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REVIEW ARTICLE

The taste of the pandemic—contemporary review on the current state of research on gustation in coronavirus disease 2019 (COVID-19)

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Abstract

Subjectively perceived impairment of taste is a common and distinct symptom of coronavirus disease 2019 (COVID-19). Large meta-analyses identified this symptom in approximately 50% of cases. However, this high prevalence is not supported by blinded and validated psychophysical gustatory testing, which showed a much lower prevalence in up to 26% of patients. This discrepancy may be due to misinterpretation of impaired retronasal olfaction as gustatory dysfunction. In addition, we hypothesized that COVID-19–associated hyposmia is involved in the decrease of gustatory function, as found for hyposmia of different origin. This indirect mechanism would be based on the central-nervous mutual amplification between the chemical senses, which fails in COVID-19–associated olfactory loss. However, further research is necessary on how severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) may directly impair the gustatory pathway as well as its subjective perception.

KEYWORDS
ageusia, COVID-19, gustation, smell, taste

1 | INTRODUCTION

The coronavirus severe acute respiratory syndrome-coronavirus-2(SARS-CoV-2) was described for the first time in December 2019 and still keeps the entire world in suspense with massive medical, economic, and social consequences. The symptoms of coronavirus disease 2019 (COVID-19) are very diverse and not always specific, but the sudden onset of a subjective loss of smell or taste is highly suspicious of COVID-19 especially if the nose is not blocked.[1–5] During the last year, knowledge about olfactory loss in COVID-19 has steadily grown. Several studies confirmed self-reported hyposmia through psychophysical testing.[6,7] The impaired sense of smell has been shown to improve within 1 to 2 months in most of the patients[8] and appears to persist in 5% to 20%.[9] A potential pathomechanism has been proposed: The angiotensin converting enzyme 2 (ACE2) and the serine protease transmembrane protease, serine 2 (TMPRSS2) facilitate viral invasion of non-neuronal cells of the olfactory epithelium.[10,11] Olfactory neurons, at least in mice, are presumably damaged indirectly.[12]

This situation is less conclusive for gustatory dysfunction as a consequence of COVID-19. Many questions about this symptom remain unclear. In the following, we outline the current state of research and discuss potential pathomechanisms of hypogeusia in COVID-19.

TABLE 1 Studies on psychophysical tested gustation in COVID-19

Study	*n*	Prevalence of psychophysically tested hypogeusia (%)	Prevalence of subjective taste impairment (%)	Level of evidence	Type of test[a]	Test
Bocksberger et al.[23] (2020)	10	0	–	4	1	4-item suprathreshold Taste Strips test
Cao et al.[24] (2021)	8	[b]	73	2b	1	20-item threshold SA-WETT test
Hintschich et al.[25] (2020)	41	20	44	3b	1	4-item suprathreshold Taste Strips test
Le Bon et al.[27] (2021)	93	12	48	2b	1	16-item threshold Taste Strips test
Niklassen et al.[7] (2021)	61	26	–	3b	1	16 item threshold Taste Strips test / 4-item suprathreshold taste spay test
Singer-Cornelius et al.[30] (2021)	39	26	100	2b	1	16-item threshold Taste Strips test
Konstantinidis et al.[26] (2020)	39	–	–	4	0	4-item homemade suprathreshold test
Mazzatenta et al.[28] (2020)	100	47	85	4	0	2-item homemade suprathreshold test
Petrocelli et al.[29] (2020)	300	61	–	4	0	4-item homemade suprathreshold test
Vaira et al.[31] (2020)	33	48	52	4	0	4-item homemade suprathreshold test
Vaira et al.[32] (2020)	256	45	68	4	0	4-item homemade suprathreshold test
Vaira et al.[33] (2020)	138	68	–	4	0	4-item homemade suprathreshold test
Vaira et al.[34] (2020)	72	46	54	4	0	4-item homemade suprathreshold test

Abbreviations: COVID-19, coronavirus disease 2019; SA-WETT, self-administered version of the Waterless Empirical Taste Test; SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2.

[a]Standardized, prefabricated test = 1; homemade, unblinded = 0.

[b]No difference compared to SARS-CoV-2 negative control group.

2 | PREVALENCE OF SELF-REPORTED GUSTATORY LOSS

According to a meta-analysis including more than 38,000 patients, 43% and 45% of SARS-CoV-2–positive patients exhibit hyposmia and hypogeusia, respectively.[13] In another meta-analysis, the prevalence of gustatory dysfunction was reported to be even higher, at 48%.[14] Affected patients typically report the simultaneous occurrence of a sudden loss of smell and taste during the acute infection.[15] However, when patients describe a "loss of taste," they might indicate an issue with flavor perception rather than impaired gustation, which encompasses only a limited number of sensations, including sweet, sour, salty, bitter, umami, and fatty.[16,17]

Much of the sensory experience during eating is not only due to the gustatory qualities but results from retronasal olfaction.[18–20] In a rat model, retronasal olfactory information but not orthonasal olfactory input was shown to be processed in the gustatory cortex.[21] In humans, orthonasal olfactory stimulation with chocolate can stimulate the insular gustatory cortex in a magnitude comparable to sweet taste.[22]

In an effort to disentangle the complaints of COVID-19 patients on taste from effects of smell loss, some studies asked about specific taste qualities. For example, Parma et al.[15] found that around 65% of COVID-19 patients reported an impairment of at least one of the taste modalities: sweet, bitter, salty, and sour. This was reported only by ~10% of patients with other respiratory disorders. In another study, COVID-19 patients were given the option to report changes in specific taste qualities (i.e., salty, sour, sweet, bitter, or umami/savory) as a "check all that apply" (CATA) question. Eleven percent (11%) reported impairment of a single taste quality and 48% reported impairment of two or more taste qualities.[4]

As already mentioned above, the majority of these publications are based on the patient's self-reported taste perception. They were collected during the acute infection or retrospectively through telephone surveys, online, or mail questionnaires.[13] In their meta-analysis, von Bartheld et al.[13] included 60 studies based on rated gustatory function and only five studies based on various psychophysical measures of gustatory function in COVID-19. The authors found the prevalence of psychophysically diagnosed hyposmia to be 42%, almost the same as the prevalence of self-reported gustatory dysfunction (45%). However, it has to be kept in mind that only one of the five studies used validated psychophysical tests, whereas the remaining studies were based on improvised tests of gustatory function.

The limited number of studies which used psychophysical tests to evaluate gustatory function during acute COVID-19 is largely due to the challenges of chemosensory testing in COVID-19 patients.[23–34] During the acute infection with SARS-CoV2, patients are quarantined because of the high risk of spreading the infection. They cannot visit ear nose and throat (ENT) departments to undergo validated, mostly operator-performed testing. And because chemosensory dysfunction improves in most cases quickly, testing after infections may not capture the worst impairment experienced by the patient during the disease. The delay between onset of COVID-19–associated gustatory dysfunction and gustatory testing might account for portions of the observed difference between reported and measured gustatory function.

3 | IMPROVISED GUSTATORY TESTING DURING COVID-19

To allow gustatory testing in quarantine, Vaira et al.[31] established an improvised suprathreshold taste test (Table 1). Quarantined patients were asked to prepare water-based solutions using salt, sugar, lemon juice, and decaffeinated coffee. After putting 1 teaspoon of each sample in the mouth, the patient had to self-evaluate the four major gustatory qualities sweet, sour, salty, and bitter using a scale from 0 to 10.[29,31] Results from the "homemade" self-administered test were compared to scores obtained in a situation where the same taste test was administered by an operator in an outpatient clinic. Although different protocols in terms of testing and scoring were used, similar gustatory scores were found in both trials.[31] These four studies—two of which included also hospitalized patients—found an impaired overall taste function in up to 64% of participants.[29,31–33] Similarly, Konstantinidis et al.[26] used an improvised home-prepared taste test to assess the course of gustatory dysfunction after COVID-19. They also found impaired gustation during the acute infection and an improvement after 4 weeks.[26] In another study, patients self-prepared water-based solutions to test for the qualities "salty" and "sweet." With this very simple two-item self-test, gustatory dysfunction was identified in 47% of COVID-19 patients.[28]

