



Olfactory dysfunction in neurodegenerative diseases: is there a common pathological substrate?

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In patients with neurodegenerative diseases, there is a spectrum of smell dysfunction ranging from severe loss, as seen in Alzheimer's disease and Parkinson's disease, to relatively little loss, as seen in progressive supranuclear palsy. Given the ubiquitous but varying degrees of olfactory dysfunction among such diseases, it is conceivable that differential disruption of a common primordial neuropathological substrate causes these differences in olfactory function. For example, the amount of damage to forebrain neurotransmitter and neuromodulator circuits, most notably those involving cholinergic transmission, appears to be correlated with quantitative smell test scores across a wide range of neurodegenerative diseases. Thus, a key question is whether damage to such a substrate is the basis for the perceptual differences in olfaction or whether disease-specific or other entities, such as respiratory infections or pollution, are responsible. In light of the early preclinical onset of smell deficits in many neurodegenerative diseases, the answer to this question might provide crucial insight into the cause of disease pathology at its earliest stages of development.

Introduction

Despite its importance, clinicians rarely test the olfactory function of their patients. As a result of quantitative testing, it is now known that most people older than 65 years have some form of olfactory dysfunction, ranging from mild loss (mild hyposmia) to total loss (anosmia).¹ This dysfunction substantially affects wellbeing and quality of life, reducing enjoyment from food, beverages, personal care products, and the natural environment. Decreased smell function increases the risk of danger from fire, environmental toxins, leaking natural gas, and spoiled food. This risk is especially relevant for those whose livelihood or safety are directly affected by the ability to smell (eg, chefs, plumbers, fire fighters, policemen, perfumers, beverage tasters, and employees in numerous industries, including the chemical, water, gas, and power industries). In fact, anosmia disqualifies applicants for "appointment, enlistment, and induction" into the US Armed Forces, including the Coast Guard, and can be a basis for discharge or retirement.²

Numerous factors influence the ability to smell, including sex, exercise and physical activity, genetic factors, smoking, nutrition, head trauma, medical procedures, and exposure to viruses and xenobiotics. Even occupation can influence smell function, as shown by increased olfactory test scores and enlarged olfaction-related brain regions in perfumers and master sommeliers.³ Particularly relevant to neurologists is the fact that olfactory dysfunction can be a clinical, or in some cases a preclinical, sign of neurological diseases such as Alzheimer's disease, Huntington's disease, Parkinson's disease, vascular dementia, and idiopathic rapid eye movement sleep behaviour disorder.⁴ Surprisingly, less than a quarter of individuals with smell dysfunction are cognisant of their sensory problem until formally tested. Importantly, olfactory dysfunction in elderly people is associated with early mortality. For example, in a longitudinal study of 1162 non-demented people aged 65 years and older,⁵ those with lowest baseline olfactory test scores had a 45% mortality rate

over a 4-year period, compared with an 18% mortality rate in those with the highest test scores.

The question arises as to whether a common neuropathological substrate can explain the similarities and differences in olfactory test scores among neurodegenerative diseases. When does loss of smell first appear? Does the loss precede the onset of disease-specific neuropathological lesions, potentially exposing yet-to-be-defined precursors, or is it simply caused or potentiated by disease-specific neuropathologies? In this Personal View, I explore these questions and suggest that differential damage to forebrain circuits, most notably those involved in cholinergic transmission, might be responsible for the differences in olfactory test scores. I also consider alternative hypotheses, including the involvement of disease-specific pathologies and the adverse effect of viruses and xenobiotics on the olfactory system, either through direct damage to the olfactory receptors or by penetration into the brain via the olfactory neuroepithelium.

Basics of olfactory anatomy and physiology

The olfactory nerve (cranial nerve I) is comprised of 6–10 million olfactory receptor cells whose ciliated dendrites and cell bodies are harboured within a specialised neuroepithelium lining the highest recesses of the nose (figure 1). These cells have the unique capability of regeneration from stem cells when injured or senescent, although such regeneration is not always complete. In human beings, nearly 400 types of odorant G-protein-coupled receptors (GPCRs) are present on the cilia of olfactory cells, with a given cell expressing only one type of receptor. Other receptors, such as trace amine-associated receptors and members of the non-GPCR four-pass transmembrane MS4A protein family, have also been found on some olfactory neurons. Such a plethora of receptor cell types does not exist in any other sensory system. The olfactory receptor cells are interspersed among other cell types, including supporting cells that stabilise the epithelium. Bowman's glands are the main source of mucus found in the

olfactory epithelium. That mucus contains multiple proteins that metabolise xenobiotics and help to maintain the integrity of the epithelium. The perception of a given odour reflects the pattern of activation across receptor cells that is interpreted by higher brain regions, such as the piriform, entorhinal, and orbitofrontal cortices.

The axons of olfactory receptor cells are encapsulated by fascicles, termed fila, that enter the brain through the foramina of the cribriform plate and terminate within glomeruli of the olfactory bulb (figure 1). Cells that express a given GPCR, despite being broadly distributed throughout the epithelium, project to only one or two common glomeruli. In many species, cells intrinsic to the bulb—ie, periglomerular and granule cells—are replenished by differentiating neuroblasts that enter the bulb's core via the rostral migratory stream from their origin within the brain's subventricular zone. However, the degree to which this process occurs in human beings is controversial. Such replenishment, along with the regeneration of olfactory receptor cells, makes the olfactory bulbs one of the regions of the mammalian brain with the highest metabolic activity.

