







COVID-19: Recovery from Chemosensory Dysfunction. A Multicentre study on Smell and Taste

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Objective/Hypothesis: With the COVID-19 pandemic, chemosensory dysfunction are among the most prevalent symptoms. Most reports are subjective evaluations, which have been suggested to be unreliable. The objective is to test chemosensory dysfunction and recovery based on extensive psychophysical tests in COVID-19 during the course of the disease.

Study Design: Prospective cohort study.

Methods: A total of 111 patients from four centers participated in the study. All tested positive for SARS-COV-2 with RT-PCR. They were tested within 3 days of diagnosis and 28 to 169 days after infection. Testing included extensive olfactory testing with the Sniffin' Sticks test for threshold, discrimination and identification abilities, and with the Taste Sprays and Taste Strips for gustatory function for quasi-threshold and taste identification abilities.

Results: There was a significant difference in olfactory function during and after infection. During infection 21% were anosmic, 49% hyposmic, and 30% normosmic. After infection only 1% were anosmic, 26% hyposmic, and 73% normosmic. For gustatory function, there was a difference for all taste qualities, but significantly in sour, bitter, and total score. Twenty-six percent had gustatory dysfunction during infection and 6.5% had gustatory dysfunction after infection. Combining all tests 22% had combined olfactory and gustatory dysfunction during infection. After infection no patients had combined dysfunction.

Conclusions: Chemosensory dysfunction is very common in COVID-19, either as isolated smell or taste dysfunction or a combined dysfunction. Most people regain their chemosensory function within the first 28 days, but a quarter of the patients show persisting dysfunction, which should be referred to specialist smell and taste clinics for rehabilitation of chemosensory function.

Key Words: COVID-19 smell taste recovery psychophysical.

Level of Evidence: 3

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INTRODUCTION

The coronavirus disease of 2019 (COVID-19) pandemic in 2020 made olfactory and gustatory dysfunction known to everyone, although olfactory dysfunction is common in the general population.^{1–3} Apart from aging and chronic rhinosinusitis one of the most frequent causes is post-infectious (post-viral) olfactory dysfunction with frequency rates of 31% to 39% of patients presenting at specialized smell and taste clinics.^{4,5} Gustatory dysfunction is much less prevalent with a rate up to 5%.⁶ This all changed dramatically in early 2020 with the COVID-19 pandemic, as smell and taste dysfunction are among the most common symptoms of the disease—even in absence of other symptoms. Reported frequencies range from 0% to 98%.⁷

Most studies are based on subjective findings, and only few studies have tested the dysfunction with psychophysical tests.^{7–11} These studies mainly used self-administered tests or short and coarse screening tests of olfactory function.^{12–14} Previous studies have found self-ratings of olfactory function unreliable and inaccurate.^{15,16} For this reason, to provide us with deeper knowledge into COVID-19 detailed extensive objective tests are needed to truly access the related chemosensory dysfunction during the infection, but also to learn about recovery rates after infection. For this reason, the aim of this study was to objectively test chemosensory

dysfunction in COVID-19 patients during infection and after the infection with the Sniffin' Sticks olfactory test¹⁷ for threshold, discrimination and identification, and the Taste Strips for detailed gustatory testing with quasi-threshold and identification abilities¹⁸—to evaluate olfactory and gustatory function and recovery during the course of the disease.

MATERIALS AND METHODS

Participants

A total of 111 real-time polymerase chain reaction (RT-PCR) confirmed COVID-19 patients participated in the study. Inclusion criteria were: >18 years of age and COVID-19 positive. Exclusion criteria were: Previous sinus or nasal surgery, previously diagnosed neurological or psychiatric disorders, and previously diagnosed olfactory or gustatory dysfunction. They were recruited from four sites in Italy and Germany: Smell and Taste Clinic, Department of Otