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Letter to the Editor

Parosmia after COVID-19: olfactory training, neuroinflammation and distortions of smell

Dear Editor,

Distortions of smell, including parosmia and phantosmia, are increasingly recognized as important late sequelae of COVID-19-related olfactory injury[1]. Significant research examined how COVID-19 may affect the olfactory pathway to anosmia and hyposmia[2]; however, far fewer data are available on sensory distortions, or how they may relate overall smell recovery. Insights into potential mechanisms may afford clues to relieving symptoms in afflicted patients[3,4].

To better understand the associations with parosmia, we collected data about the presence of self-reported parosmia from a sample of 480 (PCR-confirmed) COVID-19 patients with persistent olfactory dysfunction. These data were extracted from the database of a tertiary referral COVID-19 smell disorder center. All patients had persistent olfactory dysfunction at least 6 months after a negative follow-up COVID-19 PCR test. Primary olfactory complaints included anosmia (n = 39; 8.1%), hyposmia (n = 249; 51.9%), or parosmia (n = 192; 40%). A subset of individuals with parosmia (n = 32; 16.6%) reported that their parosmia involved the same odors used during olfactory rehabilitation (Figure 1A).

What is the link between olfactory training and parosmia? Could neuroinflammation caused by SARS-CoV-2 mediate distortions of smell through aberrant regeneration or other alterations to the circuitry of smell pathways?

Olfactory training remains the only evidence-based intervention with established efficacy for treating olfactory dysfunction[4]. However, other emerging approaches targeting neuroinflammation are now being combined with olfactory training, offering the possibility of improved recovery COVID-19 related disorders[5]. Available evidence from human studies[5,6] suggests that olfactory impairment after COVID-19 arises from a combination of peripheral damage in the neuroepithelium[6] and injury to the olfactory bulbs (OBs). Loss of olfactory receptor neurons, interneuronal loss in the olfactory bulb, and erroneous targeting by regenerating fibers may all be factors in postviral parosmia. This peripheral theory attributes abnormalities of the olfactory neuroepithelium as the primary cause, whereas the central theory proposes alteration of higher integrative centers of the smell.

We hypothesize that the pathogenesis of COVID-19 parosmia may incorporate both peripheral and central elements. Injury to the olfactory neuroepithelium occurs due to the viral infection[5] but may also be possible from excessive exposure to environmental stimuli, such as synthetic essential oils[7], altering odor perception with consequent distortion (Figure 1B). The latter phenomenon could explain parosmia for the scents used in olfactory training, and reinforcement may occur with iterative exposures that are part of such exposure.

The olfactory epithelium has a remarkable capacity to undergo neurogenesis and to establish new connections to the olfactory bulb, but this finely tuned process is susceptible to environmental influences. Restoring normal function requires that the glomeruli of the olfactory bulb preserve the topographical/spatial mapping of odorant receptors (Figure 1B). We hypothesize that inflammation and neuronal damage in the olfactory bulb may predispose to the patterns of dysfunction[6] observed in parosmia. Aberrant regeneration of the olfactory nerves, analogous to the delayed onset of synkinesis observed after a facial palsy (Figure 1B), often coincides with recovery of function, and may reflect miswiring and possible contribution of central mechanisms.

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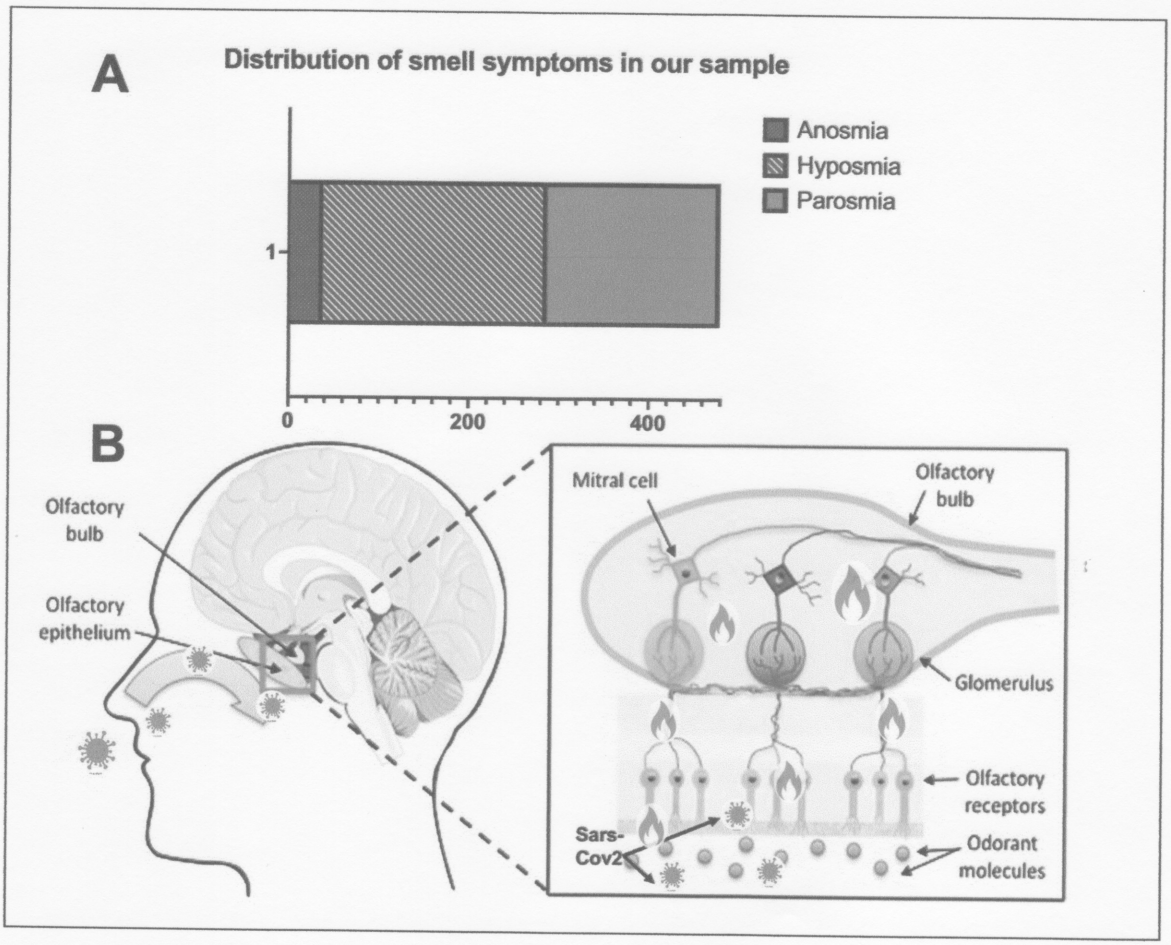