The olfactory bulb is unique in terms of the nature of its microglia. Unlike microglia in other brain regions, many cells within the bulb are pre-set to a primed state in which they are continuously expressing Toll-like receptor 2 (TLR2), which mediates cytokine production.⁸

In a study in mice,⁸ olfactory bulb microglia were activated by ischaemic brain injury far from the bulb hours before such activation occurred in tissues near the injury, and remained for months after the injury.⁸ In the same study, a single small dose of lipopolysaccharide from *Escherichia coli* introduced into the mouse's nose induced a widespread wave of TLR2 activation from the bulb to higher regions of the brain.⁸ These findings suggest that olfactory bulb microglia might serve as sensors or modulators of brain inflammation in general.

When does olfactory dysfunction appear?

Although olfactory dysfunction can precede the clinical diagnosis of some neurodegenerative diseases, estimates vary of when such dysfunction occurs. This variation reflects numerous factors, not least of which is the fact that awareness of olfactory deficits is often absent until formal testing or substantial loss occurs. Thus, an accurate determination of dysfunction onset requires longitudinal administration of sensitive smell tests to large numbers of at-risk asymptomatic people who initially have normal smell function (panel). Only a few studies are available that shed light on this issue.

In Parkinson's disease, olfactory dysfunction typically occurs 4–8 years before diagnosis, although in some cases it can occur as early as 20 years before diagnosis.⁹ In a study of 34 patients with idiopathic rapid eye

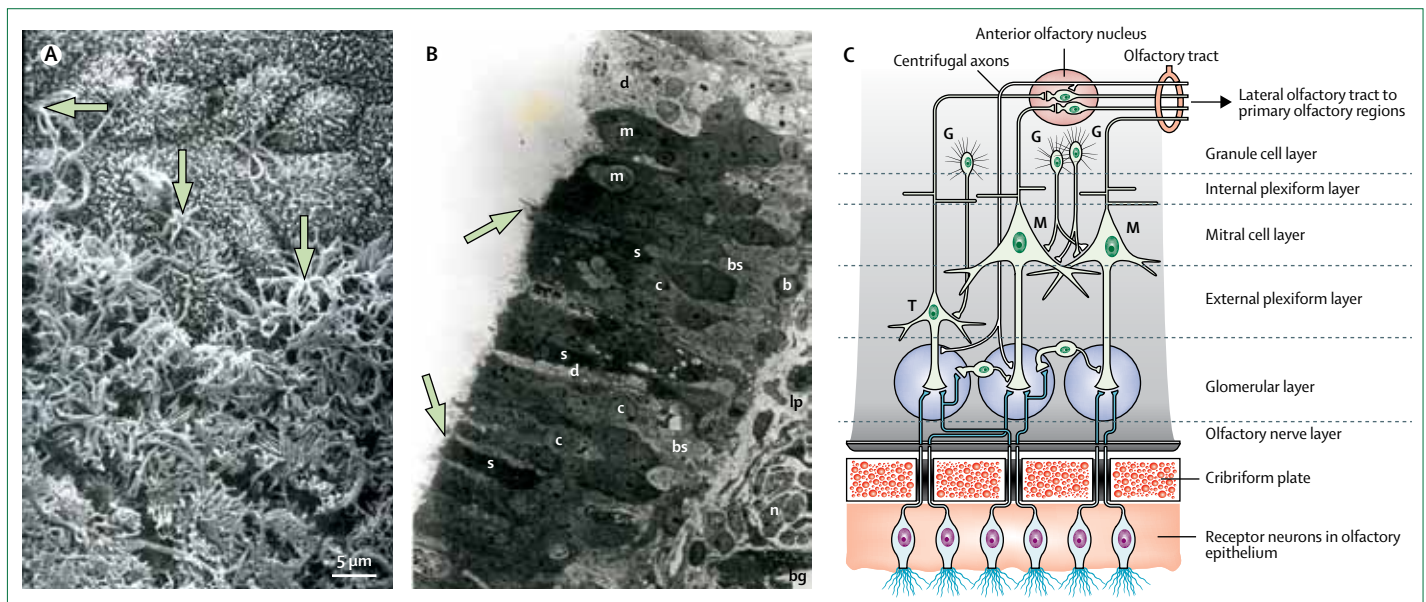


Figure 1: The olfactory system

(A) A transition zone between the human olfactory epithelium (bottom) and the respiratory epithelium (top). Arrows signify three olfactory receptor cell dendrites, the upper two being those with cilia that have been largely cut off. Bar=5 μm. Reproduced with permission from Menco and Morrison.⁶ (B) Photomicrograph of a cross section of the human olfactory epithelium. Four main types of cells can be discerned: bipolar receptor cells (c=cell body), sustentacular cells (s), microvillar cells (m), and basal cells (b). Most of the mucus in this region comes from Bowman's glands (bg). Arrows point to largely denuded cilia at dendritic knobs; some cilia can be seen projecting into the mucus. Photo courtesy of David Moran, Longmont, CO. bs=basal cell undergoing mitosis. d=degenerative cell. lp=lamina propria. n=collection of axons within an ensheathing cell. (C) Diagram of the main cell types and layers of the olfactory bulb, the first relay station of the olfactory system. The bulb is located at the base of the brain immediately over the cribriform plate and receives axons from the olfactory receptor cells. These axons synapse with dendrites of the main output neurons, the mitral and tufted cells, within glomeruli, which are spherical masses of neuropile that make up a distinct layer of the bulb. Cells located between the glomeruli (periglomerular cells) often extend across several glomeruli. Note the centrifugal input from central brain regions onto the granule (G), mitral (M), and tufted (T) cells. Modified from Duda and colleagues.⁷

movement sleep behaviour disorder by Mahrknecht and colleagues,¹⁰ poor odour identification test scores were associated with a 7·3 times increase in the risk of developing either Parkinson's disease or dementia with Lewy bodies in nine (27%) participants.¹⁰ In these cases, the olfactory dysfunction presumably pre-dated the diagnosis of Parkinson's disease or dementia with Lewy bodies by more than 5 years. In non-demented older people, low olfactory test scores have been associated with future cognitive decline and an increased probability of an Alzheimer's disease diagnosis over the course of the subsequent 2–5 years.¹¹ However, as in the study by Mahrknecht and colleagues,¹⁰ some participants already had smell loss when they were first evaluated,

making the actual period between olfactory loss and the Alzheimer's disease diagnosis somewhat longer. Genetics comes into play, since asymptomatic relatives of patients with Alzheimer's disease are more likely to exhibit smell loss than non-relatives, and odour detection or identification test scores are lower, on average, in people with one or more *APOE* $\epsilon 4$ alleles.¹² Individuals with smell loss who carry such alleles are much more likely to experience greater cognitive decline over a 2-year period than either normosmic allele carriers or anosmic non-allele carriers.¹³ Whether such people are already at the earliest stages of Alzheimer's disease is unknown.

Classic neuropathological markers of neurodegenerative diseases

Most attempts to explain olfactory dysfunction in common neurodegenerative diseases have focused on neuropathological markers such as extracellular amyloid β -containing plaques, intracellular neurofibrillary tangles of abnormally phosphorylated tau, or aggregates of α -synuclein that make up Lewy bodies and Lewy neurites. Although no pre-mortem olfactory testing has been done, tau-related pathology has been found in the olfactory bulbs of people with Alzheimer's disease, Parkinson's disease, dementia with Lewy bodies, or frontotemporal dementia, but not in people with disorders associated with less smell loss, including progressive supranuclear palsy and corticobasal degeneration. In addition to aberrant accumulation of tau, the olfactory bulbs obtained post-mortem from patients with Alzheimer's disease or Parkinson's disease, but not those from patients with frontotemporal dementia, contained deposits of amyloid β or α -synuclein. It is not clear, however, whether these deposits cause smell dysfunction or are manifestations of previous damage associated with such dysfunction. For example, since acetylcholine inhibits the production of amyloid β ¹⁴ and damage to cholinergic neurons can exacerbate the development of amyloid pathology and hippocampal atrophy,¹⁵ amyloid pathology might reflect the aftermath of damage to cholinergic forebrain neurotransmitter or neuromodulator (hereafter termed neurotransmitter) circuits. A vicious circular process might ensue once abnormal deposits of amyloid β occur, a phenomenon that might be similar to situations in which α -synuclein is overexpressed.¹⁶ Results from rat studies have shown that amyloid β peptides can inhibit, even under non-pathological conditions, the synthesis and release of acetylcholine within the diagonal band of Broca,¹⁷ a structure that supplies cholinergic neurons to the olfactory bulb. Indeed, the cholinergic brain regions most susceptible to Alzheimer's disease are those in which acetylcholine release is suppressed by amyloid β .¹⁸ However, deposits of tau, amyloid β , or α -synuclein cannot explain the olfactory dysfunction of disorders in which such abnormalities do not exist.

Panel: Olfactory tests

The most commonly used olfactory tests measure an individual's ability to identify, detect, discriminate, remember, or assess the perceived build-up of odour intensity as suprathreshold concentrations increase. Despite their different names and operational procedures, the results of most of these tests are correlated with one another and they presumably measure common underlying physiological processes. Nonetheless, comparisons between nominally different olfactory tests should be made with caution, since such tests differ in reliability, are not equated for non-olfactory task demands, and use different odorants.

The most widely used test is the University of Pennsylvania Smell Identification Test (UPSIT), a 40-odorant, microencapsulated (scratch and sniff) test that has been translated into 30 languages and administered to over 1 million people worldwide. In this and other odour identification tests, familiar odours are presented, one at a time, to an individual. The individual's task is to correctly identify each odour from a set of multiple-choice written alternatives. In a detection threshold test, the lowest concentration of an odorant that can be perceived is determined, usually by comparison with a blank. To achieve high reliability, staircase procedures analogous to some pure-tone hearing tests that repeatedly sample the perithreshold region are frequently used.

The most common odour discrimination tests require the individual to pick the odd stimulus from a set of foils, whereas the most common odour memory tests establish an individual's ability to recognise a given odour over various periods of time. The build-up in perceived intensity as a function of increasing stimulus concentrations is often assessed using rating scales and procedures in which the relative intensity is signified by numbers given in response to the relative perceived intensity. Although electrophysiological (eg, odour-induced event-related potentials measured from the scalp) and psychophysiological (eg, odour-induced respiration changes) tests are available, they are largely confined to research settings because of issues related to practicality, utility, and cost.

