

## Review

# Olfactory dysfunction in COVID-19: pathology and long-term implications for brain health

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**Decreased smell function is related to brain health, future mortality, and quality of life. Most people inflicted with the SARS-CoV-2 virus evidence some measurable smell dysfunction during its acute phase, although many are unaware of the loss. Long-term deficits occur in up to 30% of COVID-19 cases, although total anosmia is relatively rare. This review explores what is presently known about the nature and pathophysiology of olfactory dysfunction due to the SARS-CoV-2 virus, including reversible inflammation within the olfactory cleft, downregulation of olfactory receptor proteins, and long-lasting peripheral and central damage to olfactory structures. It also addresses the question as to whether long-term smell loss might increase the likelihood of future development of cognitive and neurological deficits.**

## Olfactory dysfunction: a marker of brain health, quality of life, future mortality, and insults from environmental microbes and xenobiotics

The smell loss associated with coronavirus disease 2019 (COVID-19) has brought to public attention the importance of olfaction in everyday life. Although largely taken for granted, this sensory system is critical for establishing the flavor of foods and beverages and for defending against such dangers as leaking natural gas, fire, spoiled food, and environmental toxins. We use smell to confirm that our clothes, homes, and offices are clean and to fully enjoy flowers, perfumes, festive occasions, personal care products, and nature (e.g., the mountains and the sea shore). It is thus not surprising that losses or distortions in the ability to smell significantly impact our safety, nutrition, and physical and psychological well-being.

Aside from aging, viruses are the primary cause of long-lasting or permanent decrements in smell function, a condition termed postviral olfactory disorder (PVOD) [1,2]. Smell deficits are associated with a number of medical conditions known to have viral underpinnings, including numerous cardiovascular, endocrine, immune, metabolic, and neurodegenerative diseases [3–5]. Several viruses, such as hepatitis B and C, confer an elevated risk for Parkinson's disease (PD) [5], a disorder with marked olfactory dysfunction [6]. In a case-control study using the Danish National Patient Registry data, those who had an influenza viral diagnosis were 1.73 times more likely to develop PD over a subsequent 10-year period [7]. Alzheimer's disease (AD) is also accompanied with significant olfactory dysfunction [8]. Recently it was found that among the top ten of 5066 genes differentially expressed between 51 AD patients and 31 controls were ones associated with viral infection signaling, namely those of herpes simplex (HSV, HSV1), Epstein-Barr, and human papillomavirus [9]. Interestingly, a gene associated with olfactory transduction, **adenylate cyclase 3 (ADCY3)** (see [Glossary](#)), was also among this group of ten. HSV 1 is found in a high proportion of brains from elderly people and, in combination with the **APOE-ε4** genotype, is a major risk for AD [10]. Remarkably, older people with smell loss have three times the likelihood of an earlier death than their peers with no smell loss, leading to the suggestion that smell function is a sign of overall brain health [11,12].

## Highlights

COVID-19 has brought to public attention the importance of the sense of smell in everyday life, with untold numbers of patients seeking treatment for decreased ability to smell, which, in many cases, may be permanent.

The neuroepithelium that harbors the olfactory receptor cells is directly exposed to the outside environment, making it susceptible to damage from toxic agents and a host of viruses, most notably SARS-CoV-2, the cause of COVID-19.

SARS-CoV-2 invades nearly all types of cells within the olfactory neuroepithelium, but does not appear to significantly invade olfactory receptor cells, which lack the primary entry receptor, angiotensin-converting enzyme II (ACE2). However, other entry receptors may also be involved.

The degree to which SARS-CoV-2 impacts central olfactory processing centers or leads to later neurological disorders has yet to be determined.

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This review explores what is presently known about the nature, prevalence, and pathophysiology of olfactory dysfunction due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for COVID-19. In common with other viruses, SARS-CoV-2 subjugates the synthetic machinery of living cells to replicate its own genetic information. Similarly, its effectiveness depends upon the presence of appropriate receptors for cell attachment and entry, tropism for particular tissues or cells, efficacy of virus genome replication, and the immune status of the host. Hypotheses regarding how the virus damages olfaction-related cells and whether long-term smell loss increases the chances for later development of psychological and neurological problems are addressed.

### Smell loss can be the most common symptom of COVID-19

A number of surveys find that the strongest and most consistent symptom associated with COVID-19 is decreased smell or taste function. One study evaluated 514 459 records from over 10 million respondents to three COVID-19 digital surveillance platforms employed in the United States, Israel, and Great Britain [13]. People reporting loss of smell (anosmia) or taste (ageusia) were 17 times more likely to test positive for COVID-19 than those without these symptoms. Those reporting fever were 6.5 times more likely, shortness of breath 4.7 times more likely, or cough 4.3 times more likely. However, prevalence rates of COVID-19-related smell or taste dysfunction vary considerably among surveys, ranging from 8% to 85% [14], conceivably reflecting not only response biases, but variations in such factors as age, race, gender, vaccination status, smoking behavior, genetics, time since infection onset, comorbidities, and the specific COVID-19 variant.

Early in the pandemic, much lower prevalence rates were noted in eastern Asian countries than in European countries [15], in spite of higher symptom severity in Asian countries [16]. One COVID-19 study of 624 pairs of monozygotic and 288 pairs of dizygotic twins found 19% of the individual differences in self-reported olfactory dysfunction was attributable to genetic factors, potentially reflecting differences in viral infection susceptibility and immune responsiveness [17]. Importantly, some SARS-CoV-2 variants appear to have greater effects than others. For example, a single nucleotide **polymorphism** from D614 to G614 in the virus' spike protein is associated with a significantly higher prevalence of smell loss [15,18]. More recent COVID-19 variants reportedly produce relatively less smell dysfunction, although objective testing is limited and a confound with vaccination status may be present. In a study of 3431 COVID-19 cases, the relationship between self-reported smell loss and COVID-19 was lower during the period of the omicron variant peak [27 December 2021–7 February 2022; **odds ratio** (OR) 0.17, 95% confidence interval (CI) 0.15–0.18] than during the period of the initial/untyped SARS-CoV-2 variant (22 June–3 August 2020) [19]. This was also true, albeit not to the same degree, for the peak periods of the alpha (19 April–31 May 2021) and delta (20 September–1 November 2021) variants [respective ORs = 0.50 (95% CI, 0.45–0.55) and 0.44 (0.41–0.48; all  $P < 0.001$ ].

