Taste dysfunction in Long COVID.

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Abstract

Persistent taste dysfunction may occur both as acute and long-term symptoms of SARS-CoV-2 infection (Long COVID), yet the underlying mechanisms are unknown at the histological, cellular, and molecular levels. This study investigates the underlying pathology in 28 non-hospitalized subjects who reported persistent taste disturbances for over 12 months after testing positive for SARS-CoV-2. To assess taste function, subjects completed the Waterless Empirical Taste Test (WETT), which quantifies the subject's ability to taste each of the five human taste qualities: sweet, umami, bitter, sour, and salty. Biopsies of fungiform papillae were collected from 20 participants and analyzed histologically for overall taste bud structure and innervation and by quantitative PCR (qPCR) for expression of markers for different taste receptor cells (TRCs). Although all subjects reported subjective taste dysfunction, only five scored below the 20th percentile on overall taste sensitivity. However, 12 subjects exhibited total loss of one or more taste qualities and another 13 subjects tested below the 95% confidence interval for at least one taste modality. Notably, loss of sweet, umami, or bitter tastes -- qualities mediated by a PLCβ2-transduction cascade -- was significantly more common than loss of sour and salty, and this loss correlated with reduced expression of PLCβ2 mRNA. Histological analysis revealed generally preserved taste bud structure and innervation in all cases, with occasional disorganization resulting in isolated PLCβ2-immunoreactive cells. Our findings suggest long-term taste dysfunction after COVID-19 disproportionately impacts PLCβ2-dependent taste qualities and is not due to widespread structural damage of the taste periphery.

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INTRODUCTION

The COVID-19 pandemic has brought unprecedented attention to impairments of olfaction and taste as hallmark symptoms of acute SARS-CoV-2 virus infection (Cooper, Brann et al. 2020, Hannum, Koch et al. 2023). In most individuals, this dysfunction resolves within weeks, but can persist for months for others. Prolonged dysfunction lasting more than 3 months is now recognized as part of post-acute COVID-19 syndrome (PACS) or Long COVID (Soriano, Murthy et al. 2022, Ely, Brown et al. 2024). Ongoing taste dysfunction may occur even after resolution of other symptoms (Boldes, Ritter et al. 2024, Xu, Wang et al. 2024) thus raising questions about the underlying mechanisms. Understanding the long-term pathophysiology of taste dysfunction and, in extreme cases, taste loss is crucial for patient care and the development of targeted rehabilitation strategies (Lee, Kisiel et al. 2025).

Sensations of taste are largely mediated by lingual taste buds (TBs) situated in three types of papillae: fungiform, vallate, and foliate. The fungiform papillae (FP), are concentrated on and around the tip of the tongue, making them easy to biopsy. A typical human has about 200 FP with 0-50 taste buds (TB) in each FP (Miller 1986, Miller 1988 , Miller 1989 , Miller and Reedy 1990, Cheng and Robinson 1991).

Taste buds are complex multicellular epithelial end organs comprising between 20 and 100 taste cells (TCs) with approximately half being taste receptor cells (TRCs) (Ohtubo and Yoshii 2011, Ogata and Ohtubo 2020, Yang, Dzowo et al. 2020, High and Finger 2025). Recent histochemical, immuno-histochemical and molecular methods, allow for correlation of TRC subtypes with specific taste qualities. Type II TRCs detect sweet, umami, and bitter tastes via distinct G-protein-coupled receptor (GPCR) pathways involving downstream PLCβ2 signaling cascades (Shi, Zhang et al. 2003, Zhang, Hoon et al. 2003). Sweet taste is mediated via TAS1R2/R3

heterodimeric receptors, and umami by TAS1R1/R3; bitter taste involves TAS2Rs, another family of taste GPCRs. In contrast, Type III cells are responsible for transduction of ionic taste qualities, i.e. sour and high concentrations of salt (Chang, Waters et al. 2010, Matsumoto, Ohmoto et al. 2011) while Type I TCs play a supporting role, like glia cells in the CNS (Bartel, Sullivan et al. 2006, Rodriguez, Roebber et al. 2021, Wilson, Lasher et al. 2025). In addition, taste buds contain a population of post-mitotic Type IV cells which mature to differentiate into the other cell types. Disruption to these distinct cellular pathways or the morphological integrity of taste buds could contribute to the observed taste dysfunction in COVID-19 (Huang, Perez et al. 2021).

TRCs undergo continuous turnover, with new TRCs differentiating only when taste fibers reach them (Farbman 1965, Farbman 1980, Hellekant, Kasahara et al. 1987)(Farbman, Guagliardo et al. 2004, Lee, Macpherson et al. 2017). Approximately 70–80% of mature TRCs form synapses with nerve fibers, highlighting the importance of neural connectivity in maintaining taste function (Lee, Macpherson et al. 2017, Wilson, Lasher et al. 2022). Ongoing post-viral disruption of the nerve-TC interactions could well lead to taste dysfunction.

SARS-CoV-2 infects cells via the ACE2 receptor and the TMPRSS2 protease, both of which are expressed in oral epithelial cells, including Type II TRCs (Doyle, Appleton et al. 2021, Yao, Doyle et al. 2023). This suggests a plausible mechanism for direct viral damage to the taste system. Additionally, inflammatory processes, immune dysregulation, or altered saliva composition may contribute to long-term taste changes following viral infection.

Given the clinical and biological implications of long-term taste dysfunction, this study aims to investigate self-reported and objectively measured taste impairment in participants who experienced non-hospitalised COVID-19. Using a combination of psychophysical testing,

histological evaluation and molecular analysis -- including quantitative polymerase chain reaction (qPCR) for taste cell markers and viral RNA detection –- this study seeks to elucidate the structural and molecular changes underlying persistent taste dysfunction following COVID-19 infection.

MATERIAL & METHODS

Study design

This study involved participants aged ≥18 years who had experienced symptomatic COVID-19 and a confirmed SARS-CoV-2 infection verified by a positive PCR test from nasopharyngeal swabs between 2020 and 2021 (inclusion criteria). All participants had non-hospitalized COVID-19 and, all but one, reported long-term taste disturbances. The study population was recruited between November 2021 and June 2022 from two sources at Uppsala University Hospital: the COMBAT post-COVID study and the Ear, Nose and Throat (ENT) outpatient clinic.

From the COMBAT post-COVID cohort, 18 participants underwent psychophysical taste evaluation. Of these, 12 consented to undergo a fungiform papilla biopsy (participants #7, 8, 9, 12, 13, 14, 15, 18, 19, 23, 24, 26). Additionally, ten participants were recruited from the ENT outpatient clinic, eight of whom underwent biopsy (participants #17, 21, 22, 24, 25, 27, 28, 29). In total, eight participants did not receive a biopsy.

