Taste, smell, and trigeminal chemesthesis in COVID-19 patients

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Abstract

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COVID-19 is an infectious disease that spreads quickly, requires hospitalization for some patients, and has prolonged effects on the lungs and other body organs. Two early prevalent symptoms of the disease are olfactory and gustatory dysfunction. While most patients regain chemosensory function following recovery from COVID-19, some patients have lingering chemosensory abnormalities. This thesis is focused on identifying a methodology suitable for assessing chemosensory function in the dental clinic. Identifying suitable tests will allow dentists and oral medicine specialist to detect COVID-19-related sensory abnormalities as well as monitor recovery of sensory function over time.

Objective: The objective was to assess the ability of selected measures of olfactory, gustatory, and chemesthesis (oral trigeminal nerve) function to detect alterations in sensory function in a cohort of patients who have recovered from COVID-19.

Methods: Subjects recruited through a flyer and social media advertising took an online survey based on one developed by the Global Consortium for Chemosensory Research **(GCCR**, https://gcchemosensr.org**)**. The survey included questions about COVID-19 diagnosis and symptoms, including changes in smell, taste, and chemesthesis function. Subjects completed objective testing of chemosensory function at the University of Washington Oral Medicine

Clinic. Olfactory sensitivity was assessed using the Smell Identification Test (SIT). Gustatory sensitivity was evaluated using a modification of the NIH Toolbox protocol for assessing gustatory function in adults.

Chemesthesis was assessed using a capsaicin-containing pullulan-based dissolving strip. All subjects were also tested using semi-quantitative sensory testing to assess trigeminal function in various receptive fields (V1, V2, V3).

Psychological assessments included the Patient Health Questionnaire (PHQ-9) and General Anxiety Disorders (GAD-7) scales. Subjects completed a medical review form. An intra-oral examination and dry mouth assessment were also performed.

Results: Eleven subjects responded to advertisements and completed the online survey. Nine completed the study protocols. Four of those completing the study had a prior COVID-19 infection, while five did not report prior COVID-19 infection. For those four subjects with prior COVID-19 infection, two reported changes in olfaction with COVID-19 infection, two reported changes in sensitivity to tastes with COVID-19 infection, and one reported change in chemesthesis with COVID-19 infection. One of the two COVID-19 patients reported that olfactory sensitivity had subsequently recovered, while the other reported lingering reductions in olfactory sensitivity.

Both patients with taste issues during COVID-19 reported that taste function had recovered to "excellent sense". The patient with COVID-19-related deficits in chemesthesis reported lingering loss of sensitivity to spicy foods. Objective testing with SIT failed to discriminate the case with lingering olfactory dysfunction from controls. No evidence of taste dysfunction was observed in any of the cases compared with controls. Objective testing with the capsaicin strip confirmed a lack of sensitivity to capsaicin in the case reporting a lingering

loss of chemesthesis. Semi-quantitative testing of the trigeminal receptive fields did not reveal any abnormalities among cases. An abnormal finding was observed in one control.

Conclusion: Although the SIT is considered a gold-standard clinical measure of olfactory dysfunction, it did not detect smell loss in a single patient with lingering olfactory complaints. No patients reported lingering taste concerns, so the usefulness of the NIH Toolbox protocol for monitoring COVID-19-related taste loss could not be assessed. The finding that a patient with reported lingering chemesthesis loss also had a muted response to the capsaicin-containing pullulan-based dissolving strip indicates that this test may be helpful in detecting, quantifying, and monitoring chemesthesis issues in long COVID.

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DEDICATION

I dedicate my thesis work to my family. Special gratitude to my loving parents, Abdalla and Fathia Borgeia, whose words of encouragement and push for tenacity ring in my ears. My sisters and brothers have never left my side and are very special. I finally dedicate this work to **Libya**, my country.

وما نيل المطالب بالتمني ولكن تؤخذ الدنيا غالبا

وما استعصى على قوم منا ل إذا اإلقدام كـــان

لــهم ركابا

أحمد شوقي

Chapter One: Background

1. Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), commonly known as COVID-19, is an infectious viral disease that spreads quickly, requires hospitalization for some patients, and has prolonged effects on the lungs and other body organs. Two early prevalent symptoms of the disease are olfactory and gustatory dysfunction. The literature's subjective olfactory disturbance ranges from 0%-93% in COVID-19 patients **(Jerome R. Lechien et al., 2020).** While anosmia is a well-known symptom among COVID-19 patients, taste dysfunction (such as ageusia) is also reported frequently. Since the beginning of the pandemic, many studies have been conducted to explore the smell and taste loss in COVID-19. Most of these research studies used subjective assessments in which they asked patients to answer survey questionnaires about anosmia and hyposmia **(Parma, V et al., 2020).** However, a few studies used objective measures, such as Sniffin' Sticks® kits **(Burghard, Gronigen, the Netherlands)** and taste strips that were provided to patients with COVID-19 **(Le Bon, S et al., 2021) (Lechien, J. et al., 2020).** These studies indicate that COVID-19 infection leads to short-term and long-term smell and taste impairment in many patients. Some patients regain their smell within 28 days, however, others develop persistent anosmia, hyposmia, or parosmia **(Niklassen, A et al., 2021).** In one study, taste and smell loss was found to persist 90 days post-infection in 30% of patients with mild COVID-19 infection **(Nielsen, K et al., 2021)**.

Compared to rates of smell and taste loss during the early phase of the pandemic in 2020 before variants were identified, chances of smell and taste loss were just 17% for omicron, 44% for delta and 50% for the alpha variant **(Michael, M 2022), (VCU Health, 2022)**.

The SARS-COV-2 virus enters cells by binding to the ACE2 receptor **(Luigi V et al., 2020)**. The olfactory epithelium and the oral cavity's mucous membranes exhibit these receptors on the surface of olfactory supporting cells, making them a pathway for virus entry**. (Lechien, J. et al., 2020).** The exact mechanism for this olfactory and gustatory impairment is not confirmed, but recent evidence suggests that COVID-19 mediated disruption of nuclear architecture in developing olfactory neurons may affect olfactory function (**Lomvardas et al, 2022).** Other theories explain that the inflammation process that accompanies the infection, along with secreting of inflammatory mediators and cytokines, make it difficult for olfaction to function well. A few studies suggest that the virus affects the central nervous system and, in turn, disables our smell detection centrally **(Luigi V et al., 2020)**.

Post-viral infection anosmia is well-documented in the literature, and the association between olfactory loss and upper respiratory tract infection is high. However, the prevalence of olfactory loss in COVID-19 seems to be much higher than for other viral infections. It is important to note that different research techniques used by various studies affect the reported rate of anosmia. It is essential to understand the difference between olfactory and gustatory dysfunction in COVID-19 compared with a common cold infection. It appears that COVID-19 behaves differently when it comes to affecting olfactory function compared to other respiratory viruses. Loss of smell in common cold infections tends to be due to nasal congestion, which is not the case in COVID-19. Most COVID-19 patients do not have congestion or post-nasal drip **(Huart C et al., 2020)**.

A few studies have reported gustatory impairment in the COVID-19-positive patient **(Cirillo N et al., 2020)**. It is unclear whether taste loss in the COVID-19 patient is related to olfactory loss, in which patients' ability to perceive flavors is affected by the concomitant olfactory loss. There is a close relationship between smell and taste chemosensory function within the central nervous system, where the perception of flavor is processed. Research

articles investigating the cause of anosmia and ageusia in COVID-19 are based mainly on subjective findings, and only a few studies have tested these symptoms using a formal psychophysical methodology **(Niklassen, A et al., 2021)**, **(Adamczyk, K et al., 2021)**, **(Le Bon, S et al., 2021)**.

The trigeminal and olfactory systems are different yet interacting pathways within the nasal cavity. They interact with each other, as many odorants stimulate both systems. The olfactory (**CN I**) and trigeminal (**CN V**) nerves interact by inhibiting or enhancing each other. The location and the degree of interactions are unknown, though one of the potential interaction sites is the nasal mucosa. Most chemosensory stimulants upon accessing the nasal cavity produce both olfactory and trigeminal sensations. Evidence suggests that the trigeminal nerve works concurrently with the olfactory nerve to bring about smell perception **(Iannilli, E et al., 2007)**. Variations in trigeminal nerve sensitivity also have been reported to occur in patients with olfactory disorders **(Thomas, D et al., 2020)**.

A patient with idiopathic or iatrogenic trigeminal sensory loss could also develop taste disturbance. For instance, patients with burning mouth syndrome suffer from taste loss, taste sensation gain, and taste phantoms during their disease. Moreover, since the intranasal trigeminal and the olfactory system are closely connected **(Frasnelli & Hummel 2007)**, the trigeminal nerve chemesthesis might be disturbed concomitant with post-COVID-19 anosmia as a complication of the olfactory dysfunction. We see that it is essential to have a protocol for lost senses testing, including the chemosensory function of the trigeminal nerve. Putting together a roadmap for researchers and clinicians to better assess these inter-related lost senses is essential to monitoring the progress of their subjects and patients.

2. Specific Aims

- **The specific aims**:
    1. Develop a protocol for objectively quantifying chemosensory loss post-COVID-19 infection.
    2. Assess the feasibility of using the protocol in the dental clinic.
    3. Collect preliminary data comparing protocol measures to self-reported symptoms based on validated questionnaires.

- **Hypotheses:**
    1. The testing protocol will be acceptable to patients.
    2. The testing protocol will be feasible to administer in the clinic during a 50-minute dental appointment.
    3. The initial results from objective testing will match self-reported changes in chemosensory function.

Chapter Two: Materials and Methods

Participants

Four subjects who responded to flyers on the University of Washington campus and reported olfactory loss after COVID-19 infection as well as five healthy subjects were recruited to Oral Medicine Clinical Services (OMCS), at the University of Washington.

Inclusion criteria for cases were: >18 years of age, COVID-19 past infection confirmed by SARS-CoV-2 Real-Time Polymerase Chain Reaction (RT-PCR), self-report of olfactory loss subsequent to COVID-19 infection.