Figure 1. Prevalence and causes of parosmia. **A**, The graph shows the prevalence of parosmia in our sample. **B**, The image shows the potential mechanism at the origin of the parosmia. SARS-CoV2 enters through the nose into the olfactory bulbs causing infection and inflammation (red flame), both in the neuroepithelium and olfactory bulbs. The odorants used during the olfactory training may determine an aberrant regeneration responsible of the parosmia onset, because they stimulate inflamed areas. The presence of the inflammation negative impacts on the normal recovery process. Image modified from the original Figure 3 of "Kotecha AM, Corrêa ADC, Fisher KM, Rushworth JV. Olfactory Dysfunction as a Global Biomarker for Sniffing out Alzheimer's Disease: A Meta-Analysis. Biosensors 2018; 8: 41".

The severity, duration, and character of olfactory dysfunction in COVID-19 is variable[1,8], reflecting heterogeneity in both location and pattern of injury associated with viral insults[1,2,6].

It is well known that repeated stimulation of olfactory neurons with odorants involved in olfactory training can enhance regenerative capacity and neuroplasticity[7], but the effect of repeated stimulation in the setting of neuroinflammation is not well studied. We hypothesize that neuroinflammation increases susceptibility to development of parosmia or other sensory distortion

SARS-CoV-2 damages the olfactory neurons within the neuroepithelium, but if such damage is diffuse or selective is still unknown. Based on the variable severity of symptoms in our patients, we hypothesize that SARS-CoV-2 may cause either neuronal death or less severe injuries. Normally, the basal cells reconstitute the olfactory epithelium in those areas where the olfactory neurons died or degenerate; our hypothesis is that injury by SARS-CoV-2 to the neuroepithelium and olfactory bulb lead to altered mapping to receptor-specific targets, causing the parosmia.

Scientific reports have identified that the olfactory bulb's multi-layered cellular architecture can suffer from direct viral injury and persistent inflammation; both conditions can contribute to neuronal death[2,6]. The olfactory bulb contains both a spatial map (reflected in glomeruli) and interneurons that provide excitatory and inhibitory postsynaptic inputs. The stimulus processing in the OBs promotes odor discrimination, enhances sensitivity of odor detection, filters out of back-

ground odors, and receives inputs from higher brain areas. If there is unresolved inflammation in the OBs during (or immediately after) the recovery process of neurons and neural structures these cells might not recover their original functions. So, if parosmia reflects reparative phenomena after injury, then olfactory training could increase both recovery and parosmia.

In conclusion, unresolved neuroinflammation may negatively impact olfactory recovery, inducing distorted olfactory signals. With olfactory retraining, odors may be misperceived in the neuroepithelium, so abnormal signal arrives to the damaged or inflamed OBs, which are incapable of correctly discerning odors, so the patient presents with difficulty detecting or discriminating odors. An additional hypothesis is that peripheral stimulus may be erroneously perceived in higher brain centers involved in olfaction[9], causing the misperception reported by the patients. Repetitive, concentrated stimulation may reinforce such perceptions through synaptic connections within the glomerulus of the OBs (Figure 1B). Further research comparing standardized olfactory training protocols without and with drugs targeting neuroinflammation[5] are ongoing. Hopefully, they will clarify if olfactory training with parosmia is causal, related to the neuroinflammation or reflection of overall regeneration and recovery[7].

Conflict of Interest

The authors declare that they have no conflict of interest.

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