However, these improvised, nonvalidated tests have significant weaknesses: First, some of the tests used ingredients that have a strong smell; for example, lemon for sour or decaffeinated coffee for bitter. This potentially biases the identification and evaluation of the respective taste, because if something smells like coffee, it probably is also bitter. Second, testing is not blinded so that participants know exactly what they are confronted with. Third, subjective identifications of suprathreshold tastes are to some degree questionable because many individuals have difficulties in the correct identification of tastes.[35]

4 | VALIDATED PSYCHOPHYSICAL GUSTATORY TESTING DURING COVID-19

Different from improvised taste tests mentioned above, six studies used blinded and validated psychophysical tests to assess gustatory function during COVID-19.[7,23–25,27,30] Bocksberger et al.[23] performed a suprathreshold taste test (modified, four-item version of "Taste Strip" test[36]) in 10 hospitalized COVID-19 patients. They found normogeusia in all tested patients.[23] Hintschich et al.[25] sent the same test to home quarantined patients who used a standardized, blinded protocol to test themselves. Again, there were no significant differences in tested gustatory function between the study group 5 days after a positive SARS-CoV-2 PCR ($n = 41$) and SARS-CoV-2 antibody negative controls ($n = 30$).[25] Cao et al.[24] found similar taste scores for both the SARS-CoV-2–positive patients and a control group. Singer et al.[30] sent the more sophisticated 16-item "Taste Strip" test to home quarantined patients who tested themselves.[36] Even though all 39 patients subjectively reported decreased taste sensitivity, testing confirmed hypogeusia only in 26%. Two studies performed an operator-performed taste test: Le Bon et al.[27] tested gustatory function through the 16-item "Taste Strips" and found a preserved gustation in 88% of patients. Twelve percent (12%) were hyposmic, whereas none were anosmic.[27] Similarly, Niklassen et al.[7] showed hypogeusia in 26% of 61 patients.

Hence, there is a discrepancy between the prevalence of tested gustatory dysfunction when using two substantially different testing methods: In improvised, often self-made, and self-administered taste tests, the prevalence of hypogeusia was similar to rated gustatory function. It was two to three times higher compared to results obtained with validated and blinded tests. Unless validated and blinded psychophysical tests miss out on significant aspects of gustatory functions, improvised "homemade" tests appear to overestimate gustatory dysfunction during COVID-19.

5 | RECOVERY OF GUSTATORY FUNCTION

Many studies reported a recovery of gustatory function following COVID-19.[7,37,38] Using "homemade" tests, a recovery of gustation could be shown in two studies.[26,33] Taste recovery may occur faster than smell recovery.[9] One case report even mentioned recovery of taste in a chronically hyposmic patient.[39] This could suggest that people are able to differentiate between olfactory and gustatory sensations, and that both recovery processes are different. However, again, these publications on recovery did not use validated psychophysical tests and were based on small samples/case reports.

6 | POSSIBLE PATHOMECHANISMS

Validated and blinded gustatory testing found a lower prevalence of taste loss compared to subjective reports and to "homemade" gustatory testing. As mentioned in the paragraph "Prevalence of self-reported gustatory loss", flavor is often mistaken as taste, because "flavor" integrates taste, sounds of mastication, (retronasal) smell, and trigeminal activation, including temperature, spiciness, food texture, and mouthfeel.[18,19,40] Having said that, there is clear psychophysical evidence that COVID-19 can affect gustatory perception. Two studies[7,30] used the established 16-item Taste-Strip test and showed the prevalence of taste dysfunctions to be increased in comparison with the general population.[41] Similarly, gustatory dysfunction does occur in postviral, non-COVID-19 conditions, although the rate of occurrence is low.[18,42]

There are various hypotheses on possible pathomechanisms of COVID-19–related gustatory dysfunction[43–47]:

- ACE2 allows the cell invasion of SARS-CoV-2.[48] Although the oral mucosa also expresses ACE2, it was unclear whether taste buds also do.[43,49,50] A very recent publication showed not only the expression of ACE2 in Type II taste receptor cells, but also SARS-CoV-2 in the same subtype of cells.[51] This agrees with the findings of deteriorated gustatory function after pharmacological intervention with angiotensin II receptor blockers and angiotensin-converting enzyme inhibitors.[52,53]
- The salivary glands express high levels of ACE2 and TMPRSS2.[50,54] Moreover, the glandular epithelium is an early target of SARS-CoV-2.[55] Consequently, composition and amount of saliva could change and affect gustation.[56] However, in rats, the glandular mucosa regenerates within approximately 7 days and saliva changes are not expected to be long-lasting.[57] This is in contrast with the subjective gustatory dysfunction in COVID-19, which has been found to last a mean of 18 days and in single cases even longer than 6 months.[9]
- Another possible pathomechanism could be due to the much-discussed central neurotropism of COVID-19. SARS-CoV-2 was detected in vivo in the cerebrospinal fluid and postmortem in various central nervous system (CNS) structures.[58,59] Clinically, this manifests itself in various neurological symptoms such as encephalitis, seizure, and Guillain-Barré syndrome. However, the prevalence of neuronal symptoms other than chemosensory dysfunction as well as the detection of SARS-CoV-

2 is much lower than the prevalence of self-reported hypogeusia.[43,58,60]

- The so-called "cytokine storm" due to an overshooting inflammatory response with high levels of tumor necrosis factor α (TNF-α), interferon γ (IFN-γ), and interleukin 6 (IL-6) could affect gustation. Because these cytokines can impair stem cell function, they could also decelerate cell renewal.[43,61,62]

7 | COMPLEMENTARY HYPOTHESIS TO HYPOGEUSIA RELATED TO COVID-19

Flavor perception includes the integration of gustatory, olfactory, and trigeminal information.[63] Even though their afferents enter the CNS through different channels, these senses share distinct brain projection areas and integrative processing.[40,64–66] They mutually amplify each other and do not exhibit strong compensation for the impairment of other chemical senses, as is known for other senses such as vision and hearing.[67]

For pre-COVID-19 conditions, it has been shown that an impaired sense of smell is associated with a decrease in gustation. In general, in lasting hyposmia, gustatory function of sweet, sour, salty, and bitter is impaired.[68–70] Moreover, Han et al.[71] showed impaired gustation for umami in hyposmic patients. This was confirmed through a decreased sensitivity to electrogustometric stimuli in patients with psychophysically confirmed hyposmia compared to a healthy control group.[71] However, when acute hyposmia was induced through mechanical obstruction of the olfactory cleft, this effect could not be observed.[69,72] This gustatory dysfunction in association with lasting hyposmia is most likely due to a reduced amplification of gustatory input on a central nervous level.

After COVID-19, impaired olfaction improves in most cases.[73] However, some patients still suffer from olfactory dysfunction weeks after the infection, which has been confirmed through psychophysical testing.[38] Persisting hyposmia due to COVID-19 could potentially lead to a consecutive dysfunction in gustation as shown before in posttraumatic, idiopathic, postinfectious, and chronic rhinosinusitis–related hyposmia.[15,70] This is in line with Huart et al.,[74] who conducted psychophysical tests 2 weeks after the acute SARS-CoV-2 infection and revealed a significantly decreased taste function in a group of hyposmic patients. Moreover, this idea is supported by recent work from Le Bon et al.[27] showing that 48 of 93 patients (52%) considered themselves to have abnormal taste function right before testing, whereas only 12% of them were found to be dysgeusic following psychophysical evaluation. In their study, they also observed that the olfactory score—rather than the gustatory score—correlated better with the patients' self-assessed taste rating.

8 | CONCLUSION

A sudden onset of olfactory and gustatory dysfunction was characterized as highly suspicious for COVID-19. Their prevalence was shown to be approximately 50%. However, it appears that hyposmia and not hypogeusia is the leading chemosensory symptom in acute COVID-19. Although taste dysfunction clearly is part of the COVID-19 symptoms, up to now, psychophysical evidence confirms the decreased taste function at a relatively low prevalence. The pathomechanism of COVID-19–related gustatory dysfunction due to changes at the level of the oral cavity is still unclear. However, olfactory dysfunction due to COVID-19 could be associated indirectly with gustatory dysfunction, as shown for non-COVID-19 hyposmia. Further research using validated chemosensory tests in combination; for example, with histopathological methods, are needed to further explore gustatory involvement in COVID-19.

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CONFLICT OF INTEREST

None of the authors declare a conflict of interest.

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