Inclusion criteria for controls were: healthy subjects with no known history of COVID-19 infection and no self-report of olfactory dysfunction.

Exclusion criteria: a previous diagnosis of olfactory or gustatory dysfunction before COVID-19 infection, as well as any subject with a previous history of Burning Mouth Syndrome (BMS) or head and neck radiation.

Study Design

Descriptive study

1. Self-report (subjective testing):

A. Online questionnaire about olfactory, gustatory, and trigeminal chemesthesis: Subjects were pre-screened to determine their eligibility for the study through a survey questionnaire. These questions are partly adapted from the Global Consortium for Chemosensory Research (GCCR) **(Le Bon, S et al., 2021)**.

The Catalyst WebQ Survey system was used, which is a questionnaire software created by the University of Washington, Seattle. Questions to determine eligibility and to screen subjects included:

1. History of COVID-19 infection and symptoms
2. Smell and taste senses before, during, and after their COVID-19 infection
3. Trigeminal chemosensory loss screening questions
4. Date of onset of infection and symptoms
5. Duration of anosmia
6. Self-assessment of complete recovery
7. Presence of parosmia and/or phantosmia
8. Specific questions about trigeminal nerve chemosensory function that we added to the survey:
   a. Absent lacrimation while cutting an onion.
   b. Loss of nasal cooling sensation while inhaling menthol.
   c. Loss of nasal or oral burning/tingling sensation while eating spicy food, mustard, and wasabi.
9. Basic demographic information

B. Psychosocial distress evaluation: Two questionnaires described below examined psychological measures to identify participants reporting frequent or infrequent problems with senses (taste and smell) and how that impacted their daily life.

i. Generalized anxiety disorder scale (GAD-7) questionnaire: The Generalized Anxiety Disorder Assessment (GAD-7) is a brief measure of anxiety symptoms based on the generalized anxiety disorder diagnostic criteria described in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM). The GAD-7 assessment asks patients to evaluate their level of symptoms over the last two weeks. Responses can track treatment progress over time when administered on multiple occasions at the start, middle, and end of treatment **(Robert, L et al., 2006)**.

Given the simple language used in the assessment, the questionnaire is appropriate for individuals as young as 14 as a screening tool. Further evaluation is recommended when the score is greater than or equal to ten.

Responders are asked to rate the frequency of anxiety symptoms in the last two weeks on a Likert scale ranging from 0 to 3. Items are summed to provide a total score. (0 = not at all; 1 = several days; 2 = more than half the days; 3 = nearly every day). Scale score ranges from 0 to 21.

ii. Patient Health Questionnaire Depression Scale (PHQ-9) questionnaire: The 9-question Patient Health Questionnaire (PHQ-9) is a diagnostic tool introduced in 2001 to screen adult patients in a primary care setting for the presence and severity of depression. It rates depression based on the self-administered Patient Health Questionnaire **(Laura, M et at., 2015).**

This is calculated by assigning scores of 0, 1, 2, and 3 to the response categories of —" not at all," —" several days," —" more than half the days," and —" nearly every day," respectively.

C. The Hedonics of Capsaicin Containing Foods Questionnaire (Lawless, Rozin & Shenker et al., 1985): All subjects completed this questionnaire on the day of their clinical testing. This questionnaire included questions about amount, time, and

tolerance when eating spicy foods. The questionnaire aimed to determine their tolerance to eating spicy foods before they underwent capsaicin strips testing.

D. Medical update form: A medical update and medication list form was given to the subjects to assess their medical history and make certain none of them had any major medical problems that would exclude them from our study**.**

2. Clinical testing (objective testing):

After taking the online survey, qualified subjects were invited to come to the University of Washington, Department Oral Medicine, at the dental school for clinical testing:

A. Olfactory function: This assessment was performed using the Smell Identification Test (SIT) **(Sensonics International, Haddon Heights, New Jersey USA. Copyright©2013, Sensonics International)**. SIT was chosen for the olfactory test because of its demonstrated internal and retest reliability and its established efficacy in detecting anosmia in clinical populations **(Doty, Shaman, Dann et al., 1983).** A normative data table is available for score comparison. The scratch-and-sniff test booklet is also easily performed in a clinical environment, and this self-administered test can be completed in less than 20 minutes.

The SIT result is scored by summing the number of correctly answered items out of 40 odor panels, where a higher score indicates better olfaction. This forced choice test comprises four booklets, each containing ten microencapsulated ("scratch and sniff") odors released by a pencil tip. The examinee must provide an answer on each test item even if no odor is perceived or the perceived scent does not smell like one of the response alternatives (i.e., the test is forced-choice).

B. Gustatory function: This was evaluated using a modification of the NIH Toolbox protocol for assessing gustatory function in adults. Validation studies show that the

NIH Toolbox taste measures correlate with more traditional assessments and discriminate known population differences in taste. **(Coldwell, et al., 2013).**

The taste test guide and protocol are also easy to follow and use in the clinical environment, not invasive for the patient, and require little training for both clinician and subject. This test can be completed in 30 minutes or less.

The intensity of each taste was recorded by the participant using a computerized general Labeled Magnitude Scale (gLMS). The General Labeled Magnitude Scale (gLMS) is a semantic scale of perceptual intensity characterized by a quasi-logarithmic spacing of its verbal labels. The upper bound of the gLMS was defined as the 'strongest imaginable sensation of any kind **(Bartoshuk, L et al., 2004)**.

Solutions of 1 M sucrose, 1 M NaCl, 0.032 M citric acid, and 1 mM quinine HCl were directly applied to the anterior right and then the anterior left side of the subject's tongue using a cotton swab. The test with cotton swab was performed with one side stroke first on the right side, second on the left side, and subjects rinsing with deionized water after each presentation. This was followed with a whole mouth sip and spit tasting of 10 ml of each solution followed by a water rinse. The software generated a score for each of the individual trials, the scale for the score ranged from 0-100.

C. Chemosensory testing with edible capsaicin strips: Trigeminal nerve chemosensory testing was performed using five nmol capsaicin strips and blank strips without nasal airflow closure **(Smutzer et al., 2018)**. Subjects were instructed not to eat any food for at least 30 minutes and refrain from eating spicy foods, for at least 24 hours before performing the test. This test was easy to use and it did not need any training for clinician or subjects. It is still not widely validated to assess trigeminal chemosensory loss, but it is reliable, cheap, and easy to administer **(Smutzer et al., 2018).**

Each subject was asked to stick their tongue out. The control strip was placed on their anterior tongue, and the subject was asked to touch the roof of their mouth with their tongue and wait until the strip was dissolved. Immediately after, the subject was asked to use the gLMS scale on the computer to rate the intensity. The subject was asked to rinse with water, wait 30 seconds, then repeat the same process with the strip that contains the capsaicin. The subject was asked then to rate the intensity again on the gLMS scale.

D. Trigeminal semi-quantitative sensory testing: The original Quantitative Sensory Testing QST has been reported to be reliable in longitudinal studies and is therefore a candidate for measuring changes over time **(Fréderic Van der et al., 2020)**.

A semi-quantitative protocol is a short and modified version of the original quantitative sensory testing. We used the semi-quantitative test to be able to quantify the measurement, and we did not need the complete qualitative sensory testing in our study**.**

A drawback of semi QST is that it is time consuming. However, further methodological refinements and the combination of partial aspects of the full QST battery with other testing and imaging methods should provide improvements. The chairside Semi-quantitative Sensory Testing that we used is based on this technique by **(Svenson, P, Drangsholt, M et al., 2006)**.

Sensitivity was examined bilaterally in facial sites supplied by the ophthalmic (V1) infraorbital (V2) and mental (V3) nerves. General nerve sensory function (the cotton swab test), pain threshold (pinprick test), and cold and hot pain threshold (spatula test) were performed extra-orally and intra-orally.

Test details:

1. Cotton swab testing (1 minute): We made three to four touches 1 to 2 centimeters in length on both sides of their face using a cotton swab. We asked the subject if they felt the same sensation on both sides, a minor sense on one side than the other, or more sensation on one side.

2. Pinprick testing (2 minutes): We gently pressed an explorer's sharp end against each side of the subject's face (right and left). We asked them to say "sharp" as soon as they felt the slightest "pricking" or "stinging" sensation. If they thought the explorer was touching their skin without any "pricking" or "stinging," we asked them to describe it as "blunt."

3. Spatula testing (2 minutes): We cooled a metal spatula in an ice bucket until it was five °C or heated it on a hot plate until it was 40°C and applied the spatula to the six test areas on the subject's face for two to three seconds to detect sensitivity to cold and hot stimuli. We asked them if they are experiencing an increased cold sensation only on the one-side area of their face or an increased sense of heat on the one-side site of their face.

4. Intraoral tests (2 minutes): Testing for sensation changes inside the mouth included performing all three tests listed above on their gingiva in the upper and lower areas.

E. Intraoral examination including dry mouth evaluation with the Challacombe scale, and intraoral photos: Oral mucosa was inspected in the area of cheek mucosa, tongue, the floor of the mouth, and roof of the mouth to rule out any oral diseases or taste bud abnormalities.

As part of the intraoral exams, we assessed the subject's salivary function through the Challacombe Scale. This is a widely used diagnostic medical tool designed to produce a clinical oral dryness score (CODS) without collecting saliva and which quantifies the extent

of dryness of the mouth to decide whether to treat or not and to monitor its progression or regression.

This scale can be used to indirectly assess salivary flow rates and therefore calculate the risk of dental caries. In addition, it has particular use in assessing dry mouth in **Sjögren's** Syndrome.

Based on a 10-point scale of clinical physical findings, a score of one is the least severe, and ten is the most severe **(H. Jawad, N. A. Hodson & P. J. Nixon et al., 2015)** (see appendix for a copy of the scale).

Intraoral photos were taken of the tongue, cheek mucosa, and lips.

The study was approved by the proper Ethics Commission from the University of Washington human subject division, **IRB number is 03/2022- STUDY00014431.**

This work was supported by an award from the American Academy of Oral Medicine Research Advancement Committee **(AAOM-RAC)** and by the Washington Dental Service Endowed Professorship **(WSEP).**

Statistical Analysis

Descriptive statistics were calculated for subjects who completed study testing. These include patient demographics, questionnaire results clinical assessment of olfactory loss, clinical assessment of taste loss, and clinical diagnosis of trigeminal chemesthesis loss.