Study population

The COMBAT post-COVID project aimed to monitor persistent symptoms and long-term consequences among non-hospitalized patients diagnosed with COVID-19. Initially, 725 individuals who tested positive for SARS-CoV-2 between March and December 2020 were invited to complete a follow-up questionnaire 12 months after symptom onset. Of these, 401 participants responded (response rate: 74%). The cohort has been described in detail elsewhere (Kisiel, Nordqvist et al. 2021, Kisiel, Janols et al. 2022, Kisiel, Lee et al. 2023, Kisiel, Lee et al. 2023, Janols, Wadsten et al. 2024). Among the respondents, 68 individuals reported ongoing taste and/or smell disturbances. These individuals were contacted by telephone and invited to participate in the current study if they reported persistent taste loss and were available for in-person evaluation.

Ten additional patients attending the ENT outpatient clinic in 2021 were randomly selected and invited to participate in the study if they met the same inclusion criteria. In addition, one participant (#17) reported no taste loss but had an active COVID infection at the time of sampling.

Clinical and sociodemographic variables

From the COMBAT post-COVID cohort, information was documented about age, gender, symptoms at COVID-19 onset, self-reported health before and one year after COVID-19, and persistent symptoms one year following COVID-19. Comorbidities were collected from medical records obtained from primary and secondary care from January 2010 to January 2022. Symptoms at COVID-19 onset were also retrieved from medical records from the PCR testing protocols. Persistent symptoms and smoking habits were collected from the survey. Subjects

were asked to estimate their general health in the study at one-year follow-up, from 0-100, where 0 was the poorest and 100 was the best. Additional subjects (n=11) were characterized by age and sex only.

Ethical Approval

The study was approved by the institutional ethics committee of the University Hospital in Uppsala (EPN number 2020-05707) and the Swedish Ethical Review Authority (EPM number 2021-00878) and complies with the Declaration of Helsinki for Medical Research involving Human Subjects. The patients all gave written informed consent to the procedures. The Combined Institutional Review Board at the University of Colorado at Anschutz approved the transfer and analysis of the de-identified samples collected in Sweden. The study protocol in Colorado (COMIRB number 20-1325) was determined Exempt/Non-Human Subject Research and was conducted in accordance with 45 CFR 46 and institutional policies. All data were pseudonymized to protect patient privacy.

Taste evaluation

As mentioned, the human sense of taste is divided into five taste qualities: sweet, umami, bitter, sour and salty, (reviewed in:(Lindemann 1996, Hellekant 2024). To assess a subject's ability to taste we used the quantitative and qualitative Waterless Empirical Taste Test (WETT®) by Sensonics (Haddon Heights, NJ, USA). The WETT® method measures the ability to taste each taste quality with an eight-point scale from zero (no taste) to a maximum of eight (all concentrations identified). The WETT® measures the ability to identify various concentrations of the above five basic taste qualities with a minimum number of trials. It consists of 53 strips

impregnated with one tastant (a substance that produces a taste sensation) representing a specific taste quality. A monomer cellulose pad (1 × 2.5 cm) is present on one side of each strip, containing either: dried sucrose (sweet) (0.20, 0.10, 0.05, or 0.025 g/ml), citric acid (sour) (0.025, 0.05, 0.10, or 0.20 g/ml), sodium chloride (salty) (0.0313, 0.0625, 0.125, or 0.25 g/ml), caffeine (bitter) (0.011, 0.022, 0.044, or 0.088 g/ml), monosodium glutamate (umami; brothy) (0.017, 0.034, 0.068, or 0.135 g/ml), or blank control strips, with no added chemical stimulus. The subjects were instructed to place the appropriate strip on the tongue and move it along the surface of the tongue for at least 5–10 seconds. The subject indicated which taste sensation was perceived sött (sweet), bittert/beskt (bitter), surt (sour), salt, or buljongliknande smak/umami (umami), or whether no taste was sensed by verbally reporting their response to be entered on the designated line of the response form. In the WETT® test sequence, the concentrations of each stimulus are presented twice (eight total trials/tastant). In the first half of the test, the concentrations ascend from weak to strong with the different tastants presented randomly, with no tastant blanks included. In the second half of the test, the reverse presentation order is used, i.e., going from strong to weak concentrations. Scores range from 53 (all correct) to 13 (no tastes, corresponding to the number of control strips in the test). Each subject's results were compared with normative values for each gender and age given in Doty et al (Doty, Sharetts et al. 2025). The average taste score for the subjects, who had consented to the biopsy, did not differ significantly from those without biopsy in terms of total tasting ability ($t(26)=1.52$, $p>.05$). The results are presented in Table 1.

Biopsy procedures

For all but 2 subjects, five to eight fungiform papillae (FP) were biopsied from the subject's tongue immediately following or within 2 months of the WETT test as indicated in Table 1. For 2 subjects with normal taste function on the WETT test (subjects 26 and 21 ; respectively 44th and 70th percentile taste scores), biopsies were taken 4 months following the WETT test. The tongue was first anesthetized with a Xylocaine spray (100mg/ml Lidocaine with 10mg/spray dose), then blue or green food coloring was added to enhance the tongue's fungiform papillae (FP). The tongue was held steady with a gauze, and biopsies of the FP were taken with a 3-mm sterile microscissor with a curved tip. The FP was cut one by one by holding down the scissor tip at the base of the chosen FP, which was removed with a single cut and put in fixative for histology or RNA*later*™ (Thermo Fisher Scientific Inc., Waltham, MA, USA). The biopsies for histological analysis were fixed in 4% buffered formaldehyde for at least four hours or overnight and then moved to phosphate-buffered saline (PBS) solution. The biopsies were stored at 4°C until shipping for analyses from Sweden to the United States for histopathological studies. The biopsies for RNA analysis were placed in RNA*later*™ stabilization solution and stored at room temperature overnight and then stored in the freezer at -18 °C initially and then at -80°C until analyses.