Neurotransmitter dysfunction

A potential explanation for the similarities and differences in olfactory function among neurodegenerative diseases (figure 2) is the relative damage to neurotransmitter systems that affect olfaction either directly (eg, by influencing neural transmission or microglial function) or indirectly (eg, by altering regeneration within the olfactory epithelium and possibly the subventricular zone). Forebrain damage to such circuits can be assessed pre-mortem using proton magnetic resonance spectroscopy, volumetric MRI analyses, functional imaging of neurotransmitter-specific ligands, and electrophysiological measures (eg, short-latency afferent inhibition). Damage can also be determined post-mortem using neurochemical and morphological means—eg, by quantifying cell losses within the cholinergic nucleus basalis of Meynert, the noradrenergic locus coeruleus, the serotonergic raphe nuclei, and the dopaminergic ventral tegmental area, among others. In the following sections, I present evidence about the potential involvement of the major neurotransmitter circuits in olfactory dysfunction in neurodegenerative diseases. Unfortunately, because of technical or historical reasons, data are available for only some of the diseases listed in figure 2, and are frequently unavailable for olfaction-related structures, particularly in the earliest stages of disease development. Moreover, neurotransmitters do not work in isolation, but are influenced by one another and by other processes within the brain, complicating the interpretation of findings. Nevertheless, the degree of damage to several neurotransmitter circuits is usually correlated with differences in olfactory test scores.

Acetylcholine

Damage to the forebrain cholinergic system (figure 3) is a strong candidate for explaining the different degrees of olfactory loss among neurological disorders. Acetylcholine has been shown to modulate the innate immune system that, when weakened, greatly diminishes resistance to pathogens.²¹ Nicotinic acetylcholine receptors, located on macrophages and microglia, mainly regulate anti-inflammatory pathways within the basal forebrain. Additionally, acetylcholine enhances the differentiation of oligodendrocytes, the myelin-forming cells of the CNS, via increased myelin gene expression. This is an important point because myelinated nerve fibres are less vulnerable than non-myelinated fibres to Alzheimer's disease or Parkinson's disease pathology.²² Basal forebrain cholinergic neurons are more sensitive to pathogenic agents and ischaemic damage than other types of neurons, including their counterparts within the pontine cholinergic system.²³ Acetylcholinesterase inhibitors such as donepezil and galantamine can protect neuronal cells from glutamate neurotoxicity via nicotinic acetylcholine receptors.²⁴ In a mouse model of Alzheimer's disease, early microglial activation was associated with upregulation of $\alpha 7$ -nicotinic acetylcholine microglial receptors.²⁵ In a rat

model of Parkinson's disease, in which 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) was infused into the nasal cavity, olfactory dysfunction, oxidative stress, and alterations in glutathione-related antioxidant defences were detected in the olfactory bulb and other structures within 6 h.²⁶ 3-nitrotyrosine, a marker of oxidative stress, is detected post-mortem in human olfactory receptor neurons of patients with Alzheimer's disease, including the ciliated dendritic knobs.²⁷

Imbalances in the expression of a number of neuropeptides and proteins directly influence the integrity of cholinergic pathways. These molecules include the peptide galanin and neurotrophins such as NGF, its precursor proNGF, BDNF, and its precursor proBDNF. NGF, for example, alters acetylcholine release, choline acetyltransferase concentrations, high-affinity choline uptake in synaptosomes, and muscarinic and nicotinic receptor expression.^{28,29} Indeed, NGF and BDNF are crucial for maintaining the survival of forebrain cholinergic neurons; when concentrations of these neurotrophins are markedly reduced, cholinergic neurons atrophy.³⁰ Exogenous administration of neurotrophins can rescue degenerating forebrain cholinergic neurons in rats.³¹ Decreases in BDNF and proBDNF concentrations precede the decline in choline acetyltransferase activity in autopsied

Neurodegenerative disorder	N	Age (years)	UPSIT score	% difference from control	p value
Dementia with Lewy bodies	26	77.6 (7.3)	13.6 (NA)*	55.7%†	<0.001
Vascular dementia	13	79.2 (6.3)‡	12.0 (19)§	50.0%	<0.001
Sporadic Alzheimer's disease	25	69.5 (8.4)	18.5 (6.6)	46.9%	<0.001
Down's syndrome	16	14.3 (4.5)	19.3 (4.7)	46.4%	<0.001
Idiopathic Parkinson's disease	50	63.0 (47)‡	18.2 (6.8)	45.2%	<0.001
Parkinsonism-dementia complex of Guam	24	60.5 (7.5)	20.5 (7.3)	43.7%	<0.001
Huntington's disease	12	42.0 (3.6)	21.2 (7.0)	40.1%	<0.001
Vascular parkinsonism	15	73.4 (8.3)	18.3 (4.4)	40.0%	<0.001
Frontotemporal dementia	14	64.9 (10.0)	23.3 (3.6)‡	32.7%	<0.001
Mild cognitive impairment	21	73.2 (9.0)	24.2 (8.6)	28.8%	<0.001
PARK 8 (LRRK2) parkinsonism	14	69.1 (12.6)	21.5 (7.3)	27.6%	0.007
REM sleep behaviour disorder	44	70.9 (6.1)	20.4 (6.8)	26.3%	<0.001
Multiple system atrophy	29	58.6 (8.6)	26.7 (29)‡	20.3%	<0.001
Incidental Lewy body disease	13	86.2 (6.2)	22.2 (9.1)	19.9%	0.004
Corticobasal degeneration	7	67.1 (5.1)	27.1 (6.6)‡	19.1%	<0.001
Drug-induced parkinsonism	15	65.8 (7.9)	23.0 (5.3)	14.8%	0.072
Spinocerebellar ataxia type 7	28	42.6 (14.3)	24.5 (4.2)	13.2%	<0.001
Amyotrophic lateral sclerosis	37	61.7 (10.5)	30.4 (6.3)	12.5%	<0.001
X-linked dystonia-parkinsonism	20	44.6 (7.4)	28.7 (5.1)	12.3%	0.003
Progressive supranuclear palsy	21	68.0 (7.2)	31.0 (7.4)	12.1%	0.019
Multiple sclerosis	25	42.2 (7.2)	33.7 (5.1)	9.3%	<0.001
Gaucher disease	30	60.9 (11.9)	32.5 (9.3)¶	8.5%	0.01
Essential tremor	29	67.3 (NA)	31.0 (4.4)	6.1%	Not significant
MPTP-induced parkinsonism	6	26–42‡	33.9 (2.1)	2.8%	Not significant