The descriptive statistics for the quantitative variables are shown as the mean ± standard error of the mean (SEM).

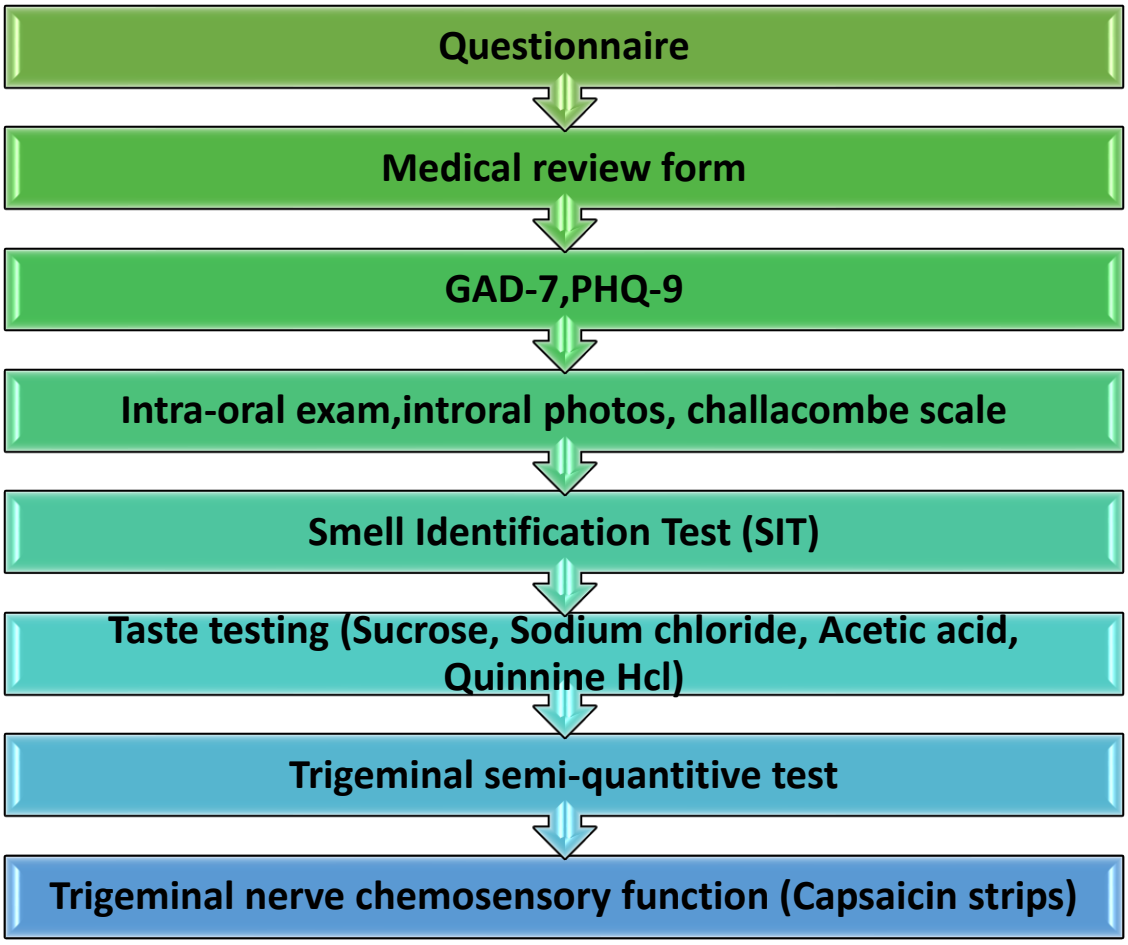


Figure 1: Flow chart of the study's procedures during one appointment.

Chapter Three: Results

Demographic information:

In total, 11 participants completed the survey, all in the USA. Participants ranged from 19 to 56 years, with a mean of 29.6 years. There were three males and eight females. The four subjects with COVID-19 infection were diagnosed with RT-PCR test except one with the rapid antigen test kit. Six subjects had a past COVID-19 infection, while five were healthy with no history of COVID-19 infection. All subjects reported having recovered from COVID-19 infection, except one that did not fully recover. None needed to be admitted to the hospital.

Participants were identified as Native American (n=1), Latin/Hispanic (n=2), African American (n=2), Asian American (n=5), and Caucasian (n=1).

Nine subjects completed the full study, including the clinical testing, and two withdrew from the study after they completed the survey. Of the nine subjects who completed the study we labeled the subjects as a control (person who did not have COVID-19 in the past) or a case (a person who had COVID-19 in the past). See table 1, 2 for demographic data and medical comorbidities.

We present the data as a self-report (survey data) compared to objective measures (clinical testing).

1. Survey (Self-report subjective results):

A. Olfactory function results: Of all cases, one reported a lingering specific change in their olfactory function (smell). They reported that their smell is less intense than before, and the quality of their smell changed. They also reported that their sense of smell worsened after the illness, from no sense of smell to a poor sense of smell. One other case reported a moderate sense of smell during COVID-19 that recovered

completely and reported an excellent sense of smell after COVID-19. All the control subjects reported excellent olfactory function **(see table 3)**.

B. Gustatory function results: Two of the cases described changes in their perceived gustatory function during COVID-19 infection. One subject described specific changes to their senses of sweet, savory, and umami, while the other subject described the change in their sweet, salty, sour, and bitter qualities. These two cases recovered with an excellent sense of taste after their COVID-19. All control subjects reported excellent gustatory function **(see table 4)**.

C. Trigeminal chemesthesis results: One of the cases reported less sensitivity to spicy food with COVID-19 infection, and her perception of spicy food remained less sensitive after COVID-19. All other subjects reported no changes in their spicy food perception **(see table 5).**

All subjects reported normal senses to tearing when cutting an onion, getting a cooling sensation using mint toothpaste, and tingling/burning when eating spicy food, except one subject did not feel tingling/burning with eating spicy food after COVID-19 infection.

D. Psychological distress scales: All nine subjects who completed the smell, taste, and trigeminal chemosensory testing also completed two forms to assess their psychosocial distress related to their COVID-19.

For the GAD-7 scale, out of nine subjects, seven scored 0-4 with minimal anxiety, one scored 5-7 with mild anxiety, and one scored 10-14 with moderate anxiety.

For the PHQ-9 scale, five scored 1-4 with minimal depression, two scored 5-9 with mild depression, and one scored 15-19 with moderately severe depression **(see table 6).**

E. The hedonics of capsaicin-containing foods questionnaire: Five subjects scored three on the 7-category Likert Scale, which indicates they consume spicy food

1-3 times per month on average, one subject scored four, which indicates they consume spicy food once a week on average, and one subject scored five, which indicates they consume spicy food equal to 3-4 times a week, one subject scored six which indicates they consume spicy food every day. Three out of nine consumed food that contained pepper before the testing **(see table 7)**.

F. Medical update form: Subjects reported their past and current medical problems and their medication list **(see table 1,2)**.

2. Clinical testing (objective assessment):

The characteristics of taste, smell, and trigeminal chemosensory dysfunctions have been analyzed more in-depth and objectively.

A. Olfactory function results: Smell test scores ranged from 29-35 (maximum score is 40) one subject had normosmia, and eight had mild microsmia. Figure 2 shows the difference in smell score between cases vs. controls). Even though one subject reported some change in their smell quality, the SIT test could not detect that objectively **(see table 3)**.

B. Gustatory function results: There was no difference in taste testing results between COVID-19 subjects and healthy subjects. Figure 3 shows the whole mouth taste test difference between cases vs. controls. The NIH Toolbox did not detect any differences **(see table 4)**.

C. Trigeminal chemesthesis results: After recovering, one subject with a COVID-19 infection reported a change in their spicy food perception. Figure 4 shows the capsaicin test difference between cases vs. controls. With the exception of the case with lingering chemesthesis complaints, all subjects rated the intensity of the capsaicin strip as having substantially more sensation than the blank strip **(see table 5)**.

D. Trigeminal semi-quantitative testing: Among all the subjects, one control subject has a decreased sensitivity on V3 of the trigeminal nerve, intra-orally, and extra-orally. Other subjects had normal trigeminal semi-quantitative testing **(See table 5)**.

E. Dry mouth evaluation and Challacombe scale results: One control subject scored two on the Challacombe scale; all other subjects scored zero (see table 6).

F. Intraoral examination and photos: All subjects were within normal limits (WNL) for their mouth inspection, and intraoral photos did not show any abnormalities. "**WNL"** refers to no gross pathology, adequate saliva pooling in the floor of mouth, and no sign of oral cancer.

3. The effectiveness of running the objective tests:

A. SIT test: Although this test was expensive (27 US dollars for one test), subjects thought it was fun to take it. The test took less than 15 minutes, there was no pain, and none of the subjects refused to proceed with the olfactory testing.

B. Gustatory with modification of NIH Toolbox: Sucrose, sodium chloride, and citric acid were not expensive to purchase, whereas quinine HCl was more expensive. A total of 867 US dollars was spent for all the ingredients which will cover approximately 100 complete tests.

Subjects thought the quinine was the worst tasting due to the bitterness of the solution. Time to take the test ranged from 15-20 minutes per subject, and the time to prepare the taste solutions ranged from 25-50 minutes. There was no pain in taking the test, and none of the subjects refused to complete taste testing**.**

C. Trigeminal chemesthesis with capsaicin strips: The capsaicin-dissolving strips and blank strips cost 300 US dollars for the bulk of blanks and capsaicin

strips. That purchase was enough for running the whole study. We used enough of them for only nine subjects. One of the risks of performing this test was that subjects may feel a burning sensation in their mouth. None of them felt burning and none needed milk to soothe their mouth following testing. The time to take the test ranged from 5-7 minutes per subject. There was no pain reported in taking the test, and none of the subjects refused to proceed with the chemesthesis testing.