Histology

Upon receipt, all specimens were cryoprotected in 20% Sucrose in 0.1M phosphate buffer overnight at 4°C. Then, the tissues were cryo-sectioned (12-14µm) onto Superfrost Plus microscope slides (Thermo Fisher Scientific, (Catalog# 1255015) and air-dried. Slides were rinsed in 0.1M PBS pH 7.2. Antigen retrieval was performed with 10 mM sodium citrate buffer of pH 6.0 at 85°C for 10 minutes before incubation in blocking solution (2% normal donkey

serum, 1% bovine serum albumin, and 0.3% Triton in 0.1M PBS) for an hour at room temperature. Slides were then incubated for four days in specific primary antibodies in blocking solution at 4°C including the following antisera:

- Mouse anti-Tubulin β3 (clone TUJ1) at 1:1000 dilution (BioLegend, San Diego, CA, USA, catalog# 801202; RRID:AB_2313773) (for total innervation),
- Goat anti-GNAT3 at 1:500 dilution (Aviva Systems Biology, San Diego, CA, USA, catalog# OAEB00418; RRID:AB_10882823) (for TRCs expressing the taste-associated G-protein gustducin),
- Rabbit anti-PLCβ2 (PhosphoSolutions, Denver, CO, USA, catalog# 1640-PLC; RRID:AB_2801663), or guinea pig anti-PLCβ2 (PhosphoSolutions, AP8/24; RRID: AB_2910247) (for identification of Type II TRCs).
- Rabbit anti P2X3 (Alamone, catalog #APR-016, RRID AB_2313760) (for labeling of taste bud-specific innervation).

After washing in 0.1M PBS, the slides were incubated 2 hours with fluorescent secondary antibodies, Alexa Fluor 488 donkey anti-mouse (Invitrogen, catalog# A21202; RRID:AB_141607), Alexa Fluor 568 donkey anti-rabbit (Invitrogen, catalog# A10042), Alexa Fluor 647 donkey anti-goat (Invitrogen, catalog# A21447; AB_2534017), Alexa Fluor 647 donkey anti-guinea pig (Jackson Immuno Research Laboratories, West Grove, PA, USA, catalog# 706605148; RRID: AB_2340476) or Donkey anti-Rabbit IgG (H+L) Highly Cross-Adsorbed Secondary Antibody, Alexa Fluor™ 647 (ThermoFisher Catalog # A-31573; AB_2536183) at 1:800 dilution each at room temperature. Lastly, the slides were washed twice

for 10 minutes each in 0.1M PBS and then once for 10 minutes in 0.05M PBS before coverslip slides with DAPI Fluoromount-G (SouthernBiotech, Birmingham, AL, USA, catalog# 010020).

RNA extraction

The papillae tissue samples were stored in RNA*later*™ at -20°C RNA was extracted with the RNeasy fibrous tissue mini kit (Qiagen, Hilden, Germany). A small piece of the biopsy was taken with a pipet tip into a 1.5 ml tube containing 300 ul of RLT buffer and mashed manually with a micro pestle. The pestle was rinsed when pipetting 590 ul of RNase free water into the tube. The kit protocol was followed, and a DNase treatment was performed with a DNA-free DNA removal kit (Invitrogen) according to their protocol. The resulting RNA concentrations and quality were checked with Nanodrop 8000 (Thermo Fisher Scientific) and Tapestation High Sensitivity RNA tape (Agilent, Santa Clara, CA, USA).

Reverse transcription

High-Capacity cDNA Reverse Transcriptase Kit (Applied Biosystems, Waltham, MA, USA) was used to obtain cDNA from the RNA samples. 100 ng of RNA per sample, according to Tapestation concentrations, was taken into the reverse transcription reaction. The kit protocol was followed. The reverse transcription was performed in duplicates to obtain enough product for all the qPCR runs.

qPCR

Quantitative PCR (qPCR) was performed with TaqMan (Applied Biosystems) assays for *PLCβ2* (Hs01080542), *NCAM1* (Hs00941821), and *TAS1R3* (Hs01026531) as well as for two reference

genes *RPLP0* (Hs99999902) and *GAPDH* (Hs02758991). TaqMan Gene Expression Master Mix (Applied Biosystems) was used according to its protocol, and 10 ng of cDNA was added as template. All samples were run in triplicate per gene, including a negative control. One gene per plate was run in the QuantStudio 5 (Applied Biosystems). Average Ct and standard deviation were calculated for each gene and then normalized (deltaCt=Ct(gene of interest) – Ct(reference gene)) against the reference gene *GAPDH*. The reference gene *GAPDH* gave more consistent normalization than RPLP0, and was therefore selected as a reference for the genes of interest.

SARS-CoV-2 test

A PCR test for the presence of SARS-CoV-2 virus in the tissue samples was performed in triplicate, including two assays that target SARS-CoV-2 as well as negative control samples. TaqMan microbe detection assay (Vi07918637) for SARS-CoV2N and TaqPath Blastopore Microbial Detection Master Mix (Applied Biosystems) were used according to their protocol. Positive control was TruMark Respiratory Panel 2.0 Amplification control (Applied Biosystems). The qPCR was run in the QuantStudio 5 (Applied Biosystems). None of the biopsied tissue samples tested showed the presence of SARS-CoV-2 virus, although one subject (#17) had an active COVID infection.

Statistical analysis

Statistical calculations were carried out by Excel (Microsoft) or with calculators given at www.socscistatistics.com. Both calculators gave identical values. A criterion value of $p < 0.05$ was set for statistical significance in all calculations. For comparisons of two groups, we used either Estimation Statistics (www.estimationstats.com)(Ho, Tumkaya et al. 2019) or a Students

T-test; for comparison across samples, we utilized Pearson's Correlation co-efficient or Fisher's Exact test for small sample sizes.

Means, standard deviations, and ranges were used to describe continuous variables such as age, time from infection to testing, and taste scores. Categorical variables like sex and symptom presence were summarized using counts and percentages.

Because taste ability varies substantially by sex and age, raw taste scores were normalized by sex and age using reference data from Doty et al. (2025), which included 1,392 healthy individuals. Scores below the 95% confidence interval (CI) were considered potentially abnormal, and those below the 20th percentile were flagged as indicative of possible taste deficiency.

Chi-square tests (χ^2) were used to compare (categorical data) the frequency of abnormal taste scores across groups. The results are reported as χ^2 (degree of freedom (df), sample size) = chi-square value, p-value.

Pearson's Correlation (r) was used to assess linear relationships between molecular markers (qPCR results), histological features, and taste scores. The results were reported as (df) sample size=correlation co-efficient, p-value. (Schober, Boer et al. 2018).

RESULTS

Study population

All 28 participants (24 women and 4 men) reported normal taste before the first confirmed COVID-19 infection (Table 1). The mean age was 49.9 years (SD+/-1.2) and ranged between 30

and 71 years. Most participants contracted COVID-19 in early 2020. Two participants (19 & 28) experienced a second infection in 2022, shortly before undergoing taste testing and biopsy. Considering only the first infection, the time from initial COVID-19 infection to taste testing ranged from 13.5 months to 27.0 months (mean of 21.0 months).