Most surveys fail to distinguish between olfaction and taste, the latter reflecting taste bud-mediated sensations such as sweet, sour, bitter, salty, and savory/brothy (called umami). Clinically, nearly all complaints of 'taste' loss actually reflect olfactory disturbances [1] (see [Clinician's corner](#)). During chewing and swallowing, volatiles from foods and beverages enter the olfactory receptor region from the oral cavity via the opening in the rear of the nasal cavity (nasopharynx), producing sensations misinterpreted as 'taste' (e.g., chocolate, coffee, steak sauce, mint, peach, cheese, etc.) [20]. Thus, in many cases, it is unclear whether, or to what relative degree, smell, taste, or both are compromised by infection with SARS-CoV-2. A recent meta-analysis of 241 studies concluded that taste loss is a distinct symptom of COVID-19, with a pooled prevalence rate of 39.4% [21]. However, only 2% of the studies employed validated taste tests and their findings are equivocal.

### Glossary

**Adenylate cyclase 3 (ADCY3):** an encoding gene that influences olfaction by modulating intracellular cAMP concentrations.

**APOE-ε4:** a genetic variant of the apolipoprotein E gene that is major risk factor for Alzheimer's disease.

**Apoptosis:** self-destruction of a cell by an appropriate trigger.

**Astrocyte:** a star-shaped glial cell common in the CNS.

**Astrogliosis:** an abnormal increase in astrocytes.

**Basal cell:** the primary stem cell within the olfactory neuroepithelium.

**Basigin (BSG):** a widely expressed receptor with multiple functions, including regulating responsiveness to lymphocytes and serving as receptor for SARS-CoV-2.

**Bowman's gland:** specialized gland that secretes into the olfactory mucus.

**Cathepsin L (CTSL):** an enzyme with multiple functions, including facilitation of SARS-CoV-2 spike protein cleavage and virus entry.

**Coagulopathy:** a condition that impairs the ability of blood to clot.

**Cytokine:** a protein involved in immune system activity.

**Cytokine storm:** inflammatory syndrome involving markedly elevated levels of circulating cytokines.

**Endothelial cell:** main cell type lining the heart and blood and lymph vessels.

**Entorhinal cortex:** a sector of the medial temporal lobe that receives input from the olfactory bulb and the piriform cortex; plays an important role in odor memory.

**Furin:** an enzyme that catalyzes the proteolytic maturation of prohormones and proproteins.

**Granule cells:** most common inhibitory neuron in the olfactory bulb.

**Hazard ratio:** a measure of how often an event happens in one group compared to how often it occurs in another group.

**Lymphocyte:** an immune cell made in bone marrow and found in blood and lymph tissue.

**Macrophage:** a white blood cell that kills microorganisms, removes dead cells, and activates other immune system cells.

**Microglia:** a type of cell that serves as an immune system scavenger in the CNS.

**Microgliosis:** increase in number of microglia.

Some reported no meaningful effects on average taste test scores [22–24], whereas others reported prevalence rates of 12% [25], 18% [26], 23% [27], and 26% [28].

Regrettably, surveys also suffer from reliance on self-report, which is often at odds with measured test performance. A significant number of people are unaware of a taste or smell disorder prior to being objectively tested, regardless of its cause, stressing the need for empirical testing (Box 1) [6,8,27,29–31]. In the case of COVID-19, a meta-analysis of 104 olfactory studies, of which 13 employed objective test measures, found those using objective measures had an estimated prevalence rate of 65.52% (95% CI, 52.26–76.74%), whereas those based solely on self-report had a prevalence rate of 38.84% (31.96–46.2%) [15]. In a pioneering study, the 40-item **University of Pennsylvania Smell Identification Test (UPSIT)** was administered to 60 COVID-19 patients near the end of the disease's acute phase [41]. While nearly all (98%) exhibited some degree of measured smell dysfunction [25% anosmia (total smell loss), 33% severe microsmia (lessened smell function), 27% moderate microsmia, 13% mild microsmia], only 35% were aware of their dysfunction before testing.

### Smell loss is long-lasting and probably permanent in a number of COVID-19 cases

As occurs in other PVODs [42], some patients who have been infected with SARS-CoV-2 have long lasting, and likely permanent, deficits in their ability to smell [43]. An early study found that while 61% of 82 patients objectively retested with the UPSIT recovered by 7–8 weeks after COVID-19 onset, most of the 39% who continued to have dysfunction had only mild loss and none were anosmic [44]. In a more recent study of 268 COVID-19 patients, 21.9% reported their function had not returned to normal by 1 year after initial diagnosis [43]. A systematic review of this literature identified 44 COVID-19 studies in which full olfactory recovery was reported over time, 14 of which used quantitative test measures [45]. Of these 14, follow-up was completed by four at 1 month, seven by 2 months, and three up to 6 months. The median respective recovery rates were similar at these time points: 72.6% (range: 44.3% to 94.6%), 73.3% (0% to 79.5%),

**Microvillar cell:** a small cell within the olfactory neuroepithelium of unknown function that sends microvillae into the mucus.

**Neuropilin 1 (NRP1):** a receptor involved in vascular processes; facilitates entry of SARS-CoV-2 into cells.

**Odds ratio (OR):** the odds that an outcome will occur given a particular exposure (e.g., COVID-19), compared to that of the outcome occurring in the absence of that exposure.

**Olfactory sulcus:** a groove underneath the frontal lobe that harbors the olfactory bulb.

**Piriform cortex:** largest olfactory processing and information coding brain region.

**Polymorphism:** a genetic variation upon which natural selection can operate.

**Sustentacular cell:** a major cell type in the olfactory neuroepithelium that provides structural and metabolic support to the receptor cells.

**Toll-like receptor 2 (TLR2):** a receptor that recognizes components of gram-positive bacteria.

**Transmembrane protease serine 2 (TMPRSS2):** an endothelial cell surface enzyme that facilitates viral fusing to the ACE2 receptor.

**University of Pennsylvania Smell Identification Test (UPSIT):** a 40-item self-administered microencapsulated odorant smell test.