D. Semi-quantitative chairside: This test was the most cost-effective as materials are usually readily available in the dental operatory (50 US dollars for instruments). The time to complete the test ranged from 15-17 minutes. There was no pain in taking the test for the subjects, none of the subjects refused to take the test, but there was a slight hesitation with the pinprick component of this test.

Age	**Control(n=5)**
<39	4
40-59	1
Sex	
Male	1
Female	4
Smoking	
Yes	0
No	5
Vaping	0
Allergy	
Allergic rhinitis	0
Comorbidities	
No medical history	3
Hypertension	1
Diabetes	1
Visual disturbance	1
Hypothyroidism	1
Asthma	1
Anxiety/depression	2

Chronic anemia/fatigue	0
Recovery from COVID-19	
Fully recovered	5
Partially recovered	0
Socioeconomic status	
Upper	0
Upper middle	2
Middle	0
Lower middle	3
Lower	0
Prefer not to say	0

Table 1: Demographic and clinical characteristics of the five healthy subjects.

Age	**Case(n=4)**
<39	3
40-59	1
Sex	
Male	1
Female	3

Smoking	
Yes	0
No	4
Vaping	0
Allergy	
Allergic rhinitis	1
Comorbidities	
No medical history	3
Hypertension	0
Diabetes	1
Visual disturbance	0
Hypothyroidism	0
Asthma	1
Anxiety/depression	2
Chronic anemia/fatigue	1
Recovery from COVID-19	
Fully recovered	4
Partially recovered	0
Socioeconomic status	
Upper	0

Upper middle	1
Middle	0
Lower middle	1
Lower	1
Prefer not to say	1

Table 2: Demographic and clinical characteristics of the four subjects confirmed COVID-19.

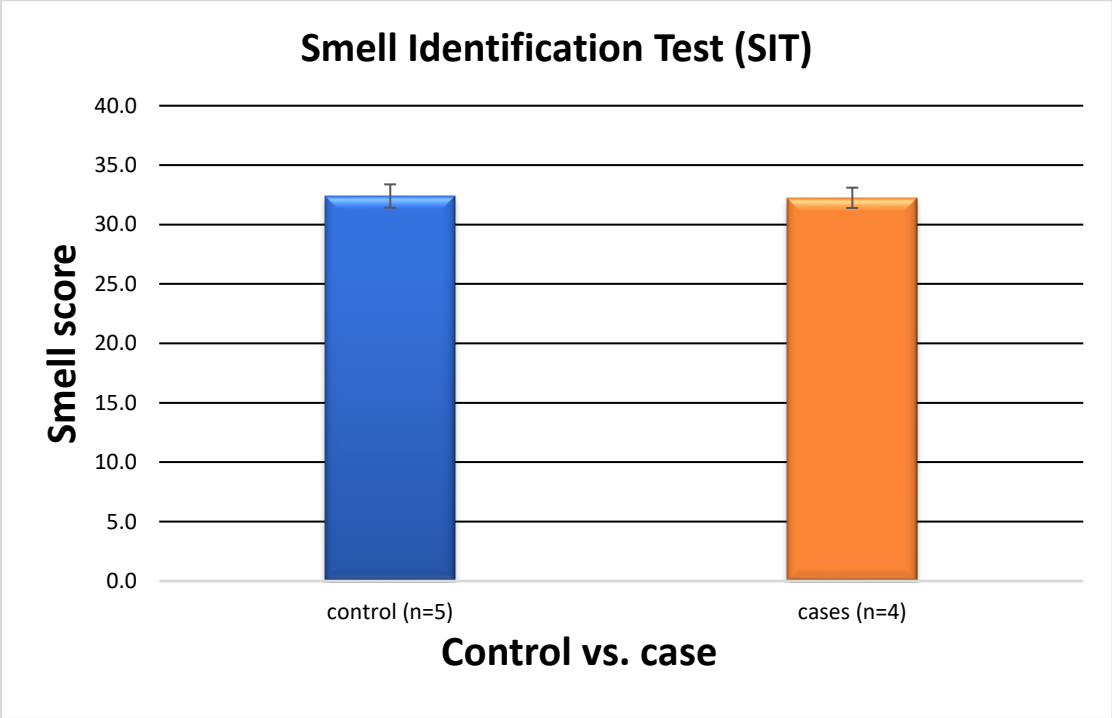


Figure 2: Smell identification test scores for all subjects, divided into, Control (healthy subjects with no COVID-19), Case (subjects who had COVID-19 infection in the past). Error bars indicate standard error of the mean (SEM).

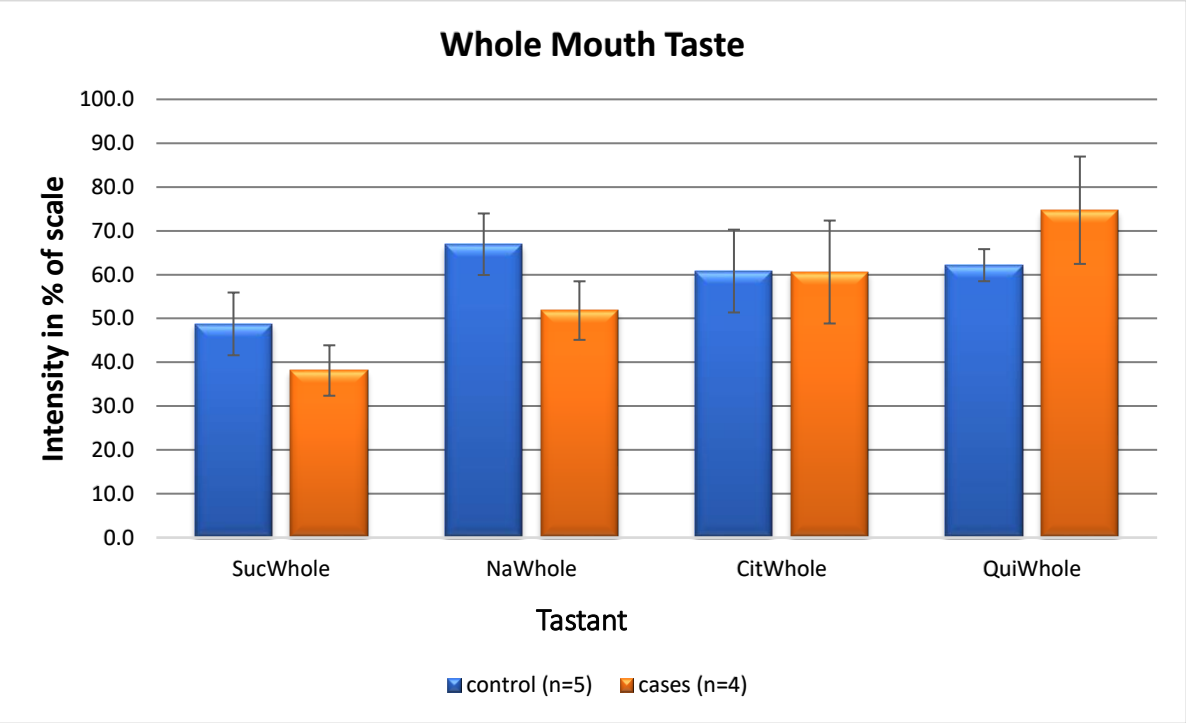


Figure 3: The whole mouth taste for the basic four tastants between case and control. Error bars indicate standard error of the mean (SEM).

SucWhole: 1 M sucrose whole mouth, **NaWhole:** 1 M sodium chloride whole mouth, **CitWhole**:0.032 M citric acid whole mouth, **QuiWhole:** 1mM quinine HCl whole mouth.

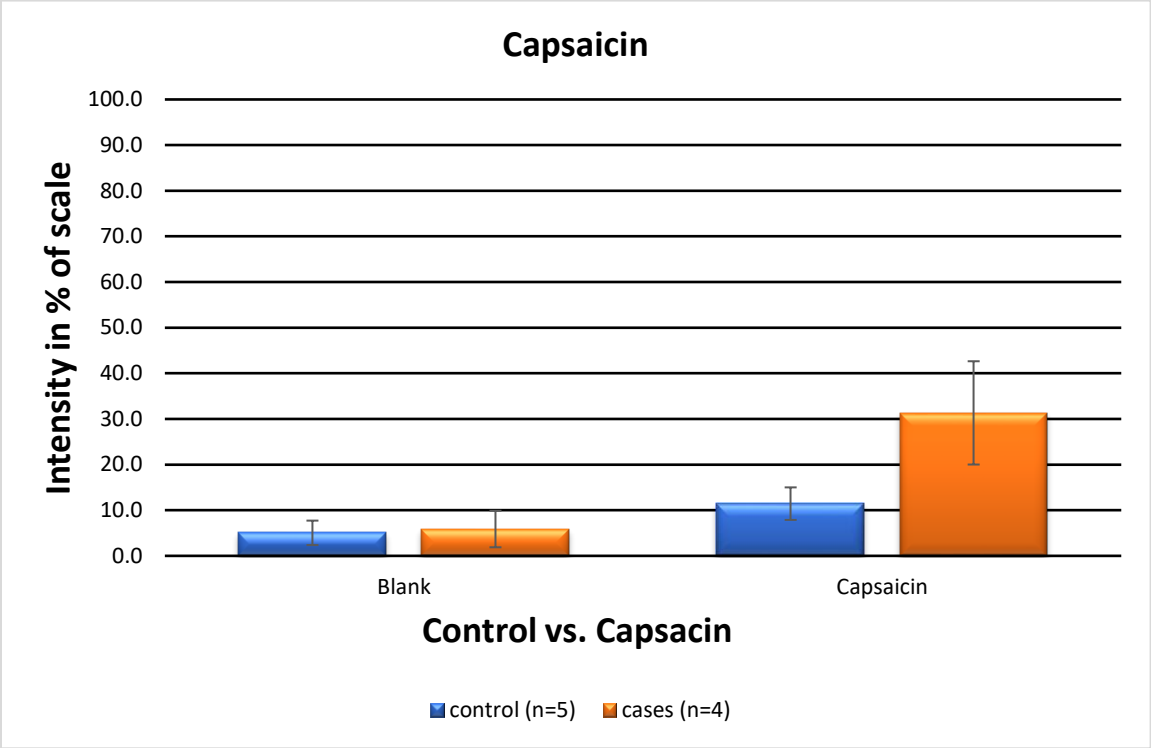


Figure 4: The capsaicin test results in cases and controls subjects. Error bars indicate standard error of the mean (SEM).

