottom) and the respiratory epithelium (top). Arrows signify two examples of olfactory receptor cell dendrites with cilia that have been cut off. Bar=5 μm. From Menco and Morrison (2003). Copyright © 2003 Marcel Dekker, Inc.

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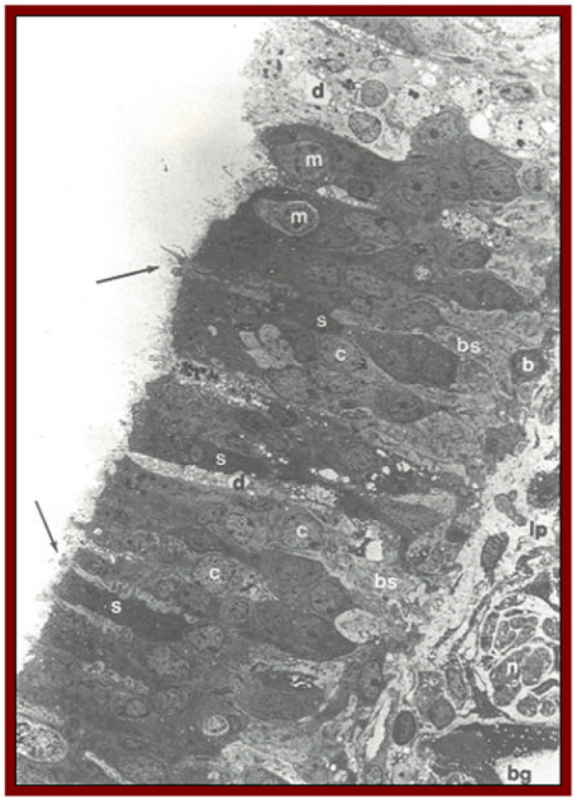

Fig. 4.

Cross-section of the human olfactory epithelium. Four main types of cells can be discerned: bipolar receptor cells (arrows point to largely denuded cilia at dendritic knobs; c, cell body), microvillar cells (m), sustentacular cells (s), and basal cells (b); bg, Bowman's gland; lp, lamina propria; n, collection of axons within an ensheathing cell; d, degenerating cell; bs, basal cell undergoing mitosis. Photo courtesy of Dr. David Moran, Longmont, Colorado.

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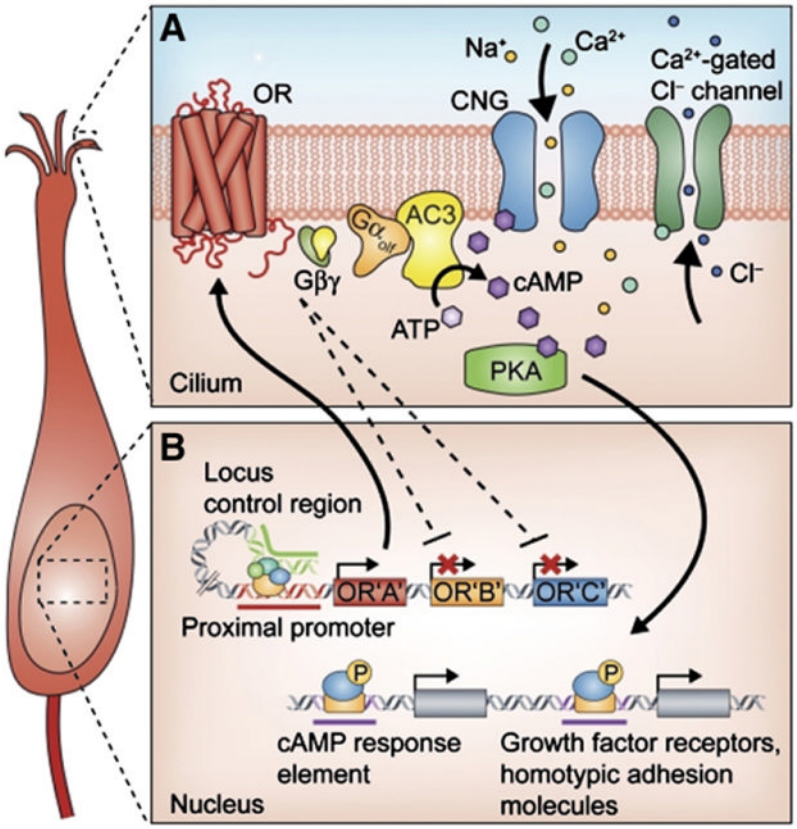

Fig. 5.