#### Box 1. Quantitative olfactory testing

Quantitative olfactory tests can be divided into three general types: psychophysical, electrophysiological, and psychophysiological. Psychophysical tests directly assess the subject's conscious perceptual function. Examples are tests of odor identification, detection, discrimination, memory, and intensity estimation [32]. Most use simple means for presenting the stimuli (e.g., 'scratch and sniff' odorized pads [33]; specialized hand-held wands [34]). Despite different names, nearly all such tests are strongly correlated with one another and appear to be measuring the same elements of the underlying physiological substrate [35]. Identification tests usually require the subject to identify the name of a presented odorant from multiple-choice alternatives. Some are commercially available in multiple languages and can be self-administered. In addition to categorical classification of function (e.g., normal or mild, moderate, severe, or total loss), some employ sex- and age-related normative data to establish a patient's performance as a percentile score relative to the performance of peers [33]. Threshold tests assess the lowest concentration of an odorant that can be perceived. This is commonly done using forced-choice paradigms in which the subject must identify the stronger of two randomly presented stimuli, one of which is a blank, at different concentration levels [36]. Threshold tests are popular since their metric is easy to interpret, language factors are not involved, and their auditory analog is familiar to clinicians. However, unless the perithreshold region is repeatedly sampled, reliability is low. Although threshold measures have been reported to uniquely measure receptor cell function, this is questionable since threshold values correlate with neuropsychological measures of verbal and visuospatial memory and are sensitive to lesions in higher order brain structures due to multiple sclerosis, epilepsy, AD, PD, and other diseases [37]. Odor discrimination tests typically require, on a given trial, the subject to identify the 'odd' odorant from a set of three odors, two of which are equivalent. Odor memory tests assess the ability to remember an odor quality over periods of time. Suprathreshold rating or magnitude estimation tests examine the build-up of perceived intensity as a function of increasing odorant concentrations. Some studies combine data from different types of tests into a global score. Although this increases test reliability, it is questionable on a number of grounds [38]. Electrophysiological tests, such as odor event-related potentials [39], and psychophysiological tests, such as autonomic system responses to odorants [40], are largely confined to laboratory settings, being less practical and more dependent upon sophisticated odorant presentation equipment.

and 73.5% (58.8% to 87.3%). In aggregate, such studies suggest that approximately a quarter to a third of people inflicted with the SARS-CoV-2 virus continue to have some degree of measurable smell dysfunction for months after their infection. Based on patients who recover from olfactory dysfunction from other viruses and disorders, the amount of long-term recovery, when it occurs, will likely depend upon such factors as the subject's age and amount of initial loss [42].

### Similarities and differences in smell dysfunction between COVID-19 and other PVODs

The average magnitude of the initial smell loss induced by COVID-19, as measured by validated olfactory tests, appears to be essentially the same as that observed for other PVODs [46], as well as for such diseases as AD and PD. For example, in one study the mean UPSIT score of 100 COVID-19 patients tested during the late acute phase of the disease was 22/40 (95% CI, 21–23) [44]. This corresponds well to UPSIT scores in a study of 132 non-COVID PVODs [mean (SD) = 23/40 (9.4)] [1], a study of 81 patients with PD [mean (SD) = 22/40 (7.3)] [6], and a study of 19 patients with early-onset AD [mean (SD) = 23/40 (6.6)] [47]. It is unknown whether such scores reflect common pathophysiological factors, although in some cases common substrates could be involved [48].

In general, the onset of the smell loss observed in COVID-19 is similar to that of most other PVODs, typically being noticed around the beginning of the infection. The trajectory of return of smell function appears to be similar for COVID-19 as that of most other PVODs, in that self-report recovery from smell loss commonly occurs over a 2- to 3-week postinfection period [49]. COVID-19 tends to have a pattern of symptoms more similar to influenza than non-influenza-related PVODs like the common cold [50–53] and its viral nucleic acid shedding pattern resembles that of patients with influenza [54]. However, COVID-19 differs from influenza in having less frequent nose running, shortness of breath, and throat irritation [52].

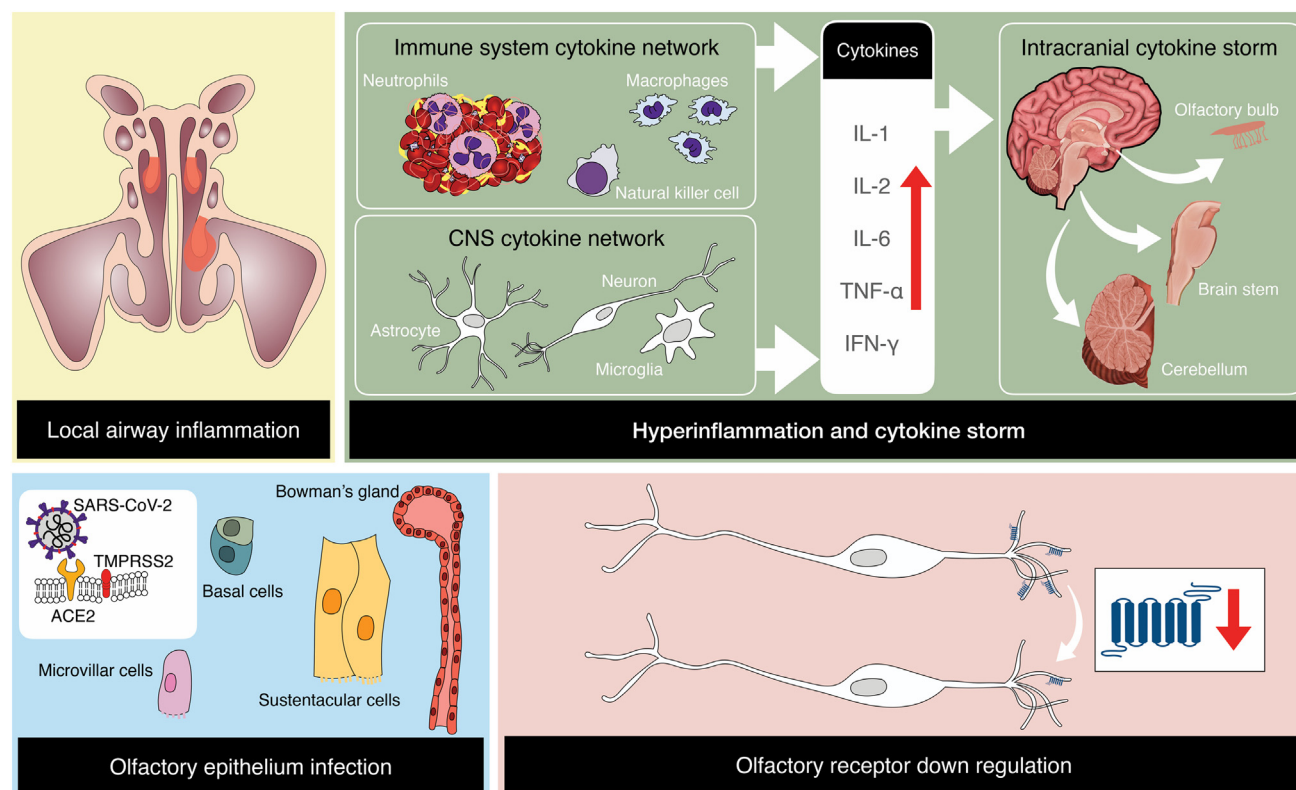
Although widespread awareness of smell loss in COVID-19 suggests that proportionately more people with COVID-19 uniquely experience smell loss, this could be illusory, at least to some degree [55]. Thus, nearly everyone experiences reversible smell loss during or immediately after contracting a head cold [56]. This loss is rarely viewed as abnormal and is typically attributed to congestion, since the ability to smell appears to return to normal when the congestion subsides. In the case of COVID-19, noticeable congestion is the exception, rather than the rule, so in most cases the smell loss is viewed as novel and cannot be readily attributed to perceived nasal blockage. Interestingly, early in the pandemic self-reported prevalence rates of smell dysfunction appeared to be positively correlated with the amount of attention paid in the popular press to the impact of COVID-19 on the sense of smell [57].