Subject ID	Changes in the smell with illness	Describe the specific changes (Quality of smell) with illness	Ability to smell after recovery	UPSIT score 0-40
Case (n=4)				
204	No sense	I cannot smell at all/smells smell less than they did before, Smells smell different than they did before (the quality of smell has changed) everything has less smell, nothing as intense as before.	Poor sense	32
205	Mild	None	Excellent	34
206	Excellent	None	Excellent	30
209	Moderate	Not that I noticed	Excellent	33
Average				32.3
Control (n=5)				
201	Excellent	None	Excellent	32
202	Excellent	None	Excellent	33
203	Excellent	None	Excellent	33
207	Excellent	None	Excellent	29
208	Excellent	None	Excellent	35
Average				32.4

Table 3: Comparison between subjective and objective olfactory function among case vs. control subjects. The subjective smell scale ranges from no sense to excellent sense. The maximum objective SIT test total score is 40 correct out of 40.

Subject ID	Changes in specific tastes with illness	Ability to taste after recovery	Whole mouth (0-100 scale)			
Case (n=4)			**Sucrose**	**NaCl**	**Citric acid**	**Quinine**
204	Sweet, salty, sour, bitter	Excellent	39.0	54.6	35.8	54.6
205	Sweet, savory/umami	Excellent	25.2	69.5	82.7	91.5
206	None	Excellent	35.3	40.1	45.4	52.8
209	None	Excellent	53.0	43.0	78.5	99.9
Average			38.1	51.8	60.6	74.7
Control (n=5)						
201	None	Excellent	53.0	71.9	48.5	63.6
202	None	Excellent	65.0	91.2	98.1	73.7
203	None	Excellent	22.1	49.6	47.7	50.7
207	None	Excellent	54.4	60.2	56.0	61.3
208	None	Excellent	49.3	61.8	53.8	61.5
Average			48.8	66.9	60.8	62.2

Table 4: Comparison between subjective and objective gustatory function among case vs. control subjects. The subjective taste scale ranges from no sense to excellent sense. The objective taste scale ranges from 0 to 100.

Subject ID	Describe other changes	Ability to feel other sensations after	Semi-quantitative Testing findings	Blank (0-100 scale) strip	Capsaicin strip (0-100 scale)
Case (n=4)					
204	No changes	Mildly sensitive	WNL	0.3	28.4
205	Less sensitive to spicy food	Not sensitive	WNL	0.9	1.1
206	No changes	Very sensitive	WNL	4.8	42.2
209	No changes	Mildly sensitive	WNL	17.5	53.6
Average				5.9	31.3
Control (n=5)					
201	No changes	Moderate sensitive	WNL	0.3	5.9
202	No changes	Very sensitive	WNL	15.2	25.2
203	No changes	Mildly sensitive	Sensitive	4.8	8.5
207	No changes	Not sensitive	WNL	4.0	6.4
208	No changes	Not sensitive	WNL	0.9	11.2
Average				5.0	11.4

Table 5: Comparison between subjective and objective trigeminal chemosensory function among case vs. control. The subjective changes in other sensations scale range from no sense to excellent sense. The objective capsaicin scale ranges from 0 to 100. Other sensations here refer to feeling the burn of spicy food. WNL: is Within Normal Limit.

Subject ID	PHQ-9 score	PHQ-9 category	GAD-7 score	GAD-7 category	Challacombe scale score	Dry mouth evaluation
Case (n=4)						
204	5	Mild depression	4	Minimal anxiety	0	WNL
205	9	Mild depression	11	Moderate anxiety	0	WNL
206	0	No depression	0	Minimal anxiety	0	WNL
209	2	Minimal depression	2	Minimal anxiety	0	WNL
Control (n=5)						
201	4	Minimal depression	3	Minimal anxiety	0	WNL
202	19	Moderately severe depression	8	Mild anxiety	0	WNL
203	4	Minimal depression	3	Minimal anxiety	0	WNL
207	1	Minimal depression	4	Minimal anxiety	2	WNL
208	4	Minimal depression	3	Minimal anxiety	0	WNL

Table 6: Psychosocial, dry mouth evaluation scores for subjects divided into case vs. control. PHQ-9's total score is 24, GAD-7's total score is 21, and the Challacombe scale (see appendix).

Subject ID	Have you consumed any spicy foods in the previous 24 hours?	Frequency of ingestion of all types of chili pepper in foods	How much do you like the taste of chili pepper in your food?	How much do you like the burn of chili pepper in your food?	'I think chili pepper makes food taste better'	'Without hot spices, I find that food tastes too bland'	'I find it hard to appreciate the flavors of the food when the food contains hot spices'
Case (n=4)							
204	No	3	4	5	True	False	True
205	Yes	5	6	4	False	False	True
206	No	3	7	6	True	False	False
209	No	3	6	4	False	False	True
Average		3.5	5.8	4.8			
Control (n=5)							
201	No	3	4	4	False	False	False
202	No	4	7	4	True	False	True
203	Yes	6	8	8	True	True	True
207	No	3	7	7	True	False	False
208	Yes	7	6	3	True	True	False
Average		4.6	6.4	5.2			

Table 7: Subjects' answers to the hedonics of Capsaicin containing Foods Questionnaire. Please see the appendix for a copy of the questionnaire.

Test	Olfactory SIT	Gustatory NIH Toolbox	Capsaicin strip	Semi-quantitative
Feasibility	Easy	Easy	Easy	Moderate
Time to administer the test battery	12-15 min	15-17 min	5 min	12-17 min
Subject feedback	Well tolerated Fun to take the test Culturally dependent	Moderately tolerated Quinine very bitter, needed a lot of rinse after	Well tolerated We did not need to give them milk after to relieve mouth burning	Moderately tolerated Worry about the pinprick test Needed a lot of explanation for subjects
Pain	Not at all	Not at all	Not at all	Slight with pinprick test
Refuse to proceed	No	No	No	Slight hesitation
Cost	27 US dollars	Total for all ingredients used in making solutions is 867 US dollars	Bulk of blank and capsaicin strips 300 US dollars	Cotton swab and spatulas 100 US dollars

Table 8: Subjects tolerance of our different objective (clinical tests) and cost.

Chapter Four: Discussion

The COVID-19 pandemic created an urgent need for specific smell and taste measures suitable for the clinical research environment, e.g., smell identification tests at home. Researchers were innovative but each developed their own method, making comparing results difficult. In this study, we assembled a series of tests that can assess the loss of chemical senses for COVID-19 patients, we chose these tests after a comprehensive search through the literature and working with experts in the field to identify reliable and valid objective chemosensory measures.

The SIT smell tests we used with our subjects gave scores ranging from 29-35 out of 40, which places most of our sample in the category of mild microsomia, except one who had 35, which place them in the category of normosmia. That could be partially explained by the fact that the seasonal allergy time in the Pacific Northwest might cause our subjects to be unable to sniff with their blocked nose.

In the most extensive study of olfaction in rhinitis and rhinosinusitis, Simola and Malmberg compared odor detection thresholds obtained from 105 rhinitis patients to those of 104 healthy control subjects. The proportion of hyposmic persons and the degree of the impairment of the sense of smell were significantly higher in the rhinitis group than in the control group. Age and rhinitis were found to be associated with smell dysfunction **(Simola, M et al., 1998)**.

Individual tests for smell identification such as SIT could be considered valid, but, being culturally dependent, they should be appropriately validated in the different country populations **(Rong-San et al., 2014).** For example, some of our subjects who grew up abroad did not know what cherry scent smelled like; cherry was not a prominent flavor in their culture.

On the other hand, the SIT smell test only analyzes for odor identification, and other smell tests determine smell intensity and magnitude of anosmia. Although the SIT test is easy to deliver, it is still costly (27 US dollars for one trial). It is generally helpful to use in research to detect olfactory loss, but it doesn't provide information regarding the mechanism of smell loss **(Parma, V et al., 2021)**.

A group of researchers at Monell Chemical Senses Center in Philadelphia have developed a new smell test called SCENTinel 1.0, which has the ability to be used to assess odor intensity **(Parma, V et al., 2021)**. Their initial findings with the test support the idea that SCENTinel 1.0 represents a rapid, accurate, flexible, and cost-effective tool to deploy a smell test in large-scale population surveillance efforts. Using the SCENTinel 1.0 test in future clinical research might give a good insight into the magnitude of anosmia. Because the SCENTtinel 1.0 test measures the perceived magnitude of tested odors rather than just odor recognition as in the case of SIT, and it might be useful to include the SCENTinel 1.0 test instead of SIT to test our future subjects **(Parma, V et al., 2021)**.

We conducted our taste testing using one concentration of four basic tastes; this method is a valid way to assess taste perception **(Coldwell, S et al., 2013)**. Numerous studies used techniques for measuring gustatory function, ranging from taste strips to taste capsules **(Le Bon S et al., 2021), (Lechien, J. et al., 2020)**, **(Mazzatenta et al., 2020)**, **(Niklassen et al., 2021)**, **(Adamczyk et al., 2020)**, **(Doty, RL et al., 2021).**

Our approach involved testing the right and left side of the tongue tip as well as the whole mouth sip and spit test. It was a convenient approach, and subjects could tolerate and understand the initial training that proceeds this test. Some of our subjects reported partial taste loss and changes during their COVID-19 infection. Even though our chosen taste testing method did not detect taste loss related to COVID-19, the test was easy to administer and did not require a lot of training for researchers and patients alike. With the

emergence of new COVID-19 variants, smell and taste complaints became less evident. We did not look specifically at the type of COVID-19 variant that our cases had. A recent study looked at chemosensory loss among COVID-19 patients with different variants, and they found out that patients infected with the new mutant have a significantly lower risk of associated chemical sensory loss **(COELHO, D et al., 2022)**. Looking at the specific COVID-19 variants could provide more information related to taste and smell loss.