Psychophysics:

Because taste ability varies substantially between individuals according to gender, age, and health status, we normalized all raw taste scores against values given for 1,392 normal subjects (Doty, Sharetts et al. 2025). Although all subjects, except one (subject #17), reported compromised taste abilities in clinical reporting, only 5 of 28 ($\chi^2(1, N = 28) = 3.39$, $p = .065$) tested subjects scored below the 20th percentile in overall taste ability (see Table 1). Nonetheless, 25 of the 28 subjects showed significant deficiency in one or more individual taste qualities (values in red shown in Table 1) compared to the 95% CI for age and gender of 1,392 normal subjects (Doty, Wylie et al. 2021). One subject, who was also anosmic, (#29) gave no correct responses to any tastant, even at the highest concentration suggesting complete taste loss. Although individuals with a profound overall deficit showed specific loss of one or more taste qualities (e.g. subject 7 shows no response to sweet, bitter or umami), the pattern of loss was not duplicated by other subjects (e.g. subject 24 with good responses to sweet and salty but total loss for bitter and umami).

Subject Number	Sex	Age	Covid Date	Taste Test Date	Biopsy Date	PLC Tastes Sweet	Umami	Bitter	Sour	Salty	No Taste	WETT score	Sex/Age-corrected %
1	F	47	Mar 2020	19/11-21		5	3	1	5	6	12	32	42
2	F	62	Apr 2020	19/11-21		3	0	1	8	8	11	31	36
3	F	50	Apr 2020	24/11-21		6	0	3	7	5	12	33	45
4	F	49	May 2020	3/12/21		0	8	6	6	7	10	37	59
5	F	53	Nov 2020	17/1-22		8	4	8	8	7	13	48	95
6	F	41	Nov 2020	18/1-21		7	2	4	5	4	12	34	51
10	F	66	Nov 2020	20/1-22		8	1	8	7	5	13	42	83
16	F	59	Apr 2020	11/2/22		5	3	6	8	7	10	39	70
7	F	68	Nov 2020	18/1-22	23/3-22	0	0	0	6	5	13	24	16
8	F	64	Mar 2020	18/1-22	23/3-22	6	0	0	6	7	13	32	45
9	M	49	Apr 2020	19/1-22	17/3-22	1	0	0	8	8	13	30	54
12	F	56	Apr 2020	21/1-22	24/1-22	3	3	6	7	4	12	35	54
13	M	45	Apr 2020	21/1-22	21/1-22	0	1	0	5	3	13	22	21
14	F	30	Apr 2020	21/1-22	21/1-22	3	8	5	8	6	10	40	70
15	F	53	Apr 2020	24/1-22	24/1-22	4	6	3	4	4	13	34	54
17	F	30	Apr 2020	31/1-22	31/1-22	8	8	8	8	8	13	53	99
18	F	63	June 2020	23/3-22	23/3-22	7	1	4	6	1	13	32	45
19	F	46	May 2020 & Jan 2022	24/3-22	24/3-22	7	4	8	6	2	9	36	59
20	F	38	Feb 2021	30/3-22	20/4-22	7	2	7	8	8	13	45	83
21	F	71	Jan 2021	17/1-22	11/5-22	4	1	5	7	4	13	34	70
22	F	56	Apr 2020	11/5/22	11/5-22	1	4	0	6	2	13	26	21
23	F	49	Nov 2020	12/5/22	12/5-22	4	4	7	6	5	13	39	67
24	M	42	June 2020	13/5-22	13/5-22	5	0	0	4	4	4	17	7
25	F	50	Mar 2020	13/5-22	13/5-22	2	4	1	0	5	7	19	4
26	F	24	June 2020	21/1-22	16/5-22	6	0	6	5	7	13	37	44
27	F	52	Mar 2020	15/6-22	15/6-22	0	0	4	2	6	13	25	15
28	F	43	Nov 2020 & Feb 2022	5/7-22	5/7-22	6	3	7	7	3	10	36	44
29	M	30	April 2020	15/7-22	15/7-22	0	0	0	0	0	13	13	1
Total	N = 28	red text <95% C.I.			Ave Taste Score	4.1	2.5	3.9	5.8	5.0	11.7	33.0	48.4
Biopsy	N = 20				zero scores	5	9	6	2	1			

Table 1: Results from WETT testing of all subjects including basic demographic information, dates of infection, taste testing and biopsy. Columns labeled as "Sweet, Umami, Bitter, Sour, Salty and No Taste" show WETT test raw scores for each taste quality and blank "No Taste" control strips. Red numerals indicate values below the 95% confidence interval for sex and age-matched controls based on Doty, et al 2025. The incidence of values below the 95% is significantly higher than expected based on the normal population ($\chi^2(1, N = 140) = 48.63$, $p < .0001$). Zero values indicate that the subject was unable to identify the tastant at any concentration offered. The total number of zero values for each tastant is shown in red along the bottom row. WETT score shows the total WETT score for each subject alongside of the corresponding sex and age match % ranking compared to the study population in Doty et al 2025. A perfect score is 53 (8 for each taste quality + 13 blanks). Complete ageusia would give a score of 13 (0 for all tastants and 13 for correctly identifying blank controls). PLCß2-dependent tastes are indicated by orange shading along the top row.

Quantitative PCR Findings

RNA prepared from taste papillae from all biopsied subjects was analyzed for expression levels of mRNAs encoding phospholipase C beta 2 (PLCß2), a marker of Type II cells; and Taste 1 receptor member 3 (*TAS1R3)* mRNA, coding for a receptor component for sweet and umami tastes; and neural adhesion molecule 1 (*NCAM1)*, a marker of total innervation and Type III TCs. All data were normalized against glyceraldehyde-3-phosphate hydrogenase (*GAPDH)* mRNA, yielding deltaCt given in Table 2 along with Taste Scores from each subject for comparison.

	taste test	deltaCt			Ave PLC +
Subject #	value	PLCb2	TAS1R3	NCAM1	Tas1R3
7	24	11.78	11.24	11.58	11.51
8	32	9.59	9.59	12.25	9.59
9	30	10.78	9.26	12.85	10.02
12	35	9.36	8.98	11.29	9.17
13	22	10.72	8.38	11.5	9.55
14	40	9.92	7.34	11.25	8.63
15	34	9.83	8.4	12.1	9.12
17	53	9	8.02	11.52	8.51
18	32	11.87	9.75	14.29	10.81
19	36	11.61	8.42	15.14	10.02
20	45	8.29	8.34	11.73	8.32
21	34	10.89	10.13	13.06	10.51
22	26	10.48	9.84	12.47	10.16
23	39	9.64	7.83	10.55	8.74
24	17	9.7	7.81	11.11	8.76
25	19	11.39	10.6	12.46	11.00
26	37	10.05	8.77	12.33	9.41
27	25	8.89	8.4	10.81	8.65
28	36	10.17	8.9	13.16	9.54
29	13	11.2	10.72	12.27	10.96

Table 2: DeltaCT values from qPCR of fungiform papillae. Taste test values as shown in Table 1 are included for comparison.