### Pathophysiological mechanisms of smell loss in COVID-19

Several non-mutually exclusive causes of smell loss from the SARS-CoV-2 virus are possible (Figure 1), as outlined in detail in this section, including:

- Blockage of transit of odorants to the olfactory receptors from local airway inflammation or changes in the volume or composition of the olfactory mucus.
- Damage to the olfactory mucosa, including the ciliated olfactory receptor cells, **Bowman's glands** within the lamina propria, and **sustentacular cells**, **basal cells**, and **microvillar cells**.
- Downregulation of olfactory receptor proteins within the olfactory receptor cells.
- Injury to the olfactory bulb or other central brain structures or circuits, including capillary **endothelial cells**, in some cases from massive activation of **cytokines**.





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**Figure 1.** Suggested mechanisms by which the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus affects the sense of smell. These include local airway inflammation, particularly in the higher recesses of the nose, infection and damage to specific cell types within the olfactory neuroepithelium, over-reactive immune responses within the brain, and downregulation of olfactory receptor proteins located on the cilia of olfactory receptor cells. As a result of viral infection, macrophages are activated, which in turn releases a multitude of cytokines, with interleukin 6 producing the most inflammation. The listed cytokines are examples and not an inclusive list of cytokines that can influence olfactory functioning. Copyright © 2022 Shima Moein. Abbreviations: ACE2, angiotensin-converting enzyme II; TMPRSS2, transmembrane protease serine 2.

The angiotensin-converting enzyme II (ACE2) receptor is believed to be the primary entry receptor for SARS-CoV-2 [58]. This ubiquitous receptor is expressed in multiple tissues and organs in addition to the upper and lower airways, including the heart, retina, vasculature, gut, kidney, testis, and brain, although it is not as highly expressed in the brain compared with other tissues [59]. Cell entry occurs when the virus' spike protein binds to the ACE2 receptor and becomes cleaved by the cell's **transmembrane protease serine 2 (TMPRSS2)** enzyme into S1 (receptor binding) and S2 (membrane fusion) domains. However, recent evidence suggests that SARS-CoV-2 can also infect cells via **neuropilin 1 (NRP1)** [60] and **basigin (BSG)** [61] receptors and that **cathepsin L (CTSL)** and **Furin** enzymes can also modify SARS-CoV-2 to facilitate infection [62]. Compared with ACE2 or TMPRSS2, NRP1 and BSG are more widely expressed in the human brain, including the olfactory bulb [62].

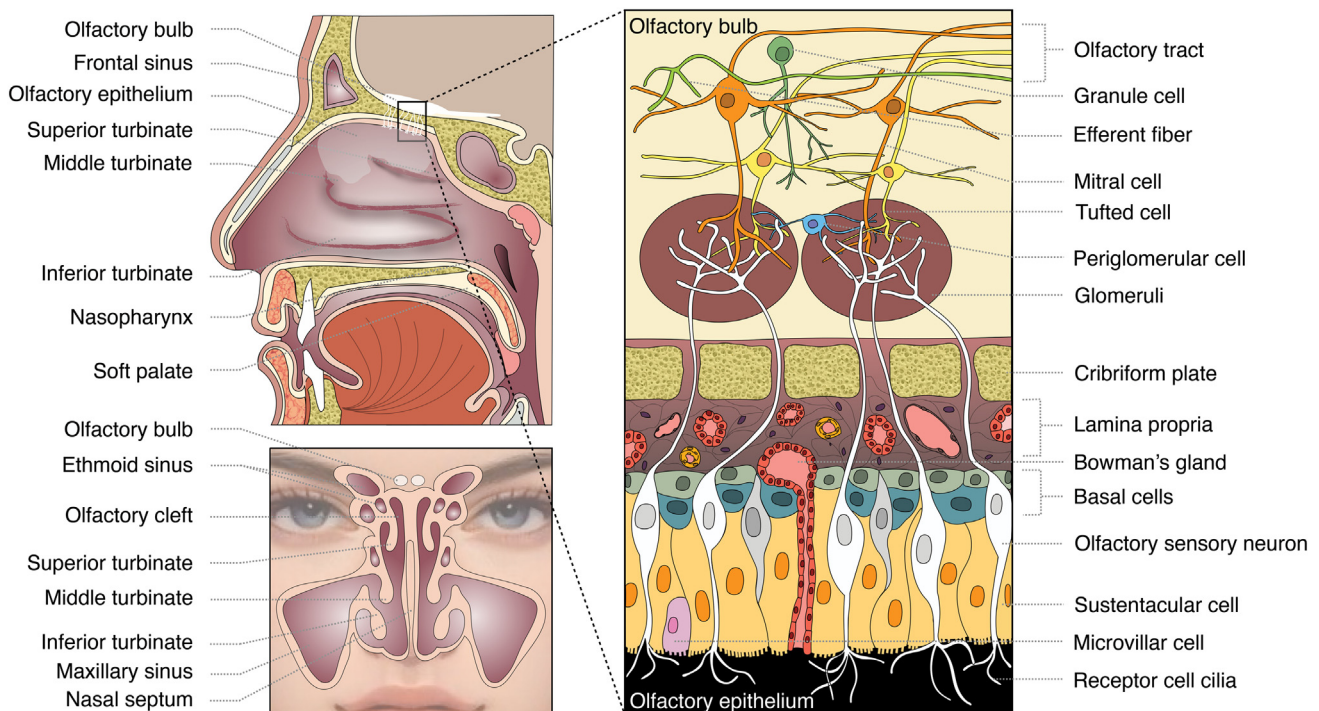
Although such receptor entry may be the genesis of, or contribute to, the pathophysiology of cells specifically involved in olfactory system function, olfactory system pathology may also occur from SARS-CoV-2 entry into cells not directly involved in such function. For example, the so-called **cytokine storm** induced by systemic infection or infection of nonolfactory cells could result in inflammatory damage to cells critical for olfactory function [63]. Moreover, non-cell-autonomous genetic influences on receptor protein regulation may also occur within olfactory receptor cells