Schematic diagram summarizing the intracellular signaling pathways implicated in mammalian olfactory transduction. (A) Representation of the receptors, enzymes, and ion channels - present in the olfactory cilia - that transduce activity of the odorant receptor (OR) into changes in membrane potential and gene expression. Binding of an odorant to its cognate OR results in the activation of heterotrimeric G protein ($G\alpha_{olf}$ plus $G\beta\gamma$). Activated $G\alpha_{olf}$ in turn activates type III adenylyl cyclase (AC3), leading to the production of cyclic AMP (cAMP) from ATP. cAMP gates or opens the cyclic nucleotide-gated (CNG) ion channel, leading to the influx of $Na^+$and Ca^{2+}, depolarizing the cell. This initial depolarization is amplified through the activation of a Ca^{2+}-dependent Cl^- channel. In addition, cAMP activates protein kinase A (PKA), which can regulate other intracellular events, including transcription of cAMP-regulated genes. (B) Events in the nucleus of OSNs important for establishing and maintaining sensory neuron identity. Selection of a particular OR gene by the cell is thought to occur via interaction of a cisregulatory locus control region with the proximal promoter of a single OR gene within a cluster of OR genes. This choice is stabilized – and the expression from all other OR genes in the genome is silenced – by an OR-dependent feedback loop, which ensures the expression of a single OR per sensory neuron. The mechanism underlying OR-mediated, OR gene silencing is at present not understood. OR-mediated activity also leads to transcriptional regulation of cAMP response element binding protein (CREB)-dependent gene expression via CREB's phosphorylation by PKA Reprinted with permission from DeMaria and Ngai, (2010). Copyright © 2010 Rockefeller University Press.

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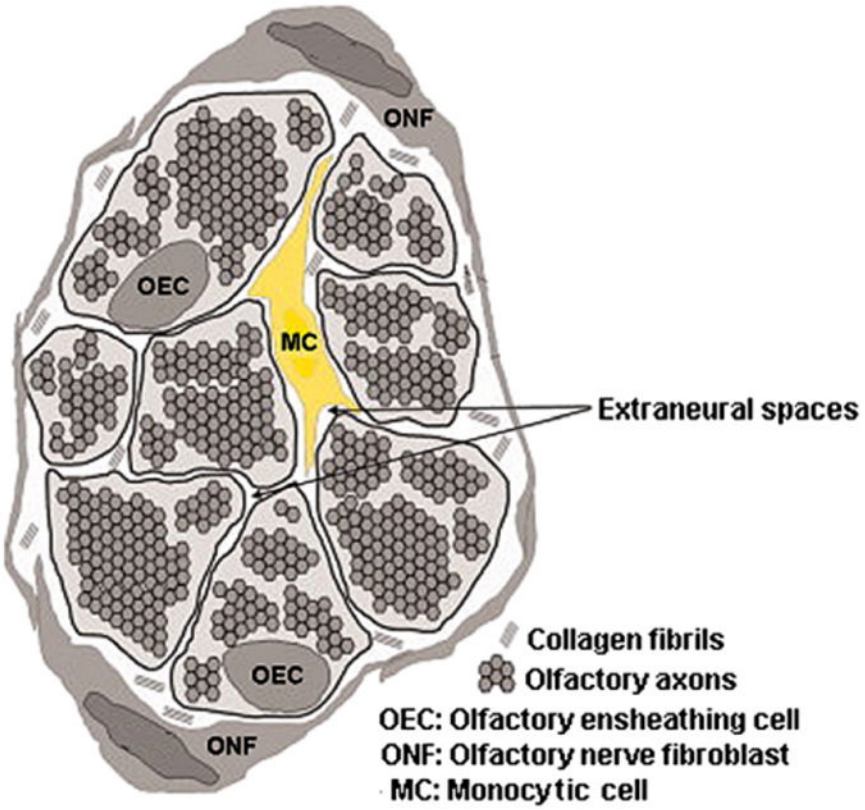

Fig. 6.