Our study is the first to add capsaicin strips to assess trigeminal chemosensory function. Strong odor stimulates the trigeminal nerve at the olfactory nerve level or the upper part of the nasopharynx. Capsaicin could help evaluate the potential loss of response to pungent and spicy foods **(Lawless, Rozin & Shenker et al., 1985).** One subjects could not distinguish between lower and higher spiciness foods after her COVID-19 infection, which was evident when she marked the intensity of blank and capsaicin strips on the gLMS scale with very similar intensity. Comparing that to the rest of our subjects revealed some difference.

Hummel and his coworkers **(Thomas, D et al., 2020),** tested the chemosensory function of the trigeminal nerve in COVID-19 patients subjectively, giving subjects questionnaires about their ability to cry while cutting an onion, for example. In this study, we measured that function objectively by using a capsaicin-containing pullulan-based dissolving strip. We adapted our technique from Dr. Smutzer's methodology, with the only difference being that he performed this test under a controlled nasal airflow. We did not feel it was necessary to block our subject's nostrils since we were interested in determining their ability to feel the spicy pepper burn in both their mouth and nasal mucosa **(Smutzer et al., 2018).**

In addition, we also evaluated trigeminal nerve sensory function. Patients with trigeminal nerve injury after surgery or who develop post-traumatic neuropathic pain tend

to lose some of their sensitivity to touch on the affected site **(Satu, K et al., 2005)**, which might diminish their ability to perceive spicy food due to this sensory loss. We performed semi-quantitative trigeminal testing on our subjects to prevent miss-diagnosing a patient with the trigeminal sensory loss for reasons other than trigeminal chemosensory loss due to COVID-19 infection.

All our subjects had normal trigeminal nerve sensory function, except one with sensory loss on the V3 trigeminal branch extra and intraorally. She was a healthy control, and the reason for that loss could be due to surgical trauma during placement of an implant in her left lower jaw a few years ago.

Orofacial QST is a reliable test method for diagnosing pathological neurosensory conditions and assessing normal neurosensory function. Although challenges remain that hinder the use of QST in routine clinical decisions and clinical trials. Disadvantages of QST include that it cannot be used to localize lesions in the neurological pathway towards the cortex, as well as the requirements that patients cooperate and understand the tasks and questions. Future improvements are expected to enable its introduction into routine practice **(Fréderic Van der et al., 2020)**.

The strength of this study is that it is the first one that combines a comprehensive battery of tests to provide a preliminary protocol to evaluate a person with COVID-19-related smell, taste, and chemosensory loss. We developed this protocol that presents logical steps for assessing chemosensory loss for the clinical researcher to use. This study is one of the first to utilize standardized basic chemosensory testing and neurosensory testing (e.g., capsaicin dissolving strips, semi- QST) as well as subjective assessments in COVID-19 patients. These tests were easy to administer and time efficient.

The limitation of this study is that the number of participants for a detailed olfactory, gustatory function, and trigeminal chemosensory function was quite limited.

Further studies must be conducted to be able to conduct statistical analysis and evaluate the protocol for effectiveness and selection of most informative tests for evaluation and monitoring of chemosensory and trigeminal nerve function in patients with COVID-19.

Secondly, the specific COVID-19 variants were not identified in the experimental (case) group in this study. For example, some COVID-19 variants may cause chemosensory loss in fewer people or not cause it at all.

Conclusion

The COVID-19 pandemic required urgent action from scientists and clinicians working to understand the new virus and the symptoms it causes. Among the many unique features of this virus, some of the most notable are smell and taste disturbances. However, as taste loss has increasingly gained attention in the scientific literature alongside smell loss, many initially speculated that the rate of taste loss is overestimated due to the confusion between taste and flavor in self-reports.

Our study focused on integrating appropriate valid tests and protocols to assess the loss of these senses in one protocol and this study may help health care providers to choose a group of tests that allow them to evaluate their patient's chemosensory loss efficiently and accurately in a cost-effective manner.

Adding up all the costs to run these tests and dividing them by the number of our subjects revealed a cost of approximately 166 US dollars per subject, a reasonable price for one subject.

Hopefully, the widespread availability of easy-to-use tests of olfactory, gustatory, and trigeminal chemesthesis functions will lead to such controlled studies.

Future plans

1. Running the battery of tests, that we put together on large numbers of subjects who have had COVID-19 to see which tests are most useful, efficient and economical.

2. Using a specific PCR test to know which variants each subject might have.

3. Replace Smell Identification Test (SIT) test with SCENTinel 1.0 to measure the magnitude of smell loss.

Appendix

Q1: Multiple choice - one answer (button)

I consent to participate

Answer choices:

a. yes
b. No

Q2: Multiple choice - one answer (button)

Have you been diagnosed with or suspect that you have a respiratory illness within the past few months?

Answer choices:

a. Yes
b. No

Q3: Short response

What date did you first notice symptoms of your recent respiratory illness? Provide your best guess or leave blank if you do not remember.

Q4: Multiple choice - one answer (button)

Have you been diagnosed with COVID-19?

Answer choices:

a. Yes - diagnosed by medical symptoms only
b. Yes - diagnosed with an RT-PCR
c. Yes - diagnosed with another antigen or antibody test
d. Unknown - I was tested but did not get my results
e. No - not diagnosed, but have symptoms
f. No - had a negative test, but still, have symptoms
g. No - do not have any symptoms

Q5: Multiple choice - multiple answers (check)

Were you diagnosed with other respiratory illnesses (not COVID-19) in the past few months?

Answer choices:

a. Strep throat (*Streptococcal* bacteria)
b. Another bacterial illness

c. Flu (influenza)
d. Another viral illness
e. Other
f. None

Q6: Multiple choice - multiple answers (check)

Have you had any of the following symptoms with your recent respiratory illness or diagnosis? (Select all that apply)

Answer choices:

a. fever
b. Dry cough
c. Cough with mucous
d. Difficulty breathing/shortness of breath
e. Chest tightness
f. Runny nose
g. Sore throat
h. Changes in food flavor
i. Changes in smell
j. Changes in taste
k. Loss of appetite
l. Headache
m. Body aches
n. Fatigue
o. Diarrhea
p. Abdominal pain
q. Nausea
r. Skin sensitivity
s. Dry mouth
t. Dry nose/irritated nose
u. None of the above

Q7: Long response

Please describe the progression or order you noticed your symptoms

Q8: Long response

What treatment(s) or medication(s) have you received for your recent respiratory illness or diagnosis?

Q9: Multiple choice - one answer (button)

Rate your ability to smell BEFORE your recent respiratory illness or diagnosis

Answer choices:

a. No sense
b. Mild sense

c. Moderate sense
d. Excellent sense

Q10: Multiple choice - one answer (button)

Rate your ability to smell DURING your recent respiratory illness or diagnosis

Answer choices:

a. No sense
b. Mild sense
c. Moderate sense
d. Excellent sense

Q11: Multiple choice - multiple answers (check)

Have you experienced any of the following changes in your sense of smell with your recent respiratory illness or diagnosis? (Select all that apply)

Answer choices:

a. I cannot smell at all/smells smell less than they did before
b. Smells smell different than they did before (the quality of smell has changed)
c. I can smell things that aren't there (e.g., I smell burning when nothing is on fire)
d. Sense of smell fluctuates (e.g. comes and goes)
e. None of the above

Q12: Long response

Describe any changes in smell

Q13: Multiple choice - one answer (button)

How blocked was your nose BEFORE your recent respiratory illness or diagnosis?

Answer choices:

a. Not blocked at all
b. Mildly blocked
c. Moderately blocked
d. Completely blocked

Q14: Multiple choice - one answer (button)

How blocked was your nose DURING your recent respiratory illness or diagnosis?

Answer choices:

a. Not blocked at all
b. Mildly blocked

c. Moderately blocked
d. Completely blocked

Q15: Multiple choice - one answer (button)

Rate your ability to taste BEFORE your recent respiratory illness or diagnosis

Answer choices:

a. No sense
b. Mild sense
c. Moderate sense
d. Excellent sense

Q16: Multiple choice - one answer (button)

Rate your ability to taste DURING your recent respiratory illness or diagnosis

Answer choices:

a. No sense
b. Mild sense
c. Moderate sense
d. Excellent sense

Q17: Multiple choice - multiple answers (check)

Have you experienced changes to specific taste with your recent respiratory illness or diagnosis? (Select all that apply)

Answer choices:

a. Sweet
b. Salty
c. Sour
d. Bitter
e. Savory/umami
f. None

Q18: Long response

Describe any changes in taste during your recent respiratory illness or diagnosis.

Q19: Multiple choice - one answer (button)

Rate your ability to feel these other sensations BEFORE your recent respiratory illness or diagnosis

Answer choices:

a. Not sensitive at all
b. Mildly sensitive
c. Moderately sensitive
d. Very sensitive

Q20: Multiple choice - one answer (button)

Rate your ability to feel these other sensations DURING your recent respiratory illness or diagnosis

Answer choices:

a. Not sensitive at all
b. Mildly sensitive
c. Moderately sensitive
d. Very sensitive

Q21: Long response

Describe any changes in these other sensations during your recent respiratory illness or diagnosis

Q22: Long response

Think about a food or beverage you consume regularly - for example, your morning coffee or tea or a piece of fruit you have each day. Has the taste, smell, or flavor changed with your recent respiratory illness or diagnosis? If so, please describe how and be sure to indicate which food or beverage you are describing.

Q23: Long response

Is there anything else you would like to tell us about how your recent respiratory illness or diagnosis has affected your sense of smell, taste, and flavor?

Q24: Multiple choice - one answer (button)

Have you recovered from your recent respiratory Illness or diagnosis? (For example, you no longer have a cough, fever, or shortness of breath.)

Answer choices:

a. No
b. Yes-partly
c. Yes-fully
d. Don't know

Q25: Multiple choice - one answer (button)

Rate your ability to smell AFTER your recovery

Answer choices:

a. No sense
b. Mild sense
c. Poor sense
d. Excellent sense

Q26: Multiple choice - multiple answers (check)

How blocked was your nose AFTER your recovery.