[64]. Wide-spread disease of fine blood vessels (microangiopathy) induced by SARS-CoV-2 may also impact blood flow to neurons involved in olfactory perception. The brain microvascular endothelial cells, which are a major component of the blood–brain barrier, express ACE2 [65] and NRP1 receptors [66].

#### Blockage of transit of odorants to the olfactory receptors

To reach the olfactory receptors, odorant-laden air must first traverse the upper airway, penetrate the narrow olfactory cleft, and absorb into a specialized mucus that covers the neuroepithelium in which the ciliated olfactory receptors are embedded (Figure 2). The olfactory cleft is the opening located above the middle and superior turbinates, the uppermost set of vascularized nasal structures critical for warming, humidifying, and cleansing the incoming airstream. When inflamed or diseased, the turbinates can block or decrease airflow to the receptors. The olfactory mucus, when desiccated or altered in composition, can also attenuate the movement of odorants to the olfactory receptor cells (Box 2). Nasal mucociliary clearance, phagocytic activity, and immune responses can be impeded by numerous factors, including cold temperatures [79,80]. Such impediment can increase the duration or presence of the virus within the nose and olfactory receptor region.

Although the nasal epithelium exhibits a higher SARS-CoV-2 viral load than does the lower respiratory tract [81], the majority of COVID-19 patients report having no blocked nose, nasal congestion, or nasal discharge [82]. Nevertheless, human imaging studies have found localized



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**Figure 2. Basic anatomy of the nose, olfactory epithelium, and olfactory bulb.** Left: Air, including aerosols and odorants, enters into the nasal cavity and a portion reaches the olfactory neuroepithelium located within the olfactory clefts on sectors of the nasal septum and superior and middle turbinates. The highly vascular turbinates warm, cleanse, and filter the air. Right: Olfactory receptor proteins are located on the olfactory cilia. The olfactory neuroepithelium is comprised of multiple cell types, which germinate from basal cells. The axons of the receptor cells extend through the bony cribriform plate to synapse with other cell types in globe-like structures within the olfactory bulb, the first relay station of the olfactory pathway. Copyright © 2022 Shima Moein.

### Box 2. Constituents of olfactory mucus

Among the constituents of the olfactory mucus are odorant binding proteins that shepherd hydrophobic molecules through the aqueous environment to the receptors [67] and numerous antioxidants, growth factors, immune factors, peptides, and antimicrobial and regulatory proteins, a number of which rapidly metabolize odorants and xenobiotics at a rate that can impact smell function [68]. Over 2500 proteins have been identified in the olfactory mucus, some of which are altered by aging and disorders associated with smell loss (e.g., chronic rhinosinusitis) [69,70]. For example, odorants with functional groups such as aldehydes and esters can be rapidly converted to the corresponding acids and alcohols [71]. Altered levels of some olfactory mucus cytokines are correlated with olfactory test scores and appear to impact the function of olfactory receptor cells and possibly their ability to regenerate [72]. This mucus affords a degree of protection of the neuroepithelium from viruses and other xenobiotics, which, in some cases, can invade the brain via receptor cells, perineural spaces, and lymphatics [73,74]. Beta-adrenergic, cholinergic, and peptidergic mechanisms control the secretory activity of the mucus [75–78].

Inflammation within the olfactory cleft early in the SARS-CoV-2 infection process, inflammation which subsides in most cases in a matter of weeks. A case–control magnetic resonance imaging (MRI) study of 20 COVID-19 patients with smell loss and 20 age-matched healthy controls found 19 of the patients (95%) displayed complete obstruction of the olfactory cleft when assessed a mean of 5.3 days (range 1–13 days) after the onset of smell loss [83]. None of the controls exhibited such obstruction. One month later, only seven of the 20 patients (35%) continued to have obstruction, a percentage similar to that reported for the prevalence of post-COVID-19 cases of olfactory dysfunction [45]. In accord with the time-related resolution of the inflammation, another study [84] noted, in 12 patients evaluated 2 weeks after anosmia onset, bilateral olfactory cleft blockage in six (50%) and partial blockage of one cleft in two (17%). No blockage was apparent in the other patients. Those with bilateral blockage exhibited lower olfactory test scores (44% correct) than those with only one-sided blockage (52% correct). A more recent study reported that total olfactory cleft opacification occurred in only one of 23 COVID-19 patients tested 1–4 months after anosmia onset, although partial opacification occurred in over two-thirds (69.6%) [85]. In accord with the lack of noticeable nasal blockage is a case study of a patient with smell loss who had no apparent nasal congestion but, upon MRI evaluation, exhibited bilateral obstructive inflammation of the olfactory clefts [86].

Expression of ACE2 receptors is not as strong in the respiratory epithelium as in the olfactory epithelium, possibly explaining the lack of significant nasal blockage. For example, less than half (nine of 19) of the biopsies of respiratory epithelium collected in one study yielded ACE2-positive epithelial cells, in contrast to all of those collected within the olfactory neuroepithelium (13/13) [87]. A possible contributing mechanism for the apparent selective inflammation of the olfactory cleft region is the differential dispersion of aerosols during inhalation. SARS-CoV-2 is largely carried in the air by aerosols. A study using inhaled fluorescein-labeled 0.5–5  $\mu$ m droplets found deposition to occur primarily within the olfactory cleft [88]. Minimal or no deposition occurred in the nasal respiratory epithelium. Interestingly, a study of 24 anosmic and 26 normosmic COVID-19 patients tested 1–34 months after infection onset found the olfactory clefts to be wider and of greater volume in the anosmics [89]. The authors suggested that people with more patent olfactory clefts may be more likely to contract long-lasting and presumably neurologically based smell dysfunction from COVID-19.

### Damage to the olfactory neuroepithelium

The olfactory neuroepithelium, which extends over the cribriform plate and anteriorly over segments of the superior and middle turbinates (Figure 2), has become the focus for studies seeking to understand the biological basis of the smell loss associated with COVID-19. This avascular pseudostratified columnar structure contains the 6–10 million ciliated bipolar receptor cells that harbor the olfactory receptor proteins to which odorants bind, along with sustentacular cells,

microvillar cells, basal stem cells, and duct cells from Bowman's glands [90]. The receptor cell axons coalesce into hundreds of ensheathed bundles or fila, collectively termed cranial nerve I (CN I), that project through the basal lamina and fine passages (fenestra) of the cribriform plate into the olfactory bulbs, the first relay stations of the olfactory system. **Microglia** and **macrophages** located within these bundles phagocytize bacteria and other foreign agents [91,92] and provide one barrier to the migration of viruses and other foreign agents from the nasal cavity into the brain through these extracellular spaces.

The location of the neuroepithelium at the interface of the environment places its cells at risk from damage from viruses [74], bacteria [93], nanoparticles [94], and other airborne xenobiotics [95]. Such damage is well established [96], with some viruses being capable of penetrating the brain from this region [74] (Box 3). Even though damaged receptor cells and other elements of the olfactory neuroepithelium can be reconstituted from basal cells if the basal cell layer is not severely damaged, full recovery of the epithelial sheet rarely occurs, leading to cumulative and pot-marked damage of the epithelium. This is one basis for age-related decreases in smell function [78].

There is general consensus that ACE2 receptors are expressed in all types of cells within the olfactory neuroepithelium, with the exception of receptor cells [105]. Sustentacular cells appear to be the most infected [106], although not all are positive for ACE2. The positive cells are often isolated or present in small clusters intermingled with negative sustentacular cells and, in rare instances, some respiratory epithelial cells [107]. Since the basal cells from which the olfactory receptors arise also appear to express ACE2 receptors, it has been suggested that the differentiated receptor cells can therefore be carrying the SARS-CoV-2 virus without expressing ACE2 receptors themselves [62]. If this is true, it is surprising that the SARS-CoV-2 virus is not found in large numbers of olfactory receptor cells [106]. Conceivably the infected cells may have undergone virus-induced cellular **apoptosis** before being able to differentiate into olfactory receptor cells [101].

It has recently been shown that SARS-CoV-2 markedly downregulates olfactory receptor proteins and associated signaling components in the olfactory receptor cells of both hamsters and humans via a non-cell-autonomous process [64]. A day after intranasal SARS-CoV-2 inoculation, viral RNA was found in about 5% of the cells of hamster olfactory epithelia; 40% of these cells were sustentacular cells and 6% olfactory receptor cells. Two days after inoculation, genes

### Box 3. Viruses and the olfactory system

A number of viruses, as well as ionized metals and other xenobiotics, can penetrate the brain via the olfactory neuroepithelium, largely bypassing the blood-brain barrier [74]. Movement of viruses from the nose to the brain can occur via olfactory receptor cell incorporation, lymphatic channels, or fluid-filled perineural channels created by ensheathing cells of the olfactory fila through which regenerating receptor cell axons are guided into the brain [74,97,98]. Numerous lymphatic ducts surround the olfactory cell nerve roots, facilitating a direct connection between the cerebral spinal fluid and lymph in the olfactory submucosa [99]. Viruses associated with the 1916–1930 epidemic known as von Economo's encephalitis in which parkinsonism was common, include western equine, coxsackie, and Japanese B viruses. Among viruses capable of entering the brain in animal models via the olfactory nerves or perineural spaces are the Japanese encephalitis virus, influenza A virus, herpesviruses, poliovirus, paramyxoviruses, vesicular stomatitis virus, rabies virus, parainfluenza virus, adenoviruses, West Nile virus, chikungunya virus, La Crosse virus, mouse hepatitis virus, and bunyaviruses [74,98]. In case of the arthropod-borne St. Louis encephalitis virus, entry into olfactory receptor cells occurs even when the virus is instilled intravenously, subdurally, or interperitoneally [100]. Once incorporated into a cell, virus-induced cellular apoptosis occurs in some cases before the replication cycle can be completed [101]. A number of viruses can suppress neuronal apoptosis by antiapoptotic genes, facilitating their replication and brain invasion [102]. Although many viruses are eliminated by neuroprotective immune responses within the olfactory bulb [103], others are not. Some viruses, once in the olfactory bulb, can target specific brain neurotransmitter systems. For example, HSV-1 inoculated into the rat olfactory bulb ultimately infects cholinergic neurons in the horizontal limb of the diagonal band, serotonergic neurons in the dorsal and medial raphe nuclei, and noradrenergic neurons in the locus coeruleus [104].



related to olfactory function, such as ADCY3, were significantly downregulated, whereas the opposite was true for genes associated with antiviral responses. The downregulation peaked at 4 days and continued through 10 days when other olfactory sensory neuron markers had recovered. SARS-CoV-2 transcripts were also found in microglia and other immune cells by three postinoculation days. Autopsied human olfactory epithelia mirrored the marked decreases of olfactory receptors and the olfactory receptor signaling gene transcription, as well as the reduction of interchromosomal olfactory receptor contacts.

#### Damage to the olfactory bulb and other olfaction-related central nervous system structures

The olfactory receptor cell axons synapse with the major output neurons of the olfactory bulb within globe-like structures termed glomeruli (Figure 2). These output neurons, the mitral and tufted cells, send axonal projections to other brain structures such as the **piriform cortex** and **entorhinal cortex**. The receptor cell activity is modified, in part, by local neurons termed periglomerular cells. Mitral and tufted cell activity is also modulated by other cells, including by small inhibitory granule cells located in the core of the bulb. The microglia within the bulb are uniquely pre-set to a primed state in which cytokine production is mediated by the expression of **Toll-like receptor 2 (TLR2)**, potentially serving as sensors or modulators of brain inflammation in general [108]. For example, in mice, ischemic brain injury far from the bulb activates olfactory bulb microglia hours before microglia are activated near the injury, activation that remains for months after the injury [108]. The intranasal introduction of a small single dose of a bacterial endotoxin was found to produce a widespread wave of TLR2 activation from the bulb to higher brain regions.