Diagram of an olfactory nerve fascicle. Olfactory axons are surrounded by bundles of olfactory ensheathing cells (OECs) which, in turn are surrounded by olfactory nerve fibroblasts. Monocytic cells (MC) and collagen fibrils are located within the extraneural spaces between the lamina bound units. Modified from Smithson and Kawaja (2010) with permission. © 2009 Wiley-Liss, Inc.

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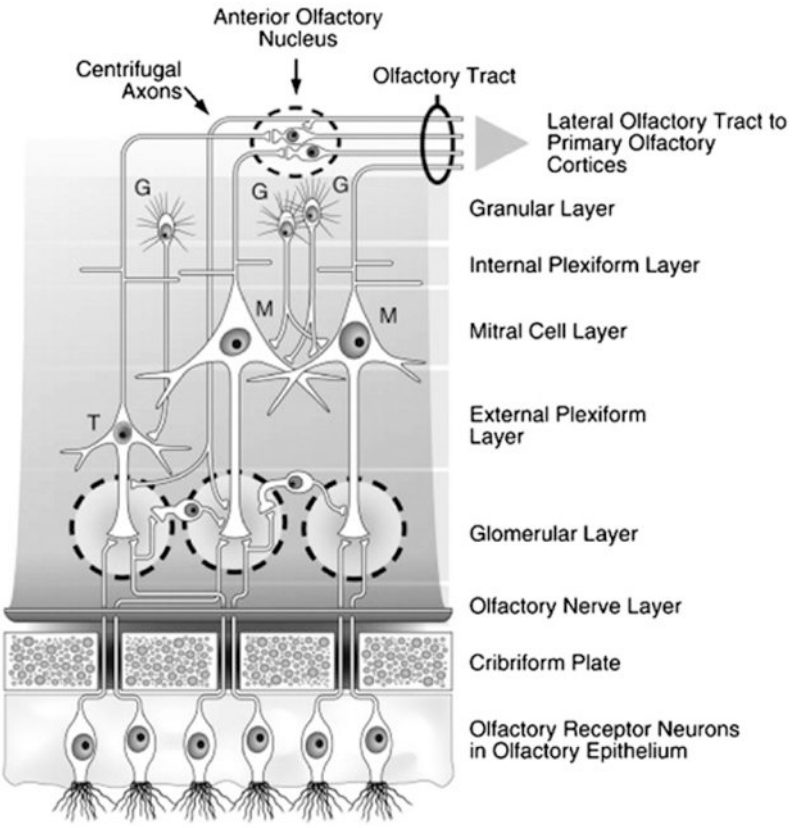

Fig. 7.

Schematic showing the major layers of the olfactory bulb and the interactions between the different types of bulbar cells. The small internal plexiform layer located between the granule cell and mitral cell layers is not depicted. Also not depicted is the fact that the secondary mitral cell dendrites extend down into the external plexi-form layer where they make connections with granule and other cell types. Reprinted with permission from Duda (2010). Copyright © 2010 Elsevier B.V.

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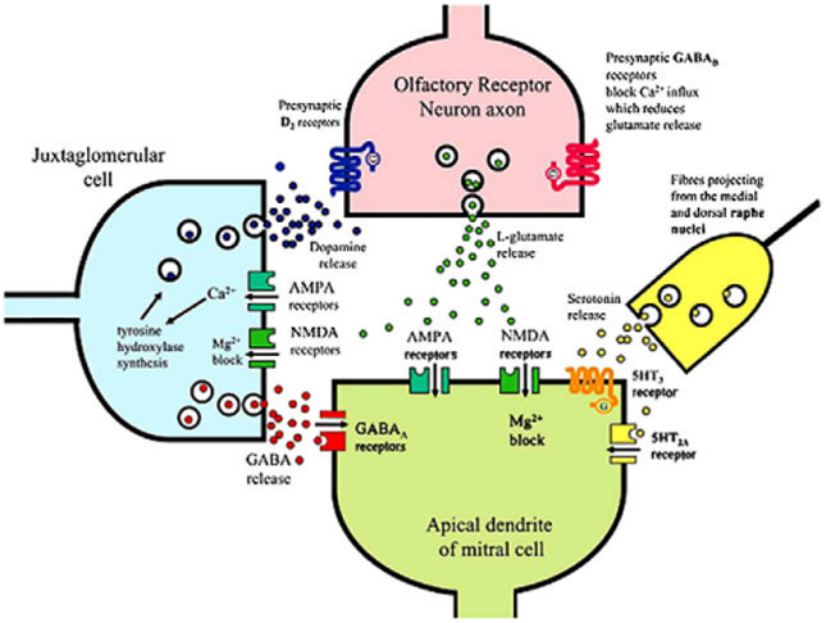

Fig. 8.

