REVIEW ARTICLE

Part 3: Perspectives on Olfactory and Gustatory Dysfunction Pathophysiology, Management and Relevance to COVID-19: Rationale for Auricular Cranial Nerve Stimulation

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ABSTRACT

The rapid global emergence of distortions of the senses of smell and taste consequential to COVID-19 has provoked an unprecedented demand for investigation into treatments capable of addressing such medical phenomena. While the pandemic's principal focus rests on interventions intended to prevent the infection and its spread, much attention must be devoted to amelioration of these common symptomatic sequelae of it. The medical historical record reveals a shocking paucity of serious consideration of olfactory and gustatory dysfunction (OGD), hardly exclusive to SARS-CoV-2 infection (as discussed in Part 1 of this article series). To date, no treatment approach has ever delivered noteworthy clinical results for chronic cases. Numerous studies and reviews have addressed the epidemiology and hypotheses of OGD pathophysiology. Past and recent studies have produced vague findings and conclusions devoid of practical clinical applications for patients who continue to experience chronic sensory distortions and deficits.

It is urgent that focused exploration be aggressively pursued for therapeutic and restorative modalities to ameliorate OGD across all medical disciplines, with no bias towards any one approach. It is imperative that approaches outside the pharmacological realm are studied; no effective medication of any merit exists. Thus, innovative and new approaches potentially capable of supporting natural self-regulation and restoration of healthy neurophysiology must be investigated, post-haste. Specifically, stimulation of cranial nerves via their auricular branches, by means of various modalities, may hold promise. A vast body of evidence exists to support its investigation. Its inclusion as an extremely safe and inexpensive approach to endeavor to resolve chronic OGD (not merely for post-COVID19 infection) is warranted. The 3-phase auricular acupuncture microsystem may be the most precise form of targeting and positively influencing specific neurological structures affected by COVID-19. (*Altern Ther Health Med.* 2023;29(7):52-61).

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INTRODUCTION

It was rapidly established at the onset of the COVID-19 pandemic that infection with the SARS-CoV-2 virus was accompanied by loss or distortion of the senses of smell and/or taste, in some cases prior to development of other symptoms. Most infected individuals have been observed to naturally resolve this condition within a month.[1] Others, however, have remained severely affected a year or more later. The focus of this study is justifiably more pertinent to individuals with persistent chronic olfactory and gustatory dysfunction (OGD). Known throughout the ages to exist from various causes, maladies of OGD have been scantly addressed in medical research. A paucity of evidence exists regarding their mechanisms, and to an even lesser extent, their treatment. The COVID-19 pandemic has precipitously propelled OGD into becoming a priority of medical focus, insufficiently considered medically previously. Distortion and dysfunction of the senses of smell and taste are hardly exclusive to the SARS-CoV-2 infection (discussed in detail in Part 1 of this series).

The term anosmia refers to the complete loss of the sense of smell. Hyposmia is reduced olfactory sense and discernment of scents. Parosmia is the distortion of the nature of scents; often normally pleasant or neutral scents smell unpleasant. The phenomenon of olfactory hallucination—smelling something that is not actually present, is known as phantosmia. Alterations in gustatory sensations have similar terminologies. The complete loss of the taste sensation is known as ageusia. Dysgeusia and parageusia are synonymous for altered taste sensation (often metallic). Hallucinatory sensation of taste without stimuli present is referred to as phantogeusia. For the purposes of this article series, all of these phenomena are referred to as OGD.

The epidemiology, symptomatology and hypotheses of pathophysiology of post-COVID-19 olfactory and gustatory dysfunction (PCOGD) have been under copious investigation. The purpose of this article series is different. Its intention is to provide the rationale (with minimal redundancy) for consideration and investigation into a potentially efficacious treatment for PCOGD. Merely reiterating the obvious existing problem and lamenting the lack of current clinical results would have little value. If a treatment method shows promise for resolving OGD; investigation into its potential would be of highest priority and greater public interest to make it accessible.

Parts 1 and 2 of this series established the dramatic upsurge of investigation into the long-term physiological changes triggered by COVID-19, including its psychological implications. It is evident through evaluation of scientific databases that disorders of taste and smell have been strikingly insufficiently acknowledged, medically. Public awareness has reached its pinnacle due to countless people worldwide simultaneously experiencing symptoms. The destructive effects of chronic OGD on quality of life, historically overlooked for its importance, now sit at center stage.

Unlike OGD associated with the coronaviruses of the common cold, rapid anosmia tends to occur with COVID-19 without nasal obstruction. Persistent post-infection OGD appears to occur via additional mechanisms. The body of knowledge regarding the various known causes (infection and non-infection) is addressed in Part 2 of this article series, as well as in a vast compendium of studies, both recent and past, that are too numerous to list. There is currently no consensus on the pathogenesis of OGD; it is hardly unique to precipitation by coronaviruses. Numerous non-COVID pathogens have long been established as triggers of OGD (addressed in Part 1 of this article series). Medically established non-infectious causes are also discussed, including mechanical, traumatic, chemical, pharmaceutical, aging, and neurodegenerative factors.[2]

CURRENT APPROACHES

Despite its long-known existence as a medical phenomena, it is only now during a global crisis that OGD is being taken seriously. The emergence of COVID-19-related OGD presents many medical unknowns. It is uncertain whether or not natural resolution will occur in chronic cases, as is its duration. The consistent theme throughout the existing medical literature is that no specific standard of care exists, nor has any specific medication been established, designated or approved by the government for treatment of OGD, not just for COVID-19, but for all known causes. Research for this article series revealed a shockingly sparse body of work. Treatment options visible in the academic record are extremely limited and are woefully lacking any major impact.

Corticosteroids have been considered as a therapeutic measure. However, long-term evidence and medical consensus is understandably unclear whether or not corticosteroid treatment in PCOGD is safe and appropriate..[3-11] It is arguably of concern to seek such an agent, considering that it is undisputed that oral and intravenous corticosteroids can impair immune system function. Essential, life supportive steroid medications should obviously be utilized, as indicated. However, physicians and patients alike may exhibit legitimate concern with any attempts to treat non-life-threatening OGD with any agent capable of decreasing one's ability to fight infection during a viral pandemic. This is an impetus for the pursuit of non-pharmacological treatments.

Nutrients, such as omega-3 fatty acids,[12] zinc,[13-20] turmeric [21, 22] and alpha-lipoic acid,[23, 24] have been studied, with limited efficacy reported. Some healthcare providers frown upon supplementation due to its potential dangers, particularly when its use seems likely in individuals desperate for anything that might restore normal taste and smell sensations. Although the public seems to assume safety is inherent in products promoted under the banner of "natural," concentrated substances derived from plants must be used with knowledge and caution. Unlike the consumption of natural whole foods rich in zinc and omega-3 fatty acids, turmeric supplementation should not be consumed indiscriminately, or taken at excessive dosages and frequency. It would seem rational that a safer approach would be for individuals with PCOGD to increase consumption of whole foods that contain the potentially beneficial substances. Nevertheless, it appears that judicious use of supplements under strict physician guidance is worth considering.

Numerous pre- and post-COVID-19 articles and reviews espouse olfactory training (OT)—also known as scent training (ST)—as the primary recommendation for the treatment of OGD to date. A plethora of studies and reviews reiterate the rationale for OT as the most appropriate currently investigated therapeutic measure for PCOGD. Without a consensus regarding any pharmacological approach in sight, OT has been the most prominent treatment considered.[3,4, 11, 25-29] To date, a smattering of clinical trials have been designed to investigate the prospect of support for PCOGD, including prescription medications such as Cerebrolysin® (a stroke, cognitive decline and brain injury drug),[30] theophylline (a phosphodiesterase inhibitor used in the treatment of asthma)[31-33] and gabapentin (seizures, nerve disorder pain reliever).[34]

PROSPECTIVE NEW PARADIGM

The olfactory and gustatory clinical manifestations of the COVID-19 pandemic have generated an urgent focus on a medical mystery for which we seek past research to provide us with clues to expedite solutions. The medical literature from a span of decades, evaluated for this 3-part article series, regarding both the pathophysiology and treatment of chronic OGD has revealed a rather bleak clinical outlook and an abundance of speculation and hypotheses. No treatment approach appears to have produced consistent and noteworthy results—certainly not in chronic cases, whether from causes other than COVID-19 or not. Parts 1 and 2 laid the foundation to support the magnitude of necessity and urgency for medical science to explore new and progressive modes for confronting the conundrum of OGD. The focus

turns to expanding investigation beyond the anatomical structures and physiological mechanisms already considered.

Autoimmune Components

The possibility of an autoimmune component must be addressed. Recent and older research arouses the suspicion of the possibility that COVID-19 triggers an autoimmune response, which may, at least in part, contribute to the pathophysiology of OGD. Insights regarding the relationship between autoimmunity and olfaction come from Benkler, et al. Their 2009 study correlated Parkinson's disease with damage to several brain regions associated with perception of odors including the cortices of orbitofrontal, amygdala, piriform, insular and the anterior cingulate.[35] In 2010, Gaines proclaimed renewed interest in olfactory disorders. He indicated the low incidence of self-reporting of such disorders and the significantly higher prevalence validated by smell identification testing. Among various proposed pathophysiological mechanisms cited by Gaines is autoimmunity.[36] Galeotti and Byry remind us that infectious diseases have been long known to trigger autoimmune and autoinflammatory diseases. COVID-19 infection precedes the appearance of these, including pediatric inflammatory multisystemic syndrome (first reported in April 2020 by Harwood) as another mystery to solve related to the coronavirus.[37, 38]

Perricone and Shoenfeld found the observation linking neurological disorders, autoimmune diseases, depression and the sense of smell to be most curious in the case of multiple sclerosis (MS).[39] Dahslet, et al linked MS olfactory deficits with anxiety and depression.[40] There is evidence that a higher prevalence of psychiatric disorders including depression and psychosis exists in individuals with autoimmune diseases than the rest of the population. Olfactory impairment is seen to be associated with these conditions. Evidence indicates that olfactory gene receptors have additional brain functions related to their anatomical connection to the limbic system.[41] Further correlation between autoimmune, psychiatric and olfactory dysfunction was made via Emmer, et al's study on the amygdala and systemic lupus erythematosus.[42] Shoenfeld's research suggested that olfactory dysfunction may be associated with autoimmune conditions of the central nervous system (CNS). Kim, et al (2018) reported that olfactory dysfunction is an early sign of neuroinflammation of the CNS. Autoimmune inflammation, as observed in MS, can cause olfactory disorders. This suggests that meningeal autoimmune inflammation interferes with the olfactory mucosa along the olfactory nerves.[43]

Geran, et al conducted the first study to investigate olfactory function and autoimmune encephalitis. The researchers concluded that inflammation in olfactory and gustatory structures was caused by autoantibodies in patients with autoimmune encephalitides.[44] Amital, et al concur that autoimmune disease and olfactory dysfunction are concomitant. Their 2014 study focused on fibromyalgia revealed a decreased sense of smell compared with healthy controls.[45] Aydin, et al (2016) observed olfactory dysfunction to occur comorbid with psoriasis. The severity of olfactory deficit was found to be in proportion to the severity of psoriasis.[46] Olfactory impairment was found by Xu, et al (2021) to be present in patients with primary Sjogren's syndrome. In a similar fashion, there was a close correlation between olfactory dysfunction and the severity of Sjogren's symptoms.[47] Yazdanpanah, et al report that an accumulating body of evidence exists concerning late-onset complications of COVID-19, which include autoimmune manifestations.

Detection of autoantibodies is the cue to the discovery of the potential for COVID-19 to induce autoimmunity. Understanding COVID-19 damage with regard to direct viral injury or autoimmunity may help the development of treatments.[48] A major challenge lies with the fact that existing pharmacological treatments for autoimmune disorders are primarily immuno*suppressive*—a factor for which manufacturers give the precaution of the adverse effect of reduced capacity for an individual to fight infection. This would seem inarguably important to avoid in the COVID-19 era.

ANATOMY AND PHYSIOLOGY OF POSSIBLE ASSOCIATED STRUCTURES

Fundamental to the development of effective treatment for post-infection chronic OGD is investigating beyond the existing medically considered anatomical neurological pathways. While early evidence reinforces the hypotheses of SARS-CoV-2 affecting nerve tissue of the olfactory bulb and nasal cells, impairment of other brain structures may be involved, such as the amygdala, hippocampus and cingulate cortex.[49] Subsequently, when reflecting upon any newly hypothesized neuropathophysiological mechanisms, the matter of treatment options is still the greatest obstacle. The vast body of literature clarifies that disturbances to olfactory and gustatory sensations can be precipitated by interference anywhere along the pathways by which the sensations of taste and smell are transmitted to the brain. In this section, brain structures and functions are discussed relevant to their likely involvement.

The Limbic System

The limbic system consists of structures that process memory and emotions. The hippocampus, amygdalae and hypothalamus—located within the cerebrum—are the primary components. Other key structures include the basal ganglia and cingulate gyrus. No universal agreement exists on what brain structures comprise the limbic system. It is notable in the context of this work that part of what is now called the limbic system used to be referred to as the rhinencephalon—its Greek origin meaning nose-brain. Research and discoveries of limbic system function have been evolving over decades.

Imperative to the ongoing investigation into developing effective treatment in post-infection OGD is considering the fact that both olfaction and taste have a significant emotional component associated with the interaction of multiple senses. As Krusemark elegantly describes it, phylogenetically the most ancient sense, olfaction is characterized by a unique intimacy with the emotional system. He aptly contends that human olfactory processing is affectively charged long before

an odorous molecule contacts the nose.[50] Hundreds of scientific studies have documented the cross-modal links between olfactory and visual stimuli.[51] A 2000 study from the *Journal of Neurophysiology* using positron emission tomography (PET) technology further defined the relationship between visual and olfactory function.[52]

The compendium of research certainly links smell and memory with brain anatomy and physiology. Scents are routed through the limbic system, notably through the amygdala and hippocampus. Nakano describes the limbic system as not being empirically proven; it is a functional concept that can explain various brain functions.[53] There are 2 fascinating studies that support this view through their curious findings involving wine tasting. Wang and Spence's study revealed that different music affected taste perception and enjoyment of flavors of wine.[54] A 2001 study, published in the journal *Brain and Language*, reveals how visual stimuli can influence olfactory and gustatory sensation. It reinforced the fact that visual processing in the brain is significantly faster than smell and taste. Tasteless red food coloring was secretly added to white wine to simulate the appearance of red wine. A total of 54 wine experts were asked to evaluate the smells and tastes. The outcome was that the color of the wine dramatically influenced taste and smell perception. The experts described the faux red wines in terms typical of authentic red wines,[55] demonstrating the complexity of the overlap and interactions of multiple sensory modalities.

In 1993, Wu, et al reported that patients with schizophrenia can have olfactory deficits, which could be correlated with limbic system dysfunction.[56] Turetsky, et al (2009) found that gross structural and functional anomalies are mirrored by cellular and molecular abnormalities that suggest decreased or faulty innervation and/or dysregulation of intracellular signaling.[57] Thus, it may be postulated that treatment approaches that support limbic system function might be beneficial in the resolution of PCOGD.

Hippocampus

Like many brain structures, the hippocampus is paired, with one in each hemisphere. It is best known as the memory center of the brain. Neural connections that are involved in memories of senses of both smell and taste have hippocampal processing.

Amygdala

The pair of amygdalae are small almond-shaped structures within the temporal lobe of the brain, adjacent to the hippocampus. The amygdala is known to be involved with the emotional meaning of our memories. The fact that evidence exists that certain odors can modulate emotion and cognition through the hippocampus and amygdala pathways has been suggested to be significant in the treatment of psychological problems.[58] The amygdala's significance goes far beyond the realm of psychology; a preponderance of published proof exists regarding the effect of various stimuli on the amygdala, as well as its functions and relevance to numerous medical conditions.[59] Investigation into its role in OGD is appropriate.

Eslinger, et al (1982) referred to multiple brain regions involved in olfaction, including the olfactory bulbs, orbitofrontal and medial temporal cortices, the thalamus and amygdala.[60] In a 1983 study, disruption of odor and taste perception was observed from injecting novocaine into the amygdala.[61] A 1993 study published in *Behavioral Neuroscience* demonstrated how amygdala lesions blocked odor preferences in rats.[62] A 2009 functional magnetic resonance imaging (fMRI) study demonstrated amygdala activity elicited by emotional and odoriferous stimuli. These findings suggested a bridging of chemical and emotional stimuli to produce neurobiological and behavioral effects.[63]

Krusemark, et al, (2013) discussed olfactory sensory relay adaptation associated with the amygdala and anxiety.[50] Zald and Pardo (1997) studied the relationship of emotion, olfaction and the amygdala. Their findings provided evidence of the amygdala's role in the processing of aversive olfactory stimulation.[64] Root, et al's 2014 data indicates that the amygdala plays a critical role in generating innate odor-driven behaviors but this does not preclude its participation in learned olfactory behaviors.[65] Also of note is a 2014 study from the *Journal of Parkinson's Disease* (PD), whose findings suggested that declining olfactory function was a predictive measure of PD with dementia, associated with dysfunction and atrophy of the amygdala and other limbic system structures.[66]

Existing knowledge of the amygdala validates the importance of any and all evaluations and treatments (established and/or proven to be without health risks) that promote functional wellness of any regions of the brain affected by COVID-19 and any other pathogens. Medical research has validated addressing amygdala function by various medical means in pursuit of managing various maladies. It is plausible that amygdala function is worth considering regarding treatment for post-COVID-19 OGD. This article series is intended to present evidence for the pursuit of approaches that appear to facilitate natural recovery. Researching medical databases regarding treatments for dysfunction of the amygdala resulted in primarily prescription medicines, such as benzodiazepines, alprazolam (Xanax), clonazepam (Klonopin), diazepam (Valium) and lorazepam (Ativan). The intended mechanism of these drugs is to *inhibit* amygdala function. There is little, if any, indication of therapies in the medical literature designed to support natural restoration of amygdala physiological function.

Thalamus

Olfaction is often considered to be different from other human senses based on the assertion that its signals bypass the thalamus en route to the forebrain. However, the thalamus transmits olfactory sensory input to the hypothalamus, hippocampus and the amygdala—structures that all are heavily involved with emotions, memory and perception. The thalamus is made up of a series of nuclei that are responsible for the relay of the different sensory signals.[67] However, since the thalamus is not part of the olfactory neurological pathway from periphery to cortex, it is rarely considered. In 1982, Eslinger, et al deemed the understanding

of how various brain areas are related to olfaction to be limited. They did indeed cite the thalamus, as well as the amygdala, as relevant to olfactory physiology.[60] Sela, et al's 2009 study determined that thalamic lesions could significantly impair olfactory identification. Thus, the thalamus plays an important functional role.[68]

Pelligrino, et al (2021) studied the post-trauma effects on olfactory loss and brain response in consideration of more than just the olfactory cortex. They unexpectedly determined that a negative association exists between response and olfactory perceptual function in the mediodorsal thalamus, ventromedial prefrontal cortex and posterior cingulate cortex.[69] Courtiol and Wilson contend that despite the unusual anatomy of the olfactory pathway, an olfactory thalamus can be identified.[70] Consideration of an olfactory physiological mechanism involving the thalamus was a factor in a 2018 case study of a 20-year-old lifelong anosmic *acquiring* the sense of smell via auricular acupuncture, which included thalamic stimulus.[71]

Taste pathways, on the other hand, are known to project from the nucleus of the solitary tract directly to the taste thalamus, and then to the taste insula.[72] It would be prudent to refrain from omitting contemplation of the contribution of any nervous system structures in the search for PCOGD solutions. This research certainly validates the inclusion of the thalamus.