As measured by MRI, the average size of the olfactory bulbs and tracts are smaller in COVID-19 cases than in controls. For example, one study [109] compared the olfactory bulb volumes, olfactory tract lengths, and **olfactory sulcus** depths of 36 COVID-19 patients with smell loss [mean (SD) age = 37.33 (7.38)] to those of 80 healthy controls [mean (SD) age = 35.74 (8.38)]. The mean (SD) volumes of the olfactory bulbs (left and right combined) were 82.34 (31.29) mm<sup>3</sup> in the patients and 131.50 (32.27) mm<sup>3</sup> in the controls ( $P < 0.001$ ), with total atrophy being noted in four cases. Significant reductions were also present in the olfactory tract lengths and sulcus depths. Nevertheless, one study found the decrement in olfactory bulb size of 31 COVID-19 patients evaluated over 1 month since illness onset was less pronounced than that seen in 97 non-COVID-19 PVOD cases [110].

The basis for the decrease in olfactory bulb size is not clear. However, such a decrease need not be due to direct viral invasion of the bulb. Thus, disruption of the receptor cells of the olfactory epithelium can result in decreased olfactory bulb volume, possibly due to loss of trophic factors from the decreased numbers of incoming receptor cell axons. Decrements in olfactory bulb sizes have been reported in elderly people [78], cigarette smokers [111], and in patients with AD [112], PD [113], head trauma [114], multiple sclerosis [115], schizophrenia [116], and chronic rhinosinusitis [117].

That being said, postmortem studies using tests to localize the distribution of SARS-CoV-2 RNA in specific brain regions have found such RNA in the olfactory bulbs, with one study reporting a 53% bulbar positivity rate (eight of 15) [118] and another a 40% positivity rate (eight of 20) [119]. The RNA was absent from the neural and glial bulbar compartments, as well as from the olfactory tubercles and lateral olfactory tract. This absence, as well as the viral presence in the endothelia of such structures, suggested that hematogenous viral spread may have occurred via the common arterial supply of the bulb [118]. If systemic hematogenous involvement was present, wider viral spread into other brain regions would have been expected. Nevertheless, the analysis they performed of homogenized autopsy specimens is unable to specifically identify

whether the RNA comes from the sampled tissue, *per se*, or from embedded fragments of endothelial cells or more distally infected tissue [120].

The neuropathological features of 43 COVID-19 brains were evaluated in one postmortem study [121]. Immunological staining was made for activated **astrocytes** and microglia, as well as cytotoxic T **lymphocytes** in the olfactory bulb, basal ganglia, brainstem, and cerebellum. The neuropathological changes were generally mild and no association between the severity of the neuropathological findings and the presence of SARS-CoV-2 in the central nervous system (CNS) was present. Most pathology was found in the brainstem and cerebellum. All olfactory bulbs had some degree of **astrogliosis** (five severe, 25 moderate, 13 slight) and all but one had **microgliosis** (five severe, 27 moderate, ten slight). Cytotoxic T lymphocytes were evident in the bulbs of all but three of the 42 cases for which data were available (zero severe, 35 slight, four moderate). It is noteworthy that the subjects were at an age when some degree of smell loss is common [median (interquartile range) = 76 (70–86) years].

In general, significant COVID-19-related pathology in CNS structures, including olfaction-related structures, appears to be relatively rare. For example, in one study of 20 COVID-19 brains, clear evidence of classic neuropathology of viral CNS infections was absent in 18 (i.e., viral inclusions, focal demyelination, lymphocytic leptomeningitis or encephalitis, microglial nodules, or pronounced or frequent perivascular lymphocytic cuffing) [119]. Only one exhibited notable pathological features and only four exhibited either acute microscopic or macroscopic hemorrhages.

### Neurological and psychiatric sequelae in COVID-19 cases evidencing persistent smell loss

A broad spectrum of acute and chronic neurological problems has been associated with COVID-19. These include confusion, dizziness, fatigue, headache, ischemic strokes, syncope, seizures, insomnia, neuropathic pain, myalgia, and Guillain-Barre syndrome [122]. Although there are a few sporadic reports based on small samples that several movement disorders may be associated with SARS-CoV-2 infection, including PD, action tremor, poor muscle control, involuntary muscle twitching, and some oculomotor disorders, these disorders are generally lacking in large multicenter studies [123]. Nonetheless, it is noteworthy that plasma levels of inflammatory mediators associated with a number of such symptoms, such as interleukin-6, are elevated during the acute phase of COVID-19 and are correlated with the degree of self-reported smell loss [124]. However, not all studies have observed such associations [125].

Reports of neuropsychiatric symptoms are common in COVID-19 patients during and after their discharge from hospital. One large cohort study of largely males employed mental health data from the US Department of Veterans Affairs national healthcare databases [126]. Data from 153 848 COVID-19 ‘long-haul’ survivors was compared with that from 5 637 840 never infected contemporaneous controls and 5 859 251 historical controls who predated the COVID-19 pandemic. Relative to the controls, the long haulers exhibited increased neurocognitive decline [**hazard ratio** (95% CI) = 1.80 (1.72–1.89)], incident sleep disorders [1.41 (1.38–1.45)], depressive disorders [1.39 (1.34–1.43)], and stress and adjustment disorders [1.38 (1.34–1.43)]. In a systematic review of 66 studies of long haulers, screened from a total of 1725 studies, 61% reported the presence of anxiety and/or depression, 48% fatigue, 41% cognitive deficits, 35% sleep disturbances, and 30% symptoms of post-traumatic stress disorder [127]. Examples of the cognitive deficits are problems with attention, concentration, short-term and general memory, language, verbal encoding, and verbal fluency. To what degree such symptoms reflect pre-existing conditions, CNS-related viral infection, systemic reactions to the virus (e.g., **coagulopathy**, sepsis, autoimmune responses), or other factors, including smell or taste dysfunction, remains unclear.

### Clinician's corner

Smell dysfunction has made the public aware of the important role that olfaction plays in their everyday life (e.g., safety and determining the flavor of foods and beverages), leading them to seek help for their problem from multiple medical practitioners.