Glomerular synapses showing the variety of receptors. The axons from the olfactory receptor neurons form the olfactory nerve which synapses on the primary apical dendrites of the mitral cells. L-glutamate is the primary excitatory transmitter at this synapse which binds to AMPA and NMDA receptors on the postsynaptic membrane. Juxtaglomerular cells are inhibitory GABAergic/dopaminergic interneurons that mediate inhibition between glomeruli. Centrifugal fibers project from the Raphe nuclei to the glomeruli modulating the mitral cell activity via postsynaptic 5HT receptors. Reprinted with permission from O'Connor and Jacob (2008). Copyright © 2008 Bentham Science Publishers.

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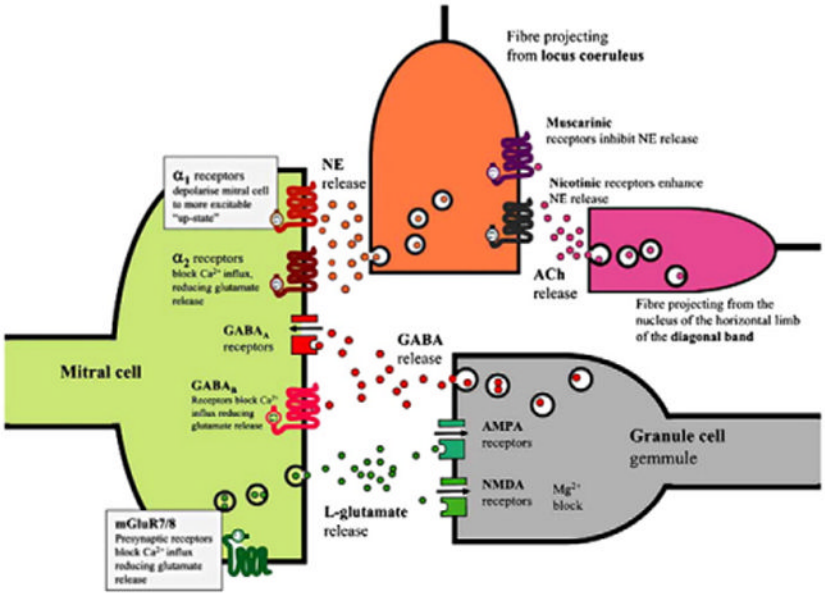

Fig. 9.

Synapses in the external plexiform layer of the olfactory bulb showing the variety of receptors and neurotransmitters. Granule cells mediate feedback and lateral inhibition between mitral cells with which they form reciprocal dendrodendritic synapses. Adrenergic and cholinergic efferent fibers project from the diagonal band and the LCrespectively. Reprinted with permission from O'Connor and Jacob (2008). Copyright © 2008 Bentham Science Publishers.

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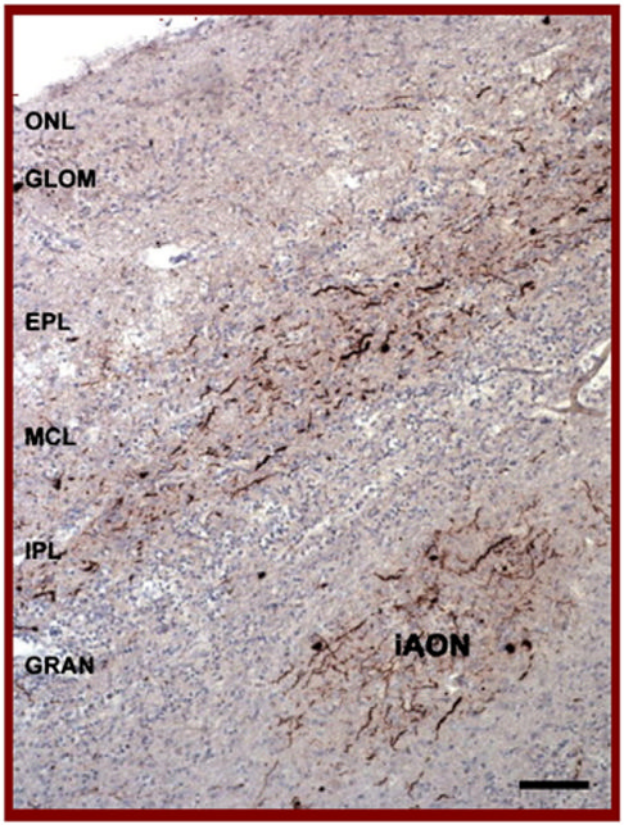