Answer choices:

a. Not blocked at all
b. Mildly blocked
c. Moderately blocked
d. Completely blocked

Q27: Multiple choice - one answer (button)

Rate your ability to taste AFTER your recovery

Answer choices:

a. No sense
b. Mild sense
c. Moderate sense
d. Excellent sense

Q28: Multiple choice - one answer (button)

Rate your ability to feel these other sensations like burning, cooling, and tingling AFTER your recovery

Answer choices:

a. Not sensitive at all
b. Mildly sensitive
c. Moderately sensitive
d. Very sensitive

Q29: Multiple choice - one answer (button)

Thinking about today, rate your typical sensitivity to other sensations in your mouth (burning, cooling, or tingling).

Answer choices:

a. Not sensitive at all
b. Mildly sensitive

c. Moderately sensitive
d. Very sensitive

Q30: Multiple choice - one answer (button)

Have you smoked at least 100 combustible cigarettes or cigars in your entire life?

Answer choices:

a. Yes
b. No
c. Prefer not to say
d. Don't know

Q31: Multiple choice - one answer (menu)

During the past 30 days, how many days did you smoke combustible cigarettes or cigars?

Answer choices:

a. 0
b. 1
c. 2
d. 3
e. 4
f. 5
g. 6
h. 7
i. 8
j. 9
k. 10
l. 11
m. 12
n. 13
o. 14
p. 15
q. 16
r. 17
s. 18
t. 19
u. 20
v. 21
w. 22
x. 23
y. 24
z. 25
aa. 26
bb. 27
cc. 28
dd. 29
ee. 30

Q32: Multiple choice - one answer (button)

Have you ever used an e-cigarette ('vaped'/'Juuled') even one time? (E-cigarettes are battery-powered devices that usually contain liquid nicotine, and do not produce smoke.)

Answer choices:

a. No
b. Yes
c. Prefer not to say
d. Don't know

Q33: Multiple choice - one answer (menu)

During the past 30 days, on how many days did you use an e-cigarette?

Answer choices:

a. 0
b. 1
c. 2
d. 3
e. 4
f. 5
g. 6
h. 7
i. 8
j. 9
k. 10
l. 11
m. 12
n. 13
o. 14
p. 15
q. 16
r. 17
s. 18
t. 19
u. 20
v. 21
w. 22
x. 23
y. 24
z. 25
aa. 26
bb. 27
cc. 28
dd. 29
ee. 30

Q34: Multiple choice - one answer (button)

Do you cry when you cut an onion?

Answer choices:

a. Yes
b. No

Q35: Multiple choice - one answer (button)

Do you get a burning sensation when you eat chili?

Answer choices:

a. Yes
b. No

Q36: Multiple choice - one answer (button)

Do you get a tingling sensation in your mouth when you drink carbonated drinks?

Answer choices:

a. Yes
b. No

Q37: Multiple choice - one answer (button)

Do you have a cooling sensation when you use mint toothpaste?

Answer choices:

a. Yes
b. No

Q38: Multiple choice - one answer (menu)

In which year (YYYY) were you born?

Answer choices:

1901-2004

Q39: Short response

What city, town, or region do you currently live in?

Q40: Multiple choice - multiple answers (check)

Which gender do you most identify with?

Answer choices:

a. Male
b. Female
c. Another gender not listed here
d. Prefer not to respond

Q41: Multiple choice - one answer (menu)

How many years of formal education have you completed? For example, school, vocational training, university, etc.

Answer choices:

a. <8
b. 9
c. 10
d. 11
e. 12
f. 13
g. 14
h. 15
i. 16
j. 17
k. 18
l. 19
m. 20-24
n. >25

Q42: Multiple choice - one answer (button)

Which of the following best describes your socio-economic group or income-bracket?

Answer choices:

a. Upper class
b. Upper middle class
c. Lower middle class
d. lower class
e. Prefer not to respond

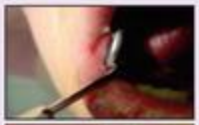
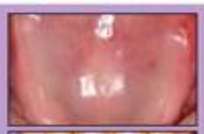
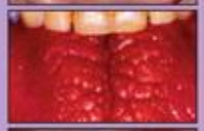
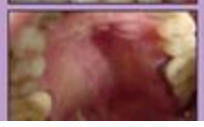
Q43: Multiple choice - one answer (menu)

How many people do you currently come into close distances (within 1.5 m or 5 feet) daily? For example, through work, public transport, etc. Do not count the members of your household.

Answer choices:

a. <5
b. 5-10
c. 11-20
d. 21-50
e. >50

Challacombe scale:

1		Mirror sticks to buccal mucosa	An additive score of 1 - 3 indicates mild dryness. May not need treatment or management. Sugar-free chewing gum for 15 mins, twice daily and attention to hydration is needed. Many drugs will cause mild dryness. Routine checkup monitoring required.
2		Mirror sticks to tongue	
3		Saliva frothy	
4		No saliva pooling in floor of mouth	An additive score of 4 - 6 indicates moderate dryness. Sugar-free chewing gum or simple sialogogues may be required. Needs to be investigated further if reasons for dryness are not clear. Saliva substitutes and topical fluoride may be helpful. Monitor at regular intervals especially for early decay and symptom change.
5		Tongue shows generalised shortened papillae (mild depapillation)	
6		Altered gingival architecture (ie. smooth)	
7		Glassy appearance of oral mucosa, especially palate	An additive score of 7 - 10 indicates severe dryness. Saliva substitutes and topical fluoride usually needed. Cause of hyposalivation needs to be ascertained and Sjögrens Syndrome excluded. Refer for investigation and diagnosis. Patients then need to be monitored for changing symptoms and signs, with possible further specialist input if worsening.
8		Tongue lobulated / fissured	
9		Cervical caries (more than two teeth)	
10		Debris on palate or sticking to teeth	

GAD-7 scale:

GAD-7

Over the last 2 weeks, how often have you been bothered by the following problems?	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it is hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3

Total Score ___ = Add Columns ___ + ___ + ___

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

PHQ-9 scale:

PATIENT HEALTH QUESTIONNAIRE (PHQ-9)

NAME:_____ **DATE:**_____

Over the last *2 weeks,* how often have you been bothered by any of the following problems?
(use "✓" to indicate your answer)

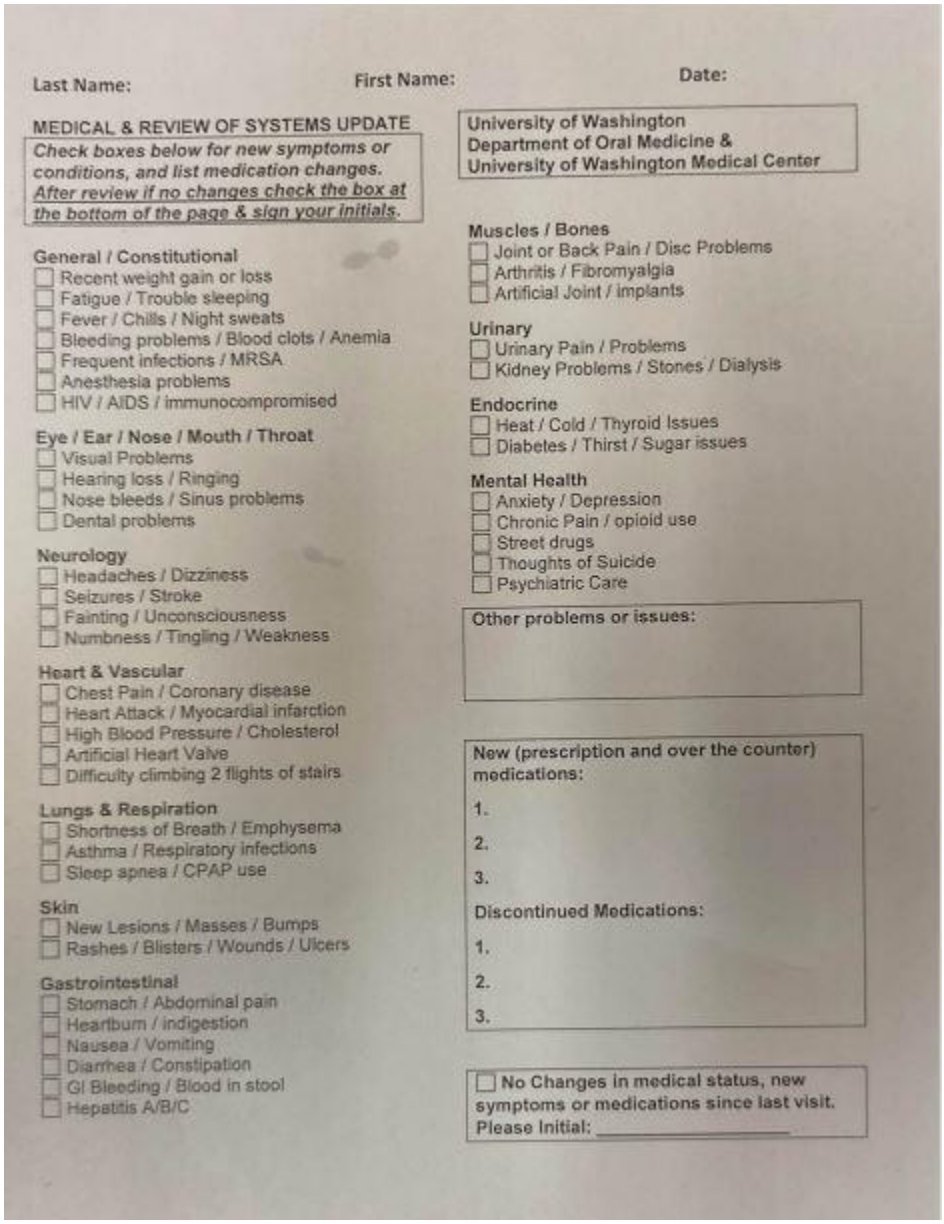
	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite — being so figety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead, or of hurting yourself	0	1	2	3
	add columns		+	+

(Healthcare professional: For interpretation of TOTAL, please refer to accompanying scoring card). TOTAL:

10. If you checked off *any problems,* how *difficult* have these problems made it for you to do your work, take care of things at home, or get along with other people?