Multiple Cranial Nerves

The bulk of the medical literature focuses on disorders of the sense of smell; taste is generally regarded as less important or simply associated with olfaction. Thus, treatment is essentially non-existent. Critical to the pursuit of solutions to the post-COVID-19 gustatory dilemma is awareness of the neurological pathways from the tongue to the brain, which are different from those of olfaction. A total of 3 cranial nerves are associated with taste: facial (VII), glossopharyngeal (IX) and vagus (X). Long prior to the current pandemic, Heckmann and Lang insisted that since gustatory disorders can result from damage at any location of the neural gustatory pathway from the taste buds via the peripheral and CNS to the cerebral cortex, clinical assessment of patients with taste disorders should include complete examination of the cranial nerves and, in particular, gustatory testing.[73]

Olfactory and gustatory dysfunction has been associated with various sensorial inputs, including the trigeminal nerve. Okuda, et al's case report from a 1994 issue of *Clinical Neurological Neurosurgery* described a patient with trigeminal sensory neuropathy associated with taste sensation impairment. In that case, no other cranial nerves were found to be involved. It was found to have been caused by an infection affecting the gasserian ganglion of the trigeminal nerve.[74] Franelli, et al stated in 2007 that the olfactory and the trigeminal systems have a close relationship. Most odorants also stimulate the trigeminal nerve. Although the mechanisms are unclear, they reported patients with no sense of smell exhibited decreased trigeminal sensitivity.[75] Siviero, et al (2010) associated somesthetic, gustatory, olfactory function and salivary flow in patients with neuropathic trigeminal pain.[76] Natoli, et al postulated the potential for SARS-Cov-2 to invade the brain via the peripheral trigeminal nerve to result in dysosmia.[77] Otte, et al concurred with this, as their study showed impaired trigeminal function associated with COVID-19 olfactory impairment.[78]

Corpus Callosum

The corpus callosum consists of white matter tracts that connect the left and right cerebral hemispheres of the brain. It is composed of approximately 200 million heavily myelinated nerves.[79] Its potential relevance in treatment for OGD is supported by Conklin, et al's 2021 study, which focused on critically ill patients with COVID-19. Brain magnetic resonance imaging (MRI) scans revealed microvascular lesions manifesting with a neuroanatomic predilection for the corpus callosum and subcortical and deep white matter.[80] While their study was not specifically relevant to OGD, the researchers concluded that it is important in the growing body of knowledge of the neurological effects of the virus and mechanisms of brain injury.

Prefrontal Cortex

Kringelbach, et al explored taste-related activity in the human dorsolateral prefrontal cortex. In 2004, the researchers lamented the insufficient amount of scientific inquiry into the sense of taste. However, their study's novel finding was a highly significant response to taste in the dorsolateral prefrontal cortex.[81] Potter and Butters assessed olfactory deficits in patients with damage to the prefrontal cortex. There findings provided evidence of thalamic-prefrontal circuitry involved in odor perception.[82]

PROSPECTIVE TREATMENT APPROACH: AURICULAR CRANIAL NERVE STIMULATION

Auricular Vagus Nerve Stimulation

The vagus nerve originates in the medulla oblongata and meanders throughout the viscera. Of all the cranial nerves, it is known to have the most extensive distribution and course. It is often described as the great wandering protector because of its involvement in functions of the autonomic, cardiovascular, respiratory, gastrointestinal, immune and endocrine systems. Vagal afferents sense various interoceptive stimuli including pressure, pain, stretch, temperature, chemical, osmotic pressure and inflammation. In a 2012 lecture by Professor J. Deuchars, the vagus nerve's functions were described as being "almost anything."[83] We must consider its possible role in PCOGD. Sakhri describes the vagus nerve as the conductor of all immune defense mechanisms. She insists investigation of the viral infection along the vagal pathway from the peripheral to the CNS to be of great importance in determining effective treatment.[84]

Vagus nerve stimulation (VNS) has been investigated thoroughly utilizing various clinical applications and devices for a variety of medical conditions. Hundreds of studies, too numerous to reference here, can be found on VNS/neuromodulation (via bioelectric devices) in the medical literature. Transcutaneous auricular vagus nerve stimulation (taVNS) provides somatosensory innervation to several

aspects of the external ear. It is a more recent intervention compared with cervical VNS, however, its therapeutic value has been demonstrated by a preponderance of positive studies for various conditions.[85-99] The auricle is considered the only anatomical region where the vagus nerve sends its only peripheral branch. It can be influenced by external stimuli, which makes it an extremely useful and powerful gateway to modulate various brain functions in an affordable and non-invasive manner.[99] It does not require surgical implantation of a device, nor does it have the adverse events that have been reported from cervical VNS and implanted devices.

A vagal-olfactory interaction was observed by Garcia-Diaz, et al. (1984). Specifically, electrical stimulation of the vagal nerve modulated electrophysiologic activity in the olfactory bulb.[100] Kirchner, et al's 2004 study evaluated the potential for affecting gustatory and olfactory function with VNS. They indeed concluded that using electrophysiological measures of olfactory function, VNS could have a significant role in olfactory processing.[101] Maharjan, et al's 2018 investigation of the effects of high-frequency auricular vagus nerve stimulation (ANVS) on olfactory function yielded positive results in human patients.[102] Their 2019 study, which investigated the effects of non-invasive, high- and low-frequency median nerve stimulation on human olfaction, provided additional support to the vagus nerve hypothesis of olfactory function. As is consistently the conclusion of auricular vagus nerve research, the investigators professed the need for further studies.[103]

In 2019, Staats, et al hypothesized that non-invasive VNS might provide clinical benefits in patients with respiratory symptoms similar to those associated with COVID-19. They referred to the associated respiratory compromise as being due to a hyperimmune reaction, often called a cytokine storm. VNS has been known to block production of cytokines in sepsis and other medical conditions. Their study concluded that VNS had a strong scientific foundation; specifically, to provide clinical benefits for patients with COVID-19 with severe respiratory symptoms.[104]