The deltaCT values for *PLCß2* and *TAS1R3*, both markers of Type

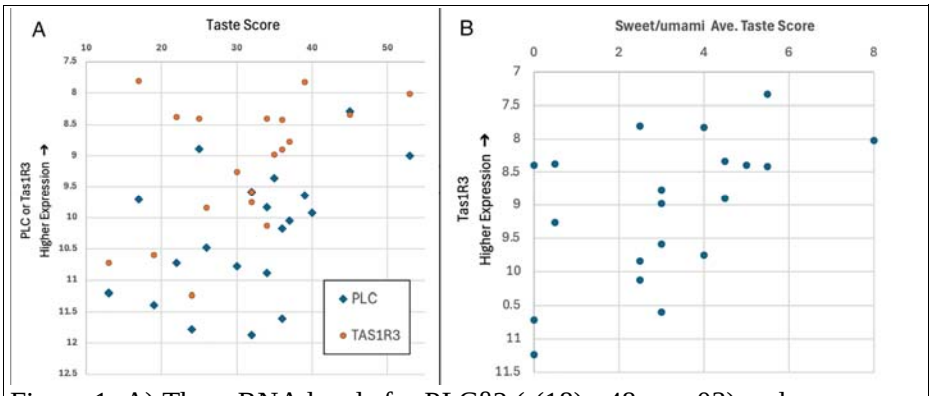

Figure 1: A) The mRNA levels for PLCß2 (r(18)=.48, p= .03) and TAS1R3(r(18)=.49, p= .03) correlate with the overall taste ability of each subject. B) The mRNA level for TAS1R3 correlates with the combined taste score for the related taste qualities (Sweet and brothy) (r(18)=.51, p= .02).

Alt Text: Graphs showing the relationship between WETT scores and qPCR data. At left, showing the correlation between expression of TAS1R3 or PLC and overall taste score. At right showing correlation between TAS1R3 and average combined score for sweet and umami.

II TCs, were highly correlated (r(18) = 0.64, p=0.002). Similarly, the deltaCT value for *PLCß2* was also correlated with the expression levels of *NCAM*, a marker of Type III cells of taste buds and total innervation (r(18) = 0.63, p=0.003) although no significant correlation exists for values of *TAS1R3* compared to *NCAM* (r(18) = 0.32, p = 0.17).

Comparing the qPCR data to the taste scores from the same subjects shows significant correlations for both *PLCß2* (r(18) = 0.48, p= 0.03) and *TAS1R3* (r(18) =-0.49, p= 0.03) but not for *NCAM* (r(18) = 0.02, p>0.05). This relationship is shown graphically in Fig. 1. Since both sweet and umami require the TAS1R3 receptor subunit, we compared the expression level of this subunit to the average of taste scores for sweet and umami for each subject. A significant correlation exists between the deltaCT values for *TAS1R3* and the average of the related taste qualities (sweet and umami) (r(18)= 0.52, p=0.02), but is not significant compared to each of the individual tastes.

Histological Findings

Fungiform samples from the subjects varied between 4 and 8 papillae, with a median of 7. Approximately half of the papillae had no identifiable TBs, as reported for human fungiform papillae in previous literature e.g. (Miller 1988). Taste buds were identified in all subjects, including subject 29, who reported no taste sensibility. While relatively

Subject #	taste score	# papillae	# TBs	ave tb/pap	plc/tb	plc/pap
7	24	7	42	6.0	2.4	14.3
8	32	8	42	5.3	2.0	10.5
9	30	8	10	1.3	2.0	2.5
12	35	6	30	5.0	2.1	10.3
13	22	4	6	1.5	1.8	2.7
14	41	5	61	12.2	2.9	35.4
16	34	6	13	2.2	2.6	5.7
17	53	8	25	3.1	2.7	8.5
18	32	7	7	1.0	1.8	1.8
19	36	6	8	1.3	2.0	2.7
20	45	7	41	5.9	2.0	11.7
21	34	7	28	4.0	3.3	13.2
22	26	8	32	4.0	1.8	7.2
23	39	7	17	2.4	2.3	5.6
24	17	6	22	3.7	2.0	7.3
25	19	6	2	0.3	1.5	0.5
26	37	5	22	4.4	2.4	10.6
27	25	7	32	4.6	2.8	12.8
28	26	8	17	2.1	2.5	5.3
29	13	7	27	3.9	1.9	7.3

Table 3: Counts of papillae sampled, number of taste buds and average PLCß2+ cells per taste bud and papilla in each case. No significant correlation was found between taste score and average number of taste buds per papilla nor of density of PLCß2+ cells per taste bud or papilla. The histological counts and density of PLCß2+ cells also did not correlate with any PCR values.

normal-appearing TBs occur in samples of all subjects (See Fig. 2), many subjects displayed disorganized TBs or relatively isolated PLCß2+ cells not associated with a cluster of cells as would occur in a normal TB (High and Finger 2025). The average number of taste bud profiles per papilla was 3.6 (+/-2.6 s.d.). Because of the significant variance in the number of TB profiles observed in a single section through a papilla, we calculated the average number of TB profiles per papilla from all papillae to measure the taste bud population for each subject (Table 3). In addition, we counted the number of PLCß2+ TCs within each section to calculate the average proportion of Type II (PLCß2+) cells per TB.

The taste score for each subject was not correlated with either the average number of TB profiles per papillae ($r(18) = 0.268$, $p = 0.25$) nor with the average number of PLCß2+ cells per papilla ($r(18)$ -0.35, $p= 0.15$) nor with the average number of PLCß2+ cells per TB ($r(18) = 0.427$, $p = .06$). Abnormal TBs or irregular PLCß2+ cells were especially noteworthy in subjects 12 (Taste Score 54%), 13(21%), 22 (21%), 24 (8 %), 25 (4%), 28 (44%) and 29 (1%). Fig. 3 shows examples of such profiles.