- Not difficult at all _____
- Somewhat difficult _____
- Very difficult _____
- Extremely difficult _____

Medical review form:



Last Name: First Name: Date:

MEDICAL & REVIEW OF SYSTEMS UPDATE

Check boxes below for new symptoms or conditions, and list medication changes. After review if no changes check the box at the bottom of the page & sign your initials.

University of Washington
Department of Oral Medicine &
University of Washington Medical Center

General / Constitutional
- ☐ Recent weight gain or loss
- ☐ Fatigue / Trouble sleeping
- ☐ Fever / Chills / Night sweats
- ☐ Bleeding problems / Blood clots / Anemia
- ☐ Frequent infections / MRSA
- ☐ Anesthesia problems
- ☐ HIV / AIDS / immunocompromised

Eye / Ear / Nose / Mouth / Throat
- ☐ Visual Problems
- ☐ Hearing loss / Ringing
- ☐ Nose bleeds / Sinus problems
- ☐ Dental problems

Neurology
- ☐ Headaches / Dizziness
- ☐ Seizures / Stroke
- ☐ Fainting / Unconsciousness
- ☐ Numbness / Tingling / Weakness

Heart & Vascular
- ☐ Chest Pain / Coronary disease
- ☐ Heart Attack / Myocardial infarction
- ☐ High Blood Pressure / Cholesterol
- ☐ Artificial Heart Valve
- ☐ Difficulty climbing 2 flights of stairs

Lungs & Respiration
- ☐ Shortness of Breath / Emphysema
- ☐ Asthma / Respiratory infections
- ☐ Sleep apnea / CPAP use

Skin
- ☐ New Lesions / Masses / Bumps
- ☐ Rashes / Blisters / Wounds / Ulcers

Gastrointestinal
- ☐ Stomach / Abdominal pain
- ☐ Heartburn / indigestion
- ☐ Nausea / Vomiting
- ☐ Diarrhea / Constipation
- ☐ GI Bleeding / Blood in stool
- ☐ Hepatitis A/B/C

Muscles / Bones
- ☐ Joint or Back Pain / Disc Problems
- ☐ Arthritis / Fibromyalgia
- ☐ Artificial Joint / implants

Urinary
- ☐ Urinary Pain / Problems
- ☐ Kidney Problems / Stones / Dialysis

Endocrine
- ☐ Heat / Cold / Thyroid Issues
- ☐ Diabetes / Thirst / Sugar issues

Mental Health
- ☐ Anxiety / Depression
- ☐ Chronic Pain / opioid use
- ☐ Street drugs
- ☐ Thoughts of Suicide
- ☐ Psychiatric Care

Other problems or issues:

New (prescription and over the counter) medications:

1.

2.

3.

Discontinued Medications:

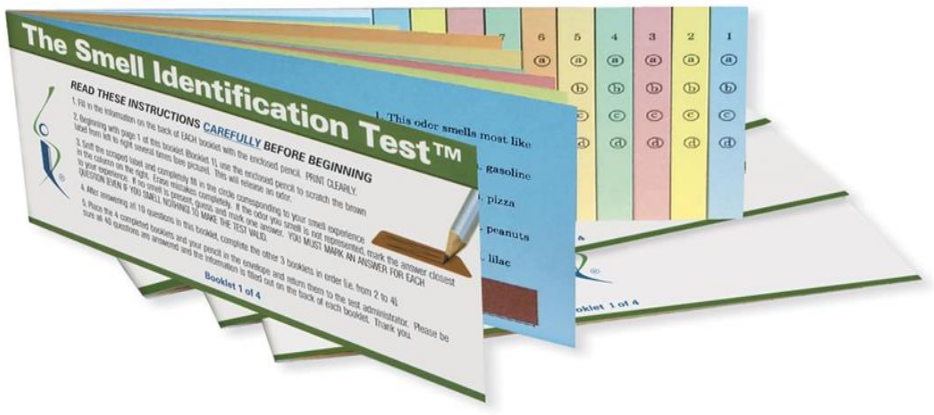
1.

2.

3.

☐ **No Changes in medical status, new symptoms or medications since last visit.**
Please Initial: _____

The 40-odorant Smell Identification Test (UPSIT) contains four booklets. Each page includes a microencapsulated odorant that is released using a pencil tip. This test, administered to approximately 200,000 patients since its development, is the most widely used olfactory test in the world (commercially known as the Smell Identification Test™). The SIT is considered the "eye chart for the nose." **(Photograph courtesy of Sensonics, Inc., Haddon Heights, NJ. Copyright 2000, Sensonics, Inc.)**



Instructions on the subject and orientation to the rating scale:

Experimenter to subject: I will ask you to use this computerized rating scale to rate how weak or strong some sensations are to you. Some of these sensations you will experience. Some of these sensations are what you recall experiencing.

This scale ranges from "no sensation" at the bottom. The scale increases to the "strongest imaginable sensation of any kind" at the top.

(Experimenter points to the bottom and draws a finger up the scale to the top)

"Any kind" means that you can use this scale to judge the strength of any experience - how sweet is the taste, how loud is the sound, or how bright is the light?

"Strongest imaginable" refers to the strength of any experience (such as loudness or brightness), even sensations that might be painful.

What is the strongest imaginable sensation to you? (sensation----------)

Now, please use this scale to rate the brightness of the light in this room. How strong or intense is the brightness

to you? Remember to use "the strongest imaginable sensation" as a reference point.

1. (FIRST TRIAL) choose the word on the scale that describes how bright. (word……)

Is the brightness you experience more than (insert word) but not (next descriptor above)? Or is the brightness you experience less than (insert word) but not (next descriptor below)? Your rating can fall anywhere on the line between (insert word) and the next descriptor. Like fine-tuning your rating.

2. (SECOND TRIAL) Please remember the brightness of a dimly lit restaurant, where the only light is from candles on the tables. Would you say the intensity of a dimly lit restaurant is less bright or brighter than the light in this room? Less bright Brighter

- Choose the word on the scale that describes the brightness of a dimly lit restaurant.

(Experimenter assesses if they pick a word descriptor that matches their assessment of less bright or brighter.)

[Note to Experimenter: if the participant chooses a word descriptor brighter for a dimly lit restaurant than it is for the examination room, then repeat the prompt for assessing a candle-lit room.]

- Fine-tune your rating.

• Please rate the strength of these recalled or remembered sensations.

[Note to Experimenter: as needed, the experimenter can re-read the instructions above to prompt the participant further.

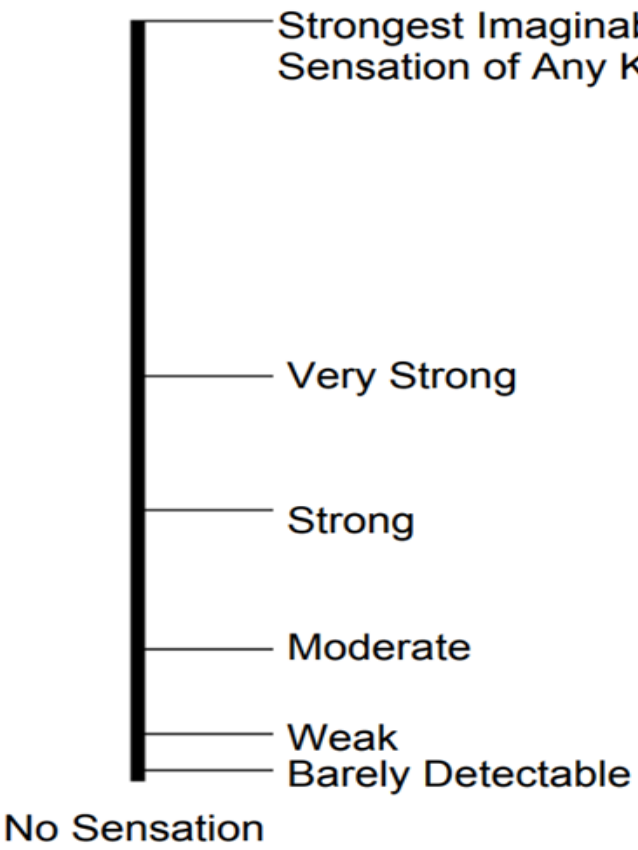
3. Brightest light you have ever seen

4. Loudness of a whisper

5. Loudness of a conversation

6. Loudest sound you have ever heard

General Labeled Magnitude Scale (gLMS):



(BARTOSHUK, L., ET AL,.2004)

The Hedonics of Capsaicin containing Food Questionnaire:

Test date _____

The Hedonics of Capsaicin Containing Foods Questionnaire

Name _____ **Ethnic Persuasion** _____
Gender _____ **Age** _____

1. Yes or No. Have you consumed any spicy foods in the previous 24 hours? _____
2. Frequency of ingestion of 'all types of chili pepper in foods including Mexican, Indian, Chinese, and other foods that contain chili pepper and cause tingling or burning' _____ (see 7 category Likert Scale below)

(7 category Likert scale)
1 = once a year or less,
2 = less than once a month,
3 = 1—3 times per month,
4 = once a week,
5 = 3—4 times a week,
6 = every day,
7 = more than once a day).

3. 'How much do you like the taste of chili pepper in your food?' (9 point hedonic scale) _____
4. 'How much do you like the burn of chili pepper in your food?' (9 point hedonic scale) _____
5. (True/False) 'I think chili pepper makes food taste better' _____
6. (True/False) 'Without hot spices, I find that food tastes too bland' _____
7. (True/False) 'I find it hard to appreciate the flavors of food when the food contains hot spices' _____

(9 point hedonic scale: 1 = dislike extremely to 9 = like extremely)

9-Point Hedonic Scale	
9	Like Extremely
8	Like Very Much
7	Like Moderately
6	Like Slightly
5	Neither Like nor Dislike
4	Dislike Slightly
3	Dislike Moderately
2	Dislike Very Much
1	Dislike Extremely

(Lawless, Rozin & Shenker et al., 1985)

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