Fig. 10.

Lewy neurite and Lewy body pathology within the olfactory bulb of a PD patient. Immunostaining with an antibody specific to aggregated alpha-synuclein (brown stain) is most dense within the internal plexiform layer (IPL) and the intrabulbar anterior olfactory nucleus (IAON). Other abbreviations: ONL: olfactory nerve layer; GLOM: glomerular layer; EPL: external plexiform layer; MCL: mitral cell layer; GRAN: granular layer. Scale bar=100 μm. From Duda (2010) with permission. Copyright © 2010 Elsevier B.V.

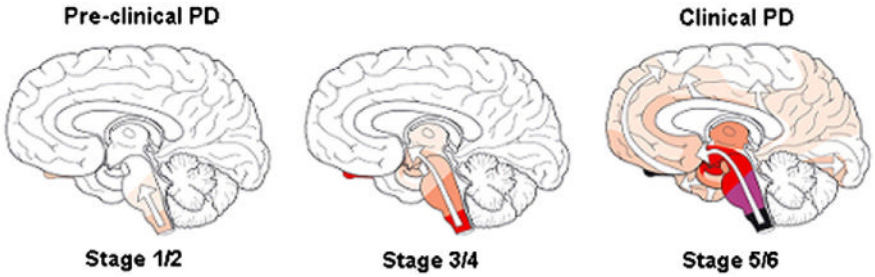

Fig. 11.

According to the staging system of Braak, PD-related Lewy body pathology evolves in predictable stages. Lewy bodies (LB) first form within in the olfactory bulb and dorsal motor nucleus of the vagal nerve (Stage 1). LB pathology then expands from these induction sites into additional brain stem nuclei (e.g., locus coeruleus and substantia nigra) and then into the amygdala (Stages 2 and 3). In Stages 5 to 6, the pathology extends into the cerebral cortex. Clinical symptoms arise during Stages 4 to 6 when the pathology involves significant regions of the substantia nigra and related brain areas. From Thal et al. (2004).

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Table 1

Genetic forms of PD or parkinsonism. Those forms for which olfactory tests have been administered are indicated in yellow. Those forms initially believed to be associated with PD but now are suspect are shown in dark pink.