Boezaart, André and Botha published 2 case studies in the journal *Neuromodulation.* Patients with stage 3 COVID-19 received taVNS in addition to paracetamol (acetaminophen) and codeine. The treatment was found to drastically reduce interleukin-6 blood levels. The researchers went as far as to recommend that taVNS should be administered before considering steroid therapy for coughing related to COVID-19. Unlike steroids, it has no known adverse effects.[93]

Auricular Acupuncture

The existing body of evidence is central to the cause of seeking supportive measures with the potential to ameliorate post-COVD-19 neurological dysfunction and its related symptoms. The bulk of taVNS research deals solely with procedures involving electrical stimulation. Its origins, however, lie in the work of French neurologist Dr. Paul Nogier (1908-1996) with auricular acupuncture. A thorough investigation of existing taVNS research reveals a peculiar absence of references to the innovator of this internationally recognized and distinct medical discipline (Nogier, 1957) lauded by the Director General of the *World Health Organization* (Nakajima, 1990).[105] The auricular acupuncture microsystem approach (auriculotherapy, auricular therapy or ear acupuncture) does not view stimulatory treatment to be solely a vagus nerve mechanism, nor are its clinical results dependent upon knowledge or speculation about such.

Auricular acupuncture is a pinpoint-specific means of stimulating nerves. How, why, where and when it is done depends upon an analytical process combined with the skill, experience and knowledge of the practitioner. Auricular acupuncture needle stimulation affects branches of several cranial nerves. Decades ago, Dr Nogier discovered and documented complex auricular energetic projection zones that are neurologically/embryologically correlated with anatomical structures. Within these zones, electrically active points can manifest as dysfunction of their correlated anatomical structures. His work has been expanded upon by various practitioners over several decades with different methodologies. There are more than 800 peer-reviewed articles and studies, for example, in the *National Library of Medicine's* Pubmed.gov database. The cutaneous distribution of vagus nerve fibers on the auricle are unique to each individual, with significant overlap existing between various nerves.[106] Thus, there is no fixed acupuncture point for any anatomical structure.

Stimulating the vagus nerve via the ear acupuncture microsystem for affecting olfactory function is not new. In 1999, Tanaka and Mukaino conducted a controlled single blind study of a randomized population of 23 healthy volunteers. Their findings suggested that auricular acupuncture of a region known to be supplied by the auricular branch of the vagus nerve affects the recognition threshold of olfactory acuity with strong odorous substances.[107] Auricular cranial nerve acupuncture can be done by various means. The Liebell Clinic case study of acquisition of the sense of smell cited earlier involved the insertion of 3 mm-long, sterilized stainless-steel semi-permanent ear acupuncture intradermal needles. The needle's ring handle remained visible, securing it and enabling easy removal. A medical adhesive was used along with layered bandage tapes to secure the needles in order to maintain continuous stimulation of nerves for several weeks.[71]

taVNS involves a general and broad electrical stimulus for a single cranial nerve. In sharp contrast, auricular acupuncture is an extremely precise, patient-specific, acupuncture needle stimulation of cranial nerves (not only the vagus nerve) provided under special conditions and analysis procedures. Its mechanisms involve the natural self-modulation of human electric currents rather than an external electric source. While the proposed intent to use it as a potential treatment for PCOGD is new, auricular acupuncture is by no means an experimental procedure. An acupuncturist may, by scope of practice, endeavor to provide wellness-based holistic care to promote natural healing responses and ameliorate symptoms. The fact of the matter is that no treatment method of any kind (from any medical

specialty or discipline, new or old) has provided evidence to designate its distinction as a front-line approach to OGD. Therefore, there is no reason to avoid investigating ear acupuncture, which minimally has as solid a neurophysiological foundation as any existing treatment.

Vent and Damm contend that olfactory function recovery after viral infection cannot be achieved reliably via pharmacology. However, their 2010 study revealed success with acupuncture.[108] A few other studies report similar success.[109, 110] Drews, et al conducted a study using traditional Chinese medicine-based acupuncture done on various established body points. In their 60-patient study, they observed a positive effect on smell discrimination in patients who had a post-infectious olfactory decrease, and suggested acupuncture as a supplementary treatment option. The investigators did report that the sooner treatment is applied after the onset of loss of smell, the more likely it would be effective.[111]

Further testimony of the rationale for the pursuit of auricular therapy for PCOGD is a recent French study. The scientific acupuncture department of the *Paris Xl Universite*, France, was contacted by the chief of the intensive care unit of Saint Antoine Paris Hospital during the COVID-19 pandemic. They were asked if acupuncture might be helpful in reducing the need for sedative drugs necessary for ventilation in severely affected patients. The team intentionally searched for, and subsequently observed a specific visual auricular marker in patients with COVID-19. This marker was not seen in healthy volunteers. Edema of the auricular region between the tragus and the ascending branch of the helix was observed in all of the 34 patients studied. This edema progressively diminished and disappeared upon patient recovery. Volf, et al described the auricular region to be known as the Interferon point, which has been reported to be effective in improving immune defenses related to viral infections.[112, 113, 114] This region had been described as the Interferon point by the German physician-acupuncturist, Frank Bahr, but had been considered scientifically controversial. In the study by Volf, et al, stimulation of this region appeared to speed up the clinical course of respiratory problems in patients with COVID-19. The researchers appropriately cited the need for further clinical trials.[115]

Auricular acupuncture cranial nerve stimulation promotes natural autoregulation to produce its positive outcomes. The intellectual pursuits of dosage, intensity, duration and other parameters of tAVNS electrical stimulation do not apply with insertion of semi-permanent ear acupuncture needles. Its mechanism of action, although not fully known, is not a matter of attempting to intentionally inhibit or artificially increase brain response, but rather to support it to resolve problems naturally via neurophysiological phenomena. The preponderance of proof in support of pursuing auricular stimulation for improving brain function appears to be without question.