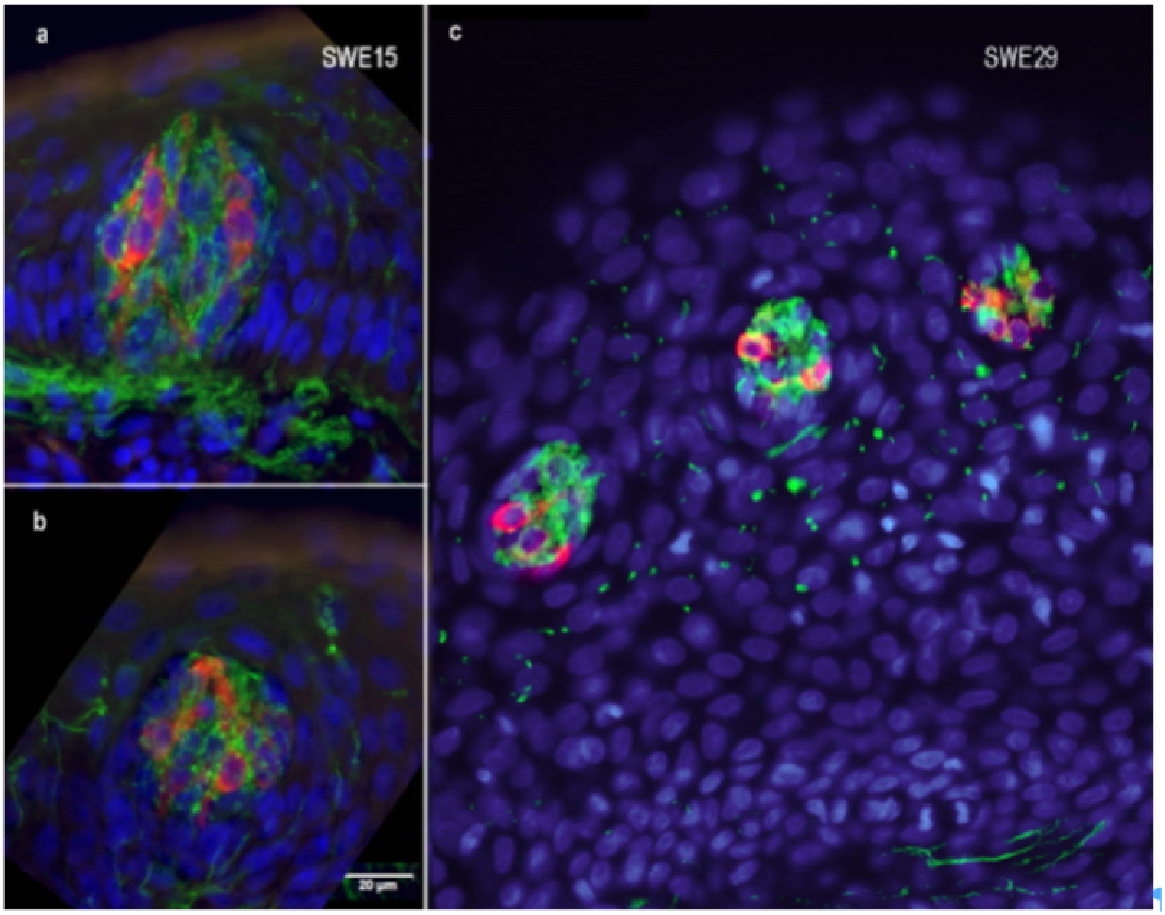

Figure 2: Appearance of normal taste buds sectioned in different planes from different subjects. Red = PLCß2 immunoreactivity showing Type II taste cells; Green = TUJ1 immunoreactivity for nerve fibers. Typical taste buds have more than one PLCß2+ cell surrounded by a dense network of TUJ1-stained nerve fibers. Green profiles outside of taste buds are extragemmal nerve fibers typical of lingual epithelium (Moayedi, Michlig et al. 2021). **a, b.** Taste buds sectioned longitudinally appear similar in shape to garlic bulbs or onions (from Subject (SWE) 15. **c)** Taste buds sectioned perpendicular to their long axis appear circular (from subject (SWE) 29 who reported a total absence of taste perception (taste score of 13, showing no correct responses to any tastant).
Scale bar in panel (b) applies to all panels.

Alt Text: Images of 3 micrographs showing the normal appearance of taste buds in our samples. Multiple PLC-positive taste cells within each bud are embraced by a dense nerve plexus.