PARK1/PARK4 (4q21-q23)	*α-synudein*	Autosomal dominant	A30P, A53T, E46K: duplications & triplications	Early onser; dementia; autonomic dysfunction, Rare and not yer observed in sporadic PD cases,
PARK2 (6q25.2-q27)	*Parkin*	Autosomal recessive	A wide variety of mutations, exonic deletions, duplications and triplications	Juvenile and early onset: slow progression; good L-DOPA response
PARK3 (2p13)	Unknown	Autosomal dominant	Not Identified	Late onset; typical PD features
PARK5 (4pl4)	*UCHL1*	Autosomal dominant	I93M, S18Y	Late onset; good L-DOPA response; typical PD features; role in PD is questionable as only one family with possible non-fully segregated pathogenic mutations has been found and no additional evidence as a genetic risk factor has come forth
PARK6 (Ip35-p36)	*Pink-1*	Autosomal recessive	G309D, exonic deletions	Early onset; slow progression; good L-DOPA response
PARK7 (1p36)	*Dj-1*	Autosomal recessive	Homozigotic exonic deletion, L166P	Early onset, slow progression; very rare
PARKS (12ql2)	*LRRK2*	Autosomal dominant (incomplete penetrance)	G2019S (most common), R1441C/C/H,Y1699C, 12020T, C2385R, others	Late onset. Tremor dominant PD symptoms
PARK9 (1p36)	*A1P13A2*	Autosomal recessive	Loss-of-function mutations	Atypical PD features; Kufor-Rakeb syndrome; juvenile and early onset (11 -16 yrs); dementia; pyramidal degeneration; spasticity; paralysis of gaze
PARK10 (1p32)	Unknown	Not clear	Not identified	Late onset, typical PD features
PARK11 (2q36-q37)	*G1CYF2*	Autosomal dominant (incomplete penetrance)	Seven missense variants	Late onset, typical PD features; however, pathogenicity of mutations have not been replicated and original PARK11 family studies now known to have no *GIGYF2* mutation, questioning a role in PD susceptibility
PARK12 (Xq21-25)	Unknown	Not clear	Not identified	Late onset PD
PARK13 (2pl2)	*0M1/HTRA2*	Not clear	A141S, G399S	Late onset PD. However, pathology of G399S mutation not replicated and A141S not found to be associated with PD risk, questioning a role in PD suscepribility
PARK14 (22ql3.1)	*PLA2G6*	Autosomal Recessive	Two missense mutations	Early cerebellar signs and visual disturbances; late-onset dystonia with PD features; good L-DOPA response
PARK 15 (22q12-ql3)	*FBX07*	Autosomal Recessive	Three point mutations	Early onset, progressive pallidio-pyramidal syndrome
PARK 16 (1q32)	*RAB7*	Risk	*RAB7L1, SLC41A1*	Late onset PD
PARK 17 (4P16)	*GAK*	Risk	Not identified	Late onset PD

PARK 18 (6P21.3)	*HLA-DRA*	Risk	Not identified	Late onset PD

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Table 2

Olfactory test results of PD patients with various PARK8 (LRRK2) mutations.

Mutation	N	Age†	UPSIT score	Relative to age	Author
3342A>G	1	81	35*	Normal	Berg et al. (2005)
G2019S	19	66.09 (10.08)	16.83 (SD: 7.12)	Abnormal	Ferreira et al. (2007)
G2019S	19	NA	"51% w/abnormal scores"	1/2 Abnormal	Healy et al. (2008)
G2019S	3	80.6 (9.9)	2 anosmic, 1 microsmic	Abnormal	Lohmann et al. (2009)
G2019S	14	62.3 (21.3)	17.5 (SD: 6.8)	Abnormal	Silveira-Moriyama et al. (2008)
G2019S	14	66 (14.6)	23.5*	Abnormal	Silveira-Moriyama et al. (2010)
G2019S	14	NA	27.7 (SD: 7.2)	Abnormal	Kertelge et al. (2010)
G2019S	25	72 (11)	33rd percentile	Abnormal	Marras et al. (2011)
G2019S	31	64.7 (9.8)	24.8 (SD: 7.08)	Abnormal	Saunders-Pullman et al. (2011)
G2019S	14	61.9 (12.6)	21.5 (SD: 7.3)	Abnormal	Valldeoriola et al. (2011)
G2385R	2	50, 73	15, 15	Abnormal	Lin et al. (2008)
I2020T	1	60	35*	Normal	Berg et al. (2005)
R793M	1	67	10*	Abnormal	Berg et al. (2005)
R1441C	3	87, 83, 65	25, 28, 34	2/3 Abnormal	Markopoulou et al. (1997)
R1441G**	39	70 (9.6)	NA	1/3 Abnormal	Ruiz-Martinez et al. (2011)
R1441H	2	56, 81	10, 24	Abnormal	Ferreira et al. (2007)
S1096C	1	78	35*	Normal	Berg et al. (2005)
S1228T	2	57, 61	25*, 35*	1/2 Abnormal	Berg et al. (2005)
Y1699C	4	67, 68, 67, 49	24, 25, 34, 36	1/2 Normal	Khan et al. (2005)

Abbreviations: CI = 95% confidence interval; NA = Not available; SD = Standard Deviation: UPSIT = University of Pennsylvania Smell Identification Test.

*UPSIT score estimated from ID score on Sniffin' Sticks by multiplying percent correct times 40.

**Based on B-SIT and a combination of 39 R1441G and 5 G2019S mutation carriers.

+mean (SD) or individual scores.