Figure 2: Olfactory dysfunction in neurodegenerative disorders

Scores are mean (SD) unless otherwise specified. Disorders are ordered in terms of relative differences in UPSIT scores compared with matched controls and are grouped into the arbitrary difference categories of >35%, 19–35%, 8–15%, and 0–7%. Whether essential tremor is a neurodegenerative disorder is highly debated,³² although it is listed here because it is often misdiagnosed as Parkinson's disease and has no meaningful olfactory loss. Data are mostly from reference 4. *Based on extrapolation to 40 odours from the 12-item Brief Smell Identification Test. †Controls based on median from age-adjusted and sex-adjusted normative data.²⁰ ‡Range. §Data are median (range). ¶Interquartile range. UPSIT=University of Pennsylvania Smell Identification Test. NA=not available. PARK 8=Parkinson disease (autosomal dominant). LRRK2=leucine-rich repeat serine/threonine protein kinase 2. REM=rapid eye movement. MPTP=1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine.

brains of patients with Alzheimer's disease.³² Since NGF is predominantly synthesised by subsets of GABAergic neurons, including those in the cortex, nucleus basalis of Meynert, medial septum, and horizontal limb of the diagonal band,³³ early cholinergic damage could reflect the dysfunction of GABAergic neurons in these brain regions.

Substantial damage to the nucleus basalis of Meynert or ascending basolateral cholinergic circuits is evident for diseases accompanied by marked smell loss, and is absent or less evident for diseases with little or no loss (figure 2). Although data are not available for all disorders listed in figure 2, this generalisation holds true for all of those for which data are available. Thus, depending on the study, the average percentage of cell loss within the nucleus basalis of Meynert ranges from 68–77% for Alzheimer's disease, 50–77% for Parkinson's disease, and 85–90% for the parkinsonism-dementia complex of Guam, to 24–50% in young (<16 years) people with Down's syndrome. In Huntington's disease and vascular dementia, compromised subcortical cholinergic fibres and marked reductions in hippocampal, neocortical, and striatal choline acetyltransferase have been described,³⁴ although the nucleus basalis of Meynert is largely spared in both diseases.^{35,36} By contrast, none or considerably less damage to the nucleus basalis of Meynert is apparent in diseases with relatively little smell loss, including amyotrophic lateral sclerosis, multiple sclerosis, and

progressive supranuclear palsy. Results from studies employing short-latency afferent inhibition (SAI), an electrophysiological measure of largely acetylcholine cortical circuits, are consistent with these findings. Thus, SAI is significantly reduced in diseases with marked smell loss (Alzheimer's disease, Down's syndrome, frontotemporal dementia, idiopathic rapid eye movement sleep behavior disorder, and Parkinson's disease), but not in progressive supranuclear palsy, which has comparatively little smell loss.^{37–41} In patients with mild cognitive impairment, only those with amnesic features show a reduction in SAI.⁴²

In patients with Parkinson's disease, but not progressive supranuclear palsy, acetylcholinesterase activity, as measured by PET, is markedly altered within ascending cholinergic pathways arising from the nucleus basalis of Meynert.⁴³ In one study, positive correlations of greater than 0·50 were found in patients with Parkinson's disease between odour identification test scores and acetylcholinesterase activity within the hippocampal formation, amygdala, and neocortex.⁴⁴ Similar to olfactory dysfunction, such cholinergic dysfunction does not progress with disease severity.⁴⁵

Dopamine

The potential involvement of dopamine in contributing to losses of olfactory function cannot be overlooked, although evidence for its influence across a range of diseases is less compelling than that for acetylcholine. Ventral tegmental area damage, as measured by cell loss, is considerable in Alzheimer's disease (40–60%),⁴⁶ middle-aged adults with Down syndrome (53%),⁴⁶ and Parkinson's disease (39–65%).⁴⁷ However, progressive supranuclear palsy, a disorder with comparatively less smell loss, is accompanied by substantial damage to mesocorticolimbic dopaminergic projections, as measured either with PET imaging of the dopamine transporter⁴⁸ or in autopsy studies.⁴⁹ Treatment with L-DOPA or dopamine agonists has no effect on the ability of people with Parkinson's disease to identify odours.⁵⁰ Moreover, in a PET study of 29 patients with Parkinson's disease, no correlation was found between cerebral dopamine transporter activity and a 10-odour identification test, suggesting that Parkinson's disease-related olfactory loss probably reflects a non-dopaminergic olfactory mechanism.⁵¹ A subsequent PET study⁴⁴ of 58 patients with Parkinson's disease found no significant correlation between University of Pennsylvania Smell Identification Test (UPSIT) scores and VMAT2, a marker for dopamine, when misapplied UPSIT data points were omitted.⁵² However, other studies have reported modest correlations between odour identification test scores and dopamine transporter activity within striatal brain regions of patients with Parkinson's disease.⁵³ The sole study⁵⁴ that assessed the potential association between olfactory test scores and SPECT imaging of the dopamine transporter in idiopathic rapid eye movement sleep behaviour disorder found no association.