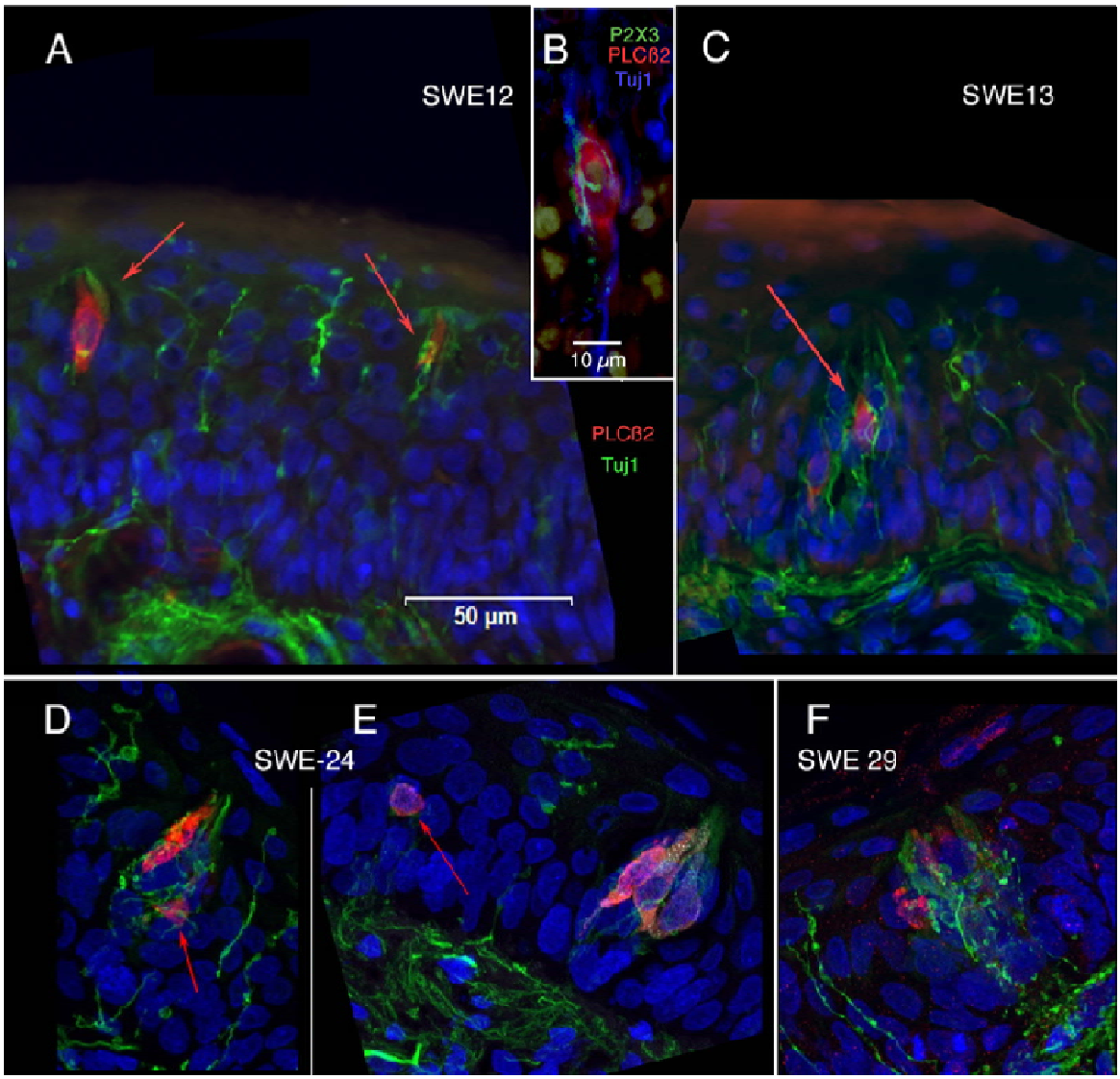

Figure 3: Examples of abnormal PLCß2+ taste-like cells from 4 cases. (A & B). Subject (SWE) 12 had a taste score of 35 (54%). (C) From subject (SWE) 13 who had a score of 22 (21%). In both cases (A & C), innervated PLCß2+ (red arrows) cells occur in relative isolation within the epithelium. Innervation of these cells (green: TUJ1) is sparse unlike innervation of taste buds (cf Fig. 2). These cells may represent very small taste buds or simply PLCß2+ cells lying outside of a taste bud structure. Panel B shows a higher magnification of one such isolated PLCß2+ cell and its innervation stained for the presence of P2X3, a neural receptor predominantly on nerve fibers that innervate taste buds. Panels D-E are from case (SWE) 24 with a taste score of 17 (4%) showing examples of aberrant PLCß2+ cells (red arrows) outside of a taste bud structure. Panel F: A disorganized taste bud from case SWE 29 who reported a total absence of taste perception (taste score of 13, showing no correct responses to any tastant). The heavy innervation is typical of taste buds, but the cellular structure revealed by PLC-staining (red) does not show typical taste bud organization.

Alt Text: Images showing abnormal isolated PLC-positive cells and abnormal taste buds within the epithelium of our subjects.

DISCUSSION

Morbidity Changes in COVID-19 Variants

Previous studies found that the frequency of chemosensory symptoms, including taste loss, varies across SARS-CoV-2 variants. Early variants, such as Wild type and Alpha, were more commonly associated with taste and smell loss, while later emerging variants, such as Omicron, show markedly lower prevalence of taste loss (Reiter, Coelho et al. 2023). Most subjects included in our study were primarily infected during the first wave of the pandemic, and their reported taste disturbances fit well with this pattern of greater taste loss early in the pandemic.

Published epidemiological data further illustrate this trend. Among individuals infected with the Wild-type strain, 241 out of 1,141 cases (21%) reported smell and/or taste disorders. For Alpha, 223 out of 1265 cases (18%), for Delta, 480 out of 1516 cases (32%), and for Omicron, only 317 out of 7431 cases (4%) presented with smell and/or taste disorders (Ota, Yumiya et al. 2025). This supports the hypothesis that the variant-dependent tropism and immune response may influence the degree and duration of taste dysfunction.

On the role of the ACE2 receptor

Relatively early in the pandemic, it was suggested that SARS-CoV-2 infects oral tissue (Huang, Pérez et al. 2021). Doyle et al. (Doyle, Appleton et al. 2021) reported that ACE2 was expressed by Type II TRCs, and further demonstrated the presence of SARS-CoV-2 in Type II TRCs, which mediate sweet, umami and bitter sensations, but not within the other taste cell types. This likely explains why their subjects in that study did not taste the “sweetness of chocolate and bitter coffee” and instead reported that it “tasted like mud” (Doyle, Appleton et al. 2021).

Research during the COVID-19 pandemic has highlighted the potential impact of SARS-CoV-2 on TBs, particularly through its interaction with ACE2 receptors (Huang, Perez et al. 2021, Yao, Doyle et al. 2023). In patients experiencing taste disturbances following COVID-19 infection, SARS-CoV-2 was detected in basal and suprabasal layers of fungiform papillae for extended periods. In one subject, virus was detected up to 63 weeks after the initial diagnosis, coincident with disrupted nerve fibers and altered taste bud architecture (Yao, Doyle et al. 2023).

Recovery of taste, and re-establishment of normal epithelial cytoarchitecture, coincided with the disappearance of the virus from the taste epithelium (Yao, Doyle et al. 2023). These findings suggest that prolonged viral presence and the associated immune response may impair the renewal and functionality of taste buds in Long COVID. In our subjects, a sensitive commercial qPCR test showed that none of the tissue samples were positive for the SARS-CoV-2 viral RNA suggesting that taste dysfunction may persist even after the virus is no longer detectable in the peripheral taste system. This offers the potential that persistent taste dysfunction in Long Covid may outlast the presence of the virus itself.

Why loss of sweet-bitter-umami tasting ability is more frequent than the loss of other taste qualities

Psychophysical results from this study indicate a significant disruption of taste with a tendency toward preferential loss of sweet, bitter, or umami tastes. A previous WETT study involving 340 long-term (1-year) COVID-19 subjects and 434 non-COVID controls (Sharetts, Moein et al. 2024) found no statistically significant differences in taste function between groups. In contrast, we note significant taste loss but our study specifically targeted subjects reporting long-term

COVID-19-associated taste loss, preventing direct comparison with the broader population surveyed in the Sharetts et al. study.

Taste dysfunction may result from disruption of taste-related intracellular transduction cascades or damage to taste buds (TBs), their receptor cells (TRCs) or the gustatory nerves. Sweet, umami and bitter tastes all involve Type II receptor cells relying on a PLCβ2-mediated transduction cascade (Zhang, Hoon et al. 2003, Zhao, Zhang et al. 2003). Sweet taste is mediated by TAS1R2/TAS1R3 receptor heterodimers, umami by TAS1R1/TAS1R3, and bitter by a distinct family of ~30 Tas2Rs. In contrast, ionic taste qualities, such as sour and salty activate Type III TRCs relying on ion channels in the apical membrane to initiate a response (Liman 2020, Liman and Kinnamon 2021).