Other Relevant Brain Structures and Auricular Nerve Stimulation

Various brain structures discussed earlier may be associated with the neurological pathways of olfactory and gustatory function. Supportive evidence exists for the potential of precise auricular stimulation beyond merely the vagus nerve. Auricular acupuncture stimulation in support of corpus callosum function can be a significant component of treatment for various conditions. King, et al, in their *Military Medicine* article, *Auricular acupuncture: a brief introduction for military providers*, cite the recognized value of the healing art in the consensus statement of the National Institutes of Health. Specifically, they cited evidence of acupuncture's effects being mediated through the CNS. PET and fMRI studies show broad responses involving limbic system-related brain structures. Furthermore, these investigators clarified that auricular acupuncture mechanisms of action may be attributed to regional innervations of the ear. Overlapping nerve distributions include the cervical plexus, trigeminal, vagus, facial and glossopharyngeal nerves.[116]

Studies such as Liu, et al's 2016 investigation into transcutaneous vagus nerve stimulation (tVNS) and amygdala modulation for depression exemplify non-pharmaceutical approaches. They demonstrated that tVNS could significantly modulate the amygdala in patients with major depression disorder, and provided insights into the brain mechanism of tVNS.[117] Ear acupuncture stimulation of regions known to be associated with the amygdala has shown relevance to many conditions, and thus might have a role in the treatment of patients with OGD.[71] Badran, et al's 2018 study demonstrated that auricular stimulation had beneficial neuromodulatory effects on the right caudate, bilateral anterior cingulate, cerebellum, left prefrontal cortex and mid-cingulate brain regions.[89] Zhang, et al, in their 2021 study on insomnia, refer to transcutaneous auricular vagus nerve stimulation (taVNS) as a combination of auricular point and vagus nerve stimulation. They determined that taVNS had an effect on the medial prefrontal cortex.[118]

A 2010 fMRI study published in the *European Journal of Neuroscience* discussed the role of the vagus nerve in acquiring learned flavor preference and the brain's response to intragastric glutamate. The researchers concluded that the abdominal vagus nerve is necessary for acquiring preferences, and that the lateral hypothalamus and limbic system may integrate the information on gut glutamate and oronasal stimuli. Structures specifically implicated included the amygdala, hippocampus and hypothalamus.[119]

Another interesting 2019 study that reinforces the need for attention to multiple neurological pathways was performed with mice. It was found that the vagus nerve is involved in a mechanism of memory function associated with the bitter taste of a chemical found in beer. Iso alpha amino acids were used to simulate the vagus nerve, which showed evidence of improving cognitive function (spatial and object recognition) through dopamine signaling in the hippocampus.[120]

DISCUSSION

It is unambiguously evident that disturbances of both taste and smell are common, but historically poorly considered or not of concern in clinical medical practice, as well as in research. It is abundantly clear that these are symptoms that medicine at large has never been faced with in such an ominous onslaught as

its emergence as a major symptom of COVID-19. It is evident that a global pandemic was required to rouse interest in long-existing medical phenomena that should have always been taken more seriously. Patients have notoriously been taken for granted by practitioners of many medical disciplines regarding OGD long prior to the pandemic. An overview of this situation compels one to draw the conclusion that losing the sense of smell or taste has been perceived as a relatively insignificant malady, perhaps as compared to becoming deaf or blind. Might this be because a loss or distortion in taste or smell is hardly life-threatening? Is it possible that its diminishing effect on one's quality of life requires an empathetic fellow sufferer to appreciate its significance? Is it, at least in part, due to the fact that no specific or consistent treatments have existed? Should it be unsurprising that when no treatment is available, it is more convenient to *ignore* the symptoms? Terms such as anosmia, ageusia, dysosmia, phantogeusia, etc. are becoming known to the lay public, accompanied by the appropriate demand for medical solutions.

An abundance of medical literature exists that repeatedly reinforces the consensus that viral infections can trigger OGD, and that the pathogenesis of sensorineural deficits is both poorly studied and uncertain. Most important, it appears universally agreed that OGD has been, and still is, extremely challenging to treat. It is not the intention of this article series to further harp upon this international consensus. Inarguably, furthering the knowledge of the pathophysiology and mechanisms of post-COVID-19 sensory dysfunction could pave the way for development of effective treatments that address neurological impairments. The demand for them is crystal clear. It is hopeful that this can manifest from innovative applications of existing therapies, medications, nutritional measures and other modalities, as well as new procedures and products.