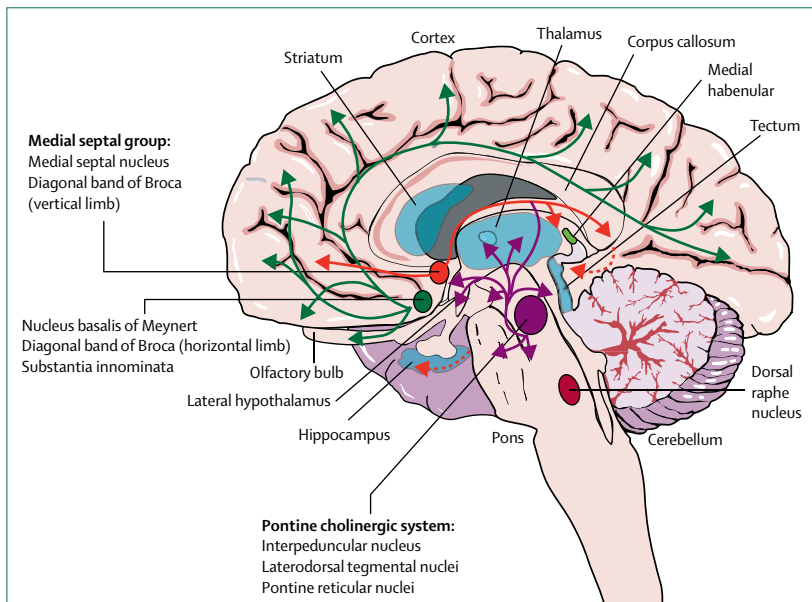


Figure 3: Major cholinergic projections of the human brain

Structures that directly affect the olfactory bulb and pyriform cortex (not shown) are the nucleus basalis of Meynert and the horizontal diagonal band of Broca. Another nearby nucleus is the substantia innominata, which apparently does not modulate olfaction. Other key cholinergic nuclei are those of the medial septal group and the pontine cholinergic group. Other cholinergic neuron groups include the medial habenular nucleus, the striatum, and the subependymal zone. Major cholinergic projection targets are the basal ganglia, cerebellum, cortex, dorsal raphe nucleus, hippocampus, interpeduncular nucleus, lateral hypothalamus, olfactory bulb, pons, pontine reticular nuclei, substantia nigra, thalamus, and tectum. Dotted red lines represent septal projections to sectors of the hippocampus that fall outside the plane of section.

Norepinephrine

The relative damage to the locus coeruleus, as measured by cell loss, is similar in magnitude to that seen for the nucleus basalis of Meynert in those neurodegenerative diseases for which data are available. However, patients with dopamine β -hydroxylase deficiency, an inherited recessive autosomal disorder in which norepinephrine synthesis is eliminated, have intact smell function.⁵⁵ Since cognitive function is intact in these patients, other neurotransmitters might subsume the role of norepinephrine in this disorder.⁵⁶ Pharmacological blocking of α -adrenergic and β -adrenergic receptors disrupts the initial learning of an odour discrimination task in rats but, once the task is learned, such disruption has no effect.⁵⁷ Depletion of bulbar norepinephrine by 6-hydroxydopamine also has no effect on a learned odour discrimination task.⁵⁸

Serotonin

Similar to norepinephrine, a general role for serotonin as an explanation for the different degrees of olfactory function in neurodegenerative diseases seems unlikely. Several non-neurodegenerative disorders with low serotonin levels, including anorexia nervosa and depression, have relatively normal olfactory function. PET studies have found no differences between patients with Parkinson's disease and healthy controls in serotonin binding in the cingulate and limbic brain regions.⁵⁹ Despite age-related deficits in smell and sleep, no age-related changes are apparent in the proportion of cells that are able to synthesise serotonin in the medial raphe nuclei.⁶⁰ Nevertheless, one study⁶¹ reported smell loss in rats within a few weeks after lesioning serotonergic projections to the olfactory bulb with the serotonergic neurotoxin 5,7-DHT. Noradrenergic fibres were spared but glomerular dopaminergic neurons were not, and the olfactory receptor cell population was markedly reduced, reflecting atrophy within the granule and the internal and external plexiform layers.

GABA

The extent to which alterations in GABA differentially influence olfactory processes in neurodegenerative diseases is unknown. Olfactory sensitivity appears to be greater in transgenic mice whose GABA_C receptor channel ρ_1 subunit has been knocked out, than in those who express the receptor, reflecting the release of inhibition of mitral cell activity.⁶² On the other hand, hyposensitivity to odours has been reported in the GABA-synthesising enzyme glutamic acid decarboxylase (GAD67^{-/-}) knockout mouse.⁶³ A general downregulation of GABA does not appear to be present in the prefrontal cortex of patients with Alzheimer's disease, since glutamate decarboxylase activity and the number of GABAergic neurons are not altered.⁶⁴ Nonetheless, reduced expression of $\alpha 1$ and $\alpha 2$ GABA_A subunits has been shown in both early and late stages of Alzheimer's

disease.⁶⁴ In Parkinson's disease, decreased mRNA expression of glutamic acid decarboxylase has been shown in the prefrontal cortex.⁵⁹