The fact that the COVID-19 virus directly infects Type II TRCs may explain why deficits in sweet, umami and bitter are more frequent than for sour and salt. In our study, however, viral RNA was not detectable in taste tissues and there was no evidence of wholesale destruction or abnormality in Type II, PLCβ2+, taste cells. Nonetheless, in our subjects overall tasting ability correlates positively with the amount of PLCβ2 and TAS1R3 present in the tissue. This leaves open the question of how prior viral infection might induce long-lasting deficits in taste.

In the olfactory epithelium, the virus infects supporting cells, but not the receptor cells (Chen, Shen et al. 2020). Nonetheless, the olfactory receptor cells respond to the viral infection of the tissue by downregulating expression of olfactory receptors and downstream signaling molecules while upregulating expression of viral response proteins (Chen, Reed et al. 2019, Zazhytska,

Kodra et al. 2022). The transduction cascade is re-established in the receptor cells once the viral infection has been cleared (Zazhytska, Kodra et al. 2022). While a similar phenomenon may occur in taste buds during viral infection, it is unlikely such a reaction would persist in the tissue after the virus is cleared and all the taste cells have been replaced during the course of normal taste cell turnover which requires a few months at most (Perea-Martinez, Nagai et al. 2013). At the time of our testing, up to 2 years after initial infection, none of the taste cells present at that time would have been present at the time of viral infection.

Furthermore, we do note some loss of non PLCβ2 taste qualities, i.e. sour and salty, in some subjects. This loss suggests that non-PLC dependent mechanisms may also be at work underlying taste dysfunction in Long COVID. One possibility is that the infection alters the function in taste nerves. Indeed, evidence exists for widespread neural dysfunction in Long COVID (Daia, Scheau et al. 2021, McFarland, Yousuf et al. 2021, Otte, Bork et al. 2022, O'Neill, De Stefano et al. 2023, Rogn, Jensen et al. 2024). If so, then some of the observed taste loss might be attributable to loss of transmission in the taste nerves rather than disruption of the taste epithelium.

Other factors that may have influenced the disease process of COVID-2 in taste

Recent studies (Finlay, Brann et al. 2022, Peluso, Ryder et al. 2023, Peluso, Hanson et al. 2024) broaden the perspective by suggesting that immune dysregulation and T cell dysfunction may play significant roles in the long-lasting effects of COVID-19. Whole-body positron emission tomography imaging with a tracer that selectively tags activated T cells show that subjects with Long COVID had specific tissues enriched for activated T cells compared to individuals without this condition (Peluso, Ryder et al. 2024). All five subjects in that study showed the presence of

intracellular SARS-CoV-2 spike protein-encoding RNA in lamina propria tissue up to 676 days after initial COVID-19. This offers evidence of viral persistance which could underlie long-term immunologic perturbations for up to two years postinfection. Whether a similar prolonged immunological response occurs in taste tissue is unknown although Yao et al (Yao, Doyle et al. 2023) report long term (>6 months) inflammatory response when virus remains in the tissue. We did not, however, detect any virus by PCR in our tissue samples from patients more than one year post infection.

On the relation between histological changes of TB by COVID-19 and taste changes

A particularly intriguing aspect of our study is that all subjects, including those with severe deficits, displayed structurally intact taste buds despite the loss of taste function. However, some dystrophic taste buds and isolated PLCß2-expressing cells were observed in many subjects. In mice, disruption of molecular signals between nerves and taste buds can result in formation of aberrant PLCß2-expressing cells outside of the taste buds themselves (Castillo, Seidel et al. 2014). This finding raises important questions about the disconnect between histological integrity and functional impairment. One possible explanation is that taste bud dystrophy, rather than outright loss, may be sufficient to alter taste sensitivity by impairing cellular turnover or disrupting synaptic communication with gustatory neurons (Wang, Liu et al. 2023). While intact taste buds might suggest some functional resilience, the significant decrease in PLCß2-dependent signaling suggests that molecular-level dysregulation may underlie the persistent taste dysfunction. In addition, the discrepancy between PLCß2 expression and taste bud morphology, especially in Subject 29 who shows complete taste loss, suggests dysfunction in peripheral nerves or at higher levels of the neuraxis.

Clinical relevance

Understanding the mechanisms behind taste loss is clinically relevant, as chemosensory loss impacts nutritional intake, emotional well-being, and quality of life. A multidisciplinary mindset is crucial for appropriate diagnostics and for providing patients with appropriate treatment and underscore the importance of developing targeted therapies to alleviate the burden of long-term taste dysfunction in COVID-19 survivors.

Here we present an integrative approach combining psychophysical taste testing, RNA expression analyses using markers for TRC type II and III, and histological evaluation of taste tissue in subjects with Long COVID. This multidimensional analysis provides a more comprehensive understanding of Long COVID taste dysfunction. While this study focuses on the loss of Type II TRC, PLCß2-dependent taste qualities (sweet, umami, bitter), the loss of other taste qualities in a limited number of subjects suggests that multiple mechanisms may underlie the sensory loss.

Conclusions

Our study suggests that persistent taste loss following COVID-19 depends neither on ongoing infection nor on wholesale loss of taste buds or their innervation. We found a correlation between taste loss for specific qualities, i.e. sweet, umami and bitter, and reduced expression of molecular elements of the corresponding taste transduction cascade. This highlights the importance of cellular signaling over structural integrity in COVID-related taste dysfunction.

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AUTHOR CONTRIBUTIONS

G.H., G.L., and T.E.F. conceived and designed this research. G.H. & G.L. wrote the ethical proposal to Etikprövningsmyndigheten. H.M. provided subjects, performed the WETT tests and took the biopsies. M.A.K. provided subjects and with A.A. assisted in analysis of the subject population. T.E.F. and M.L. designed and performed the histopathology and data analysis. G.A. and T.V. designed and analyzed the quantitative PCR experiments. T.V. performed RNA extraction and quantitative PCR experiments. T.E.F. performed statistical analysis of the quantitative data and compared results to those in the Doty et al (2015) report. G.L., G.H., G.A., H.M., and T.E.F. provided funding for the project. G.H., T.E.F., G.A., and M.A.K. prepared the manuscript and all authors have discussed and revised the manuscript.

Use of AI:

This study utilized Microsoft Copilot (GPT-4) accessed through a secure university-managed Microsoft Teams environment. The tool was utilized in the process of editing and checking calculations but was not used to generate any original content. All outputs were reviewed by the lead author.

Competing interests

The authors declare no competing financial interests.

Data Availability Statement: The data underlying this article will be shared on reasonable request to the corresponding author.

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