Large surveys suggest that decreased smell or taste function is the strongest and most consistent symptom associated with COVID-19, although significant geographic, ethnic, and genetic factors, including those related to the host and the virus itself, appear to be at play. The magnitude of the dysfunction, when measured quantitatively, appears to be similar to that observed in smell losses from other types of upper respiratory viruses as well as those related to Alzheimer's disease or Parkinson's disease.

Although the olfactory dysfunction caused by SARS-CoV-2 resolves in most people within a few weeks, long-term and likely permanent deficits appear to be present in up to 30% of those who have been infected.

COVID-19-related smell dysfunction may reflect a combination of pathophysiologic factors, including blockage of airflow to receptors due to localized inflammation and alterations in mucus within the olfactory cleft, downregulation of olfactory receptor proteins, damage to the olfactory neuroepithelium, and subtle alterations in central brain structures related to olfaction, most notably the olfactory bulb. The involvement of capillary endothelia cannot be ruled out.

With the exception of the olfactory receptor cells, SARS-CoV-2 invades all types of cells within the olfactory neuroepithelium via the angiotensin-converting enzyme II (ACE2) receptor. Entry is facilitated by cleavage of the virus' spike protein by the cell's transmembrane protease serine enzyme (TMPRSS2). Other receptors may also be involved, including neuropilin 1 (NRP1) and BSG, although to what degree this occurs in olfaction-related structures is not known.

It remains unknown whether SARS-CoV-2 invades the brain via the olfactory neuroepithelium.

A recent MRI study of 401 patients before and after contracting COVID-19, along with similarly longitudinally tested 384 non-COVID-19 controls, was designed to minimize the effects of pre-existing conditions on the brain measures [128]. This study found modest (from 0.2% to ~2%) COVID-19-related decrements in global brain size and grey matter thickness in the orbitofrontal cortex and parahippocampal gyrus, regions involved in olfactory processing. Increases in relative changes in markers of tissue damage in these and other brain regions functionally connected to piriform cortex and related areas were also noted, although no olfactory testing was performed.

The question arises as to whether COVID-19 patients with long-lasting smell loss are more likely than those who regain smell function to experience later psychological disabilities. Few studies have addressed this issue. In an online survey of 322 COVID-19 positive subjects who had experienced a loss of smell or taste, 43% reported depression and 37% loss of weight. Notably, 87% reported reduced enjoyment of food, 56% decreased enjoyment of life in general, and 55% loss of appetite [129]. One study identified subjects from user-generated posts from a Reddit subforum dedicated to people with COVID-19 [130]. Those with a history of anosmia/ageusia-related posts and who self-identified as COVID-19 positive had a 30% higher instantaneous risk of suicidal ideation or depression on posts made in suicide- or depression-related forums. Another study compared scores on an anxiety and depression scale of 84 COVID-19 patients reporting olfactory dysfunction to those of 19 COVID-19 patients who reported no olfactory dysfunction [131]. Similar comparisons were made for 25 patients reporting no taste dysfunction and 78 reporting taste dysfunction. In both the taste and smell groups, those reporting dysfunction had higher anxiety scores than those not reporting such dysfunction ( $P = 0.018$  and  $0.002$ , respectively). However, depression scores were only significant for those reporting taste dysfunction, a phenomenon also seen for a measure of distress. It is unknown to what extent the reported taste dysfunction reflected deficits in flavor sensations due to decreased retronasal olfactory function [20].

### Concluding remarks

As the pandemic spread of COVID-19 developed, smell loss became the most salient initial symptom of COVID-19. Over the past 2 years, much has been learned about such loss. First, in most cases it is not total when measured by objective quantitative tests. Second, the majority of those who are inflicted can expect to regain normal function within 4 to 6 weeks after being infected by the SARS-CoV-2 virus. Third, while the magnitude of the measured smell loss seems to be similar to that observed for other types of PVODs, the sheer number of infected people is demonstrably greater given the high prevalence of COVID-19 cases. Fourth, while the neurotropism of this virus does not appear to be as great as other coronaviruses, its influences on the brain remain enigmatic. Fifth, short-term smell loss associated with COVID-19 may reflect inflammatory processes, whereas long-term loss may reflect alterations in neurological structures, including the downregulation of olfactory receptors. Sixth, it remains to be determined whether having had COVID-19 predisposes persons to neurological disorders, including those catalyzed by subsequent exposures to solvents, pesticides, or other toxic agents. Finally, much more research is needed to fully understand how SARS-CoV-2 influences the olfactory sensory system (see [Outstanding questions](#)).

### Acknowledgments

The author wishes to thank Dr Shima Moein for providing the artwork for this review and for critically reading an earlier version of the manuscript. The preparation of this work was not funded by any outside agency.

### Declaration of interests

The author is a consultant to Eisai Co, Merck Pharmaceuticals, the Michael J. Fox Foundation for Parkinson's Research, and Johnson & Johnson. He receives royalties from Cambridge University Press, Johns Hopkins University Press, and John Wiley & Sons, and is president of, and a major shareholder in, Sensorics International, a manufacturer and distributor of smell and taste tests.

### Outstanding questions

To what degree are viral entry proteins other than ACE2 involved in the production of COVID-19-related smell dysfunction? What differences exist between variants of COVID-19 in terms of their impact on the sense of smell not confounded by vaccination status?

Are some cases of COVID-19 smell loss, particularly those which reverse themselves over the course of a few weeks, simply due to epithelial inflammatory processes that resolve or do they reflect other factors?

Do cases in which smell or taste dysfunction linger for long periods of time reflect significant neural damage to elements of the olfactory system, notably cells within the olfactory neuroepithelium? Is the degree of resolution in such cases related to the extent of damage to the stem cell layer of the olfactory epithelium? Is SARS-CoV-2 neurotropic?

Given that up to 30% of COVID-19 cases appear to continue to have some smell dysfunction long after the initial infection, how many, if any, of these cases will ultimately regain normal function?

Are COVID-19 patients more susceptible to later neurological disorders, such as AD or PD? If so, is such susceptibility associated with the degree of smell loss, as well as genetic predispositions or environmental exposures to pesticides or other toxic agents?

Do other types of viral upper respiratory infections that impact olfactory function, such as the common cold or influenza, utilize the same viral entry receptor proteins as SARS-CoV-2 to infect olfactory eloquent cells?

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