Interactions between neurotransmitter systems

Despite evidence that differential damage to some neurotransmitter systems is associated with differing degrees of olfactory dysfunction among neurodegenerative diseases, interactions between systems are evident, suggesting complexity. For example, mesolimbic and mesocortical dopamine circuits are under profound cholinergic modulation, and nicotine, a nicotinic acetylcholine receptor agonist, strongly affects the mesolimbic dopamine system.⁶⁵ Norepinephrine can influence cholinergic transmission via presynaptic $\alpha 2$ -adrenergic heteroreceptors on cholinergic terminals or cell bodies within the basal forebrain.⁶⁶ $\alpha 7$ -nicotinic acetylcholine receptors modulate the release of GABA, dopamine, and norepinephrine in numerous brain regions, including the hippocampal formation.⁶⁷ Nicotinic, cholinergic, and serotonergic receptors are found on the same presynaptic nerve terminals, where they cross-regulate each other's actions.⁶⁸ In the prefrontal cortex, dopamine modulates GABAergic transmission.⁶⁹ In turn, GABA influences dopamine release in this brain region.⁷⁰ As noted previously, imbalances in the expression of neuropeptides and proteins directly influence the integrity of cholinergic neurotransmitter pathways.

Environmental exposures to viruses and xenobiotics

Environmental exposures to viruses and xenobiotics might also provide an explanation for the olfactory losses in many diseases, either independently or in conjunction with neurotransmitter alterations or other processes, such as the breakdown of the blood–brain barrier. Some agents are capable of invading the brain via the olfactory receptor cells, perineural spaces, or lymphatic channels of the olfactory neuroepithelium, possibly catalysing neurodegenerative disease, an idea known as the olfactory vector hypothesis.⁷¹ Receptor cell cilia expose a surface area to pathogens that is conservatively estimated to be 23 cm². To protect against brain invasion and epithelial damage, various binding proteins and chemical-metabolising enzymes are secreted into the olfactory mucus by Bowman glands and sustentacular cells.⁷² Though viral and xenobiotic penetration into the brain can also occur via some other cranial nerves, such as the trigeminal nerve, the olfactory pathways are pre-eminent.

Viruses

Upper respiratory viral infections are the most common cause of permanent smell dysfunction in people without neurological disease,⁴ reflecting damage to the olfactory neuroepithelium, including the stem cells through which regeneration can occur.⁷³ Some viruses taken up by olfactory receptor cells are blocked from further transport

by virus-induced cellular apoptosis before they complete their replication cycle.⁷⁴ If the stem cells are not severely damaged, regeneration of the receptor cells can occur. Other viruses can express anti-apoptotic genes that suppress neuronal apoptosis, facilitating invasion of the brain.⁷⁵ Once inside the olfactory bulb, a number of viruses target specific brain circuits. For example, herpes simplex virus (HSV)-1, when inoculated into the rat olfactory bulb, infects the locus coeruleus, the horizontal limb of the diagonal band of Broca, the raphe nuclei, and the ventral tegmental area.^{76,77} Some blood-borne viruses, such as the Venezuelan equine encephalitis virus and the arthropod-borne St Louis encephalitis virus, eventually enter the olfactory receptor nerves via the fenestrated capillary bed underlying the olfactory neuroepithelium.^{78,79} In one of the few virus-related studies to have assessed olfactory function, 6–8-month-old C57BL/6 mice inoculated intranasally with Sendai virus showed impaired olfactory function without evidence of gross cytopathology. This virus adversely influenced epithelial regeneration and persisted within the olfactory epithelium and bulb for at least 60 days.⁸⁰

Historically, viruses were believed to be the major cause of Parkinson's disease.⁸¹ Although this view has since been tempered following the discovery of genetic forms of Parkinson's disease and risk factors for Parkinson's disease such as MPTP and pesticide exposure, a large body of literature suggests that viruses do play a role in Parkinson's disease and some other neurodegenerative diseases.⁸² Thus, antibodies or other evidence of viral infection have been found to be higher in the autopsied brains of people with neurodegenerative diseases with the most smell loss (figure 2), relative to the brains of healthy controls. Whether a close relationship exists between smell dysfunction and antibodies or other indicators of viral involvement is unknown. Included are cytomegalovirus in vascular dementia⁸³ and Alzheimer's disease,⁸⁴ HSV-6 in Alzheimer's disease,⁸⁴ HSV-1 in Alzheimer's disease,⁸⁴ and hepatitis C in vascular parkinsonism.⁸⁵ Additionally, NWS and WSN strains of neurotropic influenza A_v virus have been detected in post-encephalitic parkinsonism.⁸⁶ A meta-analysis⁸⁷ found that brains from patients with Alzheimer's disease were five times more likely to be infected with *Chlamydomydia pneumoniae* than brains from those without Alzheimer's disease.

Air pollution and smoking

Air pollution might be a risk factor for mild cognitive impairment,⁸⁸ Alzheimer's disease,^{89,90} and Parkinson's disease,⁹¹ as well as possibly vascular dementia,⁹² Down's syndrome,⁹³ schizophrenia,⁹⁴ and amyotrophic lateral sclerosis.⁹⁵ and can substantially influence smell function.⁹⁶ Although constituents of air pollution, including nanoparticles, can enter the brain via the lungs and bloodstream, the olfactory neuroepithelium is a common route.⁷¹ For example, people living in highly polluted areas of Mexico City showed olfactory bulb endothelial

hyperplasia, neuronal accumulation of nanoparticles, and immunoreactivity to amyloid β in the olfactory bulbs, indicative of nanoparticle entrance through the olfactory mucosa.⁹⁶ APOE $\epsilon 4$ carriers are at particularly high risk of olfactory loss and olfactory bulb pathology.⁹⁶ Such pathology might migrate from the olfactory bulb to other brain structures.⁹⁷

Paradoxically, data from the US National Health and Nutrition Examination Survey showed that past smokers, after adjusting for age and sex, had a decreased risk of experiencing olfactory dysfunction relative to peers who had never smoked.⁹⁸ Moreover, another study found that current smokers with Parkinson's disease, despite performing worse than healthy controls on an odour identification test, outperformed past smokers with Parkinson's disease.⁹⁹ Numerous epidemiological studies suggest that smoking decreases the risk of Parkinson's disease in the general population¹⁰⁰ and might afford at least some short-term olfactory protection from workplace exposures to airborne acrylates and methacrylates.¹⁰¹ Whether this protection reflects nicotinic stimulation of cholinergic circuits is unknown.