Whether it proves to be effective for PCOGD or not, most physicians are not familiar with auricular acupuncture, despite its 65-year presence and surprisingly significant scientific pedigree. It may be perceived as peculiar to ponder its consideration as a frontline approach. It should be no great epiphany that no potential means to manage these globally relevant maladies should be bypassed; allopathic conventional Western medicine has never established *any* treatment for chronic OGD, regardless of its cause. How could *any* approach be categorized or construed as primary over any other? No attempt within reason of safety should be proposed to the public under the banner of "alternative" medicine, since no conventional solution exists. It is furthermore reasonable to postulate that acupuncture should be considered a frontline approach; it has been administered for disorders of taste and smell for millennia, although not confirmed via clinical trials. Indeed, studies should be done to determine whether or not traditional Chinese medicine-based acupuncture (whole body) and/or auricular microsystem acupuncture can help patients with OGD.

It is incumbent upon all scientists to submit work for peer review and scientific publication. This article series serves to galvanize investigation into any means possible to resolve post-COVID-19 smell and taste disorders. However, it is emphasized with full transparency that these articles were written based upon clinical experience with auricular acupuncture and anosmia. The case study published in the journal *Medical Acupuncture* (2019) reported successful (and to date, permanent) treatment of a 20-year-old anosmic to induce the natural acquisition of the sense of smell (absent since infancy) via a single treatment of auricular acupuncture.[71] While it is customary to avoid self-citation, it is, in this case, unavoidable; the very purpose of this article series is to expand upon this remarkable case (and other similar clinical experiences) to validate the quest for further investigation and implementation of the approach taken.

CONCLUSIONS

Disorders of taste and smell sensation had been poorly addressed, representing a modicum of medical mention—until the sudden demand of COVID-19-associated symptoms transmogrified their consideration. Presented in this 3-part series of articles is an overview of the current state of knowledge on the pathophysiology and treatment options for olfactory and gustatory dysfunction triggered by COVID-19 infection. While most COVID-19-related cases of smell and taste dysfunction have been reported to naturally resolve, chronic cases are widely prevalent—with scarce evidence of any specific treatment to successfully address the problem. The history of the investigation of mechanisms, and treatment of olfactory and gustatory dysfunction, in general, is at best unremarkable and insufficient. Extremely limited evidence-based treatment has existed for any known causes. Thus, with a dismal dearth of medical support for a suddenly prevalent (but hardly novel) set of maladies, the imperative for multifaceted and broad investigation across all medical disciplines is without question.

Global demand for any treatment capable of reducing or resolving gustatory and olfactory disorders triggered by COVID-19 is unprecedented. Current treatment approaches and recent clinical trials initiated since the onset of the pandemic are discussed in Part 2 of this article series. The majority are focused on new applications of existing medications and other modalities, primarily due to the acute urgency of the taste and smell dysfunction dilemma. Treatment approaches that have already been investigated for safety and effectiveness for other disorders may be well-suited to consider for the current quandary. Specifically, seeking to support neurological structures through therapeutic options relevant to cranial nerve-related disorders appears appropriate.

Existing studies on the positive effects of auricular nerve stimulation for various conditions are plentiful and encouraging. There is a body of knowledge that validates the potential for it to be supportive in the amelioration of post-COVD-19 neurological dysfunction and its related symptoms. Stimulation of cranial nerves and related structures through their auricular nerve branches appears to be a promising approach, which has to date not been properly investigated for gustatory and olfactory disorders. This 3-part review illuminates significant successful

research involving general ANVS stimulation. Encouraged here is the pursuit of extremely *specific* approaches, based on the substantial body of evidence of the therapeutic benefits of ear acupuncture (auricular therapy), as pioneered by the French neurologist, Dr Paul Nogier in the 1950s, and furthered by others since. The neurological structures beyond those conventionally considered are pondered in the proposed auricular acupuncture-based paradigm for potentially managing post-COVID-19 olfactory and gustatory dysfunction.

Unlike the broad and general stimulation provided via taVNS and invasive methods such as deep brain stimulation, auricular acupuncture has unparalleled advantages of safety, specificity, patient ease and comfort and cost of treatment. It also addresses neurological structures beyond solely the vagus nerve. The references and evidence appear substantial enough to warrant investigation specifically for smell and taste dysfunction disorders. Formal clinical trials or government regulated approval are not required (as per scope of practice) for qualified auricular acupuncture practitioners to immediately attempt to ameliorate the chronic effects triggered by viral infection. Various medications have already been repurposed in response to urgent medical necessity presented by various symptoms triggered by COVID-19. Thus, it is medically and scientifically responsible and warranted to also pursue therapeutic approaches outside the pharmacological realm.

The urgent need for treatment for post-COVID-19 olfactory and gustatory disorders is without question. Physicians must not be handicapped by conventional constructs. Any means by which patients might restore their olfactory and/or gustatory function must be considered—especially one with an exceptional record of safety, effectiveness (for numerous conditions) and a sound neurological basis. The information provided in this 3-article series forges the foundation to predict that patient-specific and analytically determined precision auricular acupuncture stimulation of cranial nerves, provided in the context of substantially sized clinical trials, might yield positive outcomes for olfactory and gustatory disorders resulting from COVID-19 and other causes. It would seem likely that there would be no shortage of willing participants to conduct such investigations.

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