Pesticides and herbicides

Exposure to pesticides and herbicides can increase the risk of Alzheimer's disease,¹⁰² Parkinson's disease,¹⁰³ and amyotrophic lateral sclerosis.¹⁰⁴ For example, exposure to maneb, paraquat, rotenone, and ziram increases the risk of Parkinson's disease.¹⁰⁵ In one multicentre study of 519 patients with Parkinson's disease and 511 controls,¹⁰⁶ exposure to paraquat, permethrin, and 2,4-dichlorophenoxyacetic acid were associated with about three times the risk of developing Parkinson's disease. Although one cross-sectional study of 123 fumigation workers and 120 controls found statistically significant lower odour test scores in those occupationally exposed to sulfuric fluoride, the effects were very small (mean UPSIT scores=33.1 for fumigation workers vs 34.4 for controls; $p=0.03$) and other studies have not found meaningful decrements in smell function in people exposed to various pesticides.^{107,108} However, in rodents, the olfactory epithelium is damaged by intraperitoneal injections of the herbicide dichlobenil¹⁰⁹ and the pesticide diethylamine.¹¹⁰ Decreased smell function has been observed in rats following intraperitoneal injections of paraquat,¹¹¹ dichlobenil, 3,3'-iminodipropionitrile, and methimazole,¹¹² and in mice after intranasally administered rotenone.¹¹³ Degeneration of the olfactory neuroepithelium has been documented in rats after 45 days of air exposure to the fungicide benomyl.¹¹⁴

Conclusions and future directions

This Personal View posed the hypothesis that differential damage to a common, possibly primordial, pathological substrate might explain the differing degrees of olfactory dysfunction observed among numerous neurodegenerative disorders. Under the

assumption of the existence of a general cause, damage to forebrain cholinergic neurotransmitter circuits, and factors such as NGF or BDNF on which they depend, might be that substrate. Cholinergic neurotransmitter dysfunction is also common in other diseases accompanied by smell loss, such as Korsakoff psychosis, Chagas disease, and myasthenia gravis, suggesting the possibility of a general involvement of neurotransmitter dysfunction. Other possible candidates for explaining the differential loss of smell in neurodegenerative disorders are disease-specific pathology and the noxious effects of viruses and xenobiotics, such as pesticides and nanoparticles, on olfactory epithelia or CNS olfactory structures. Such effects, however, need not be independent of one another or of cholinergic neurotransmitter circuit dysfunction.

Despite the evidence in support of a common underlying cause, data from more neurodegenerative diseases are needed to further support, refute, or better delineate this hypothesis. More information regarding the influences of genetics, sex, and other risk factors, is needed. For example, in people with Alzheimer's disease, women that are *APOE* $\epsilon 4$ carriers, but not men, show a decrement in odour recognition memory compared with women who are not allele carriers.¹¹⁵ Although the risk for Parkinson's disease as a result of exposure to pesticides is increased in people with specific genetic variants, such as those in the *ABCB1* gene that encodes the xenobiotic transporter P-glycoprotein 1, it is unknown how this risk factor relates to either the severity of olfactory dysfunction or to alterations in specific neurotransmitter systems.¹¹⁶

It should be emphasised that neurotransmitter systems are complex; multiple receptors are involved even for a given neurotransmitter circuit and, as noted previously, interactions between circuits are pervasive. Hence, more detailed evidence of the specific neurotransmitter receptor classes is needed. Moreover, neurotransmitter activity in one part of the brain does not necessarily extend to other parts of the brain. For example, loss of neurons in the nucleus basalis of Meynert is less in patients with progressive supranuclear palsy than in those with Parkinson's disease, even though thalamic acetylcholinesterase is markedly reduced in progressive supranuclear palsy and

multiple system atrophy, but not in Parkinson's disease.¹¹⁷ While the nucleus basalis of Meynert can be markedly damaged in Alzheimer's disease, the pontine cholinergic projection to the thalamus is not.¹¹⁸

Therefore, in some cases, generalising neurotransmitter processes across brain regions appears problematic. Research is needed to understand how damage to cholinergic and other neurotransmitter circuits occurs in the first place, reflecting issues related to neurogenic precursors, environmental toxins, genetics, epigenetics, and the breakdown of the blood–brain barrier.

Declaration of interests

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Search strategy and selection criteria

I searched PubMed, ISI Web of Science, and Google Scholar for papers published between Jan 1, 1990, and Feb 11, 2017. Multiple search terms were used, including "olfaction", "neurotransmitters", "neuromodulators", "acetylcholine", "serotonin", "neurepinephrine", "dopamine", "GABA", "viruses", "nanoparticles", "xenobiotics", "herbicides", "pesticides", "interactions", and the names of all of the diseases outlined in figure 2. I also searched for references within reviews, including reviews that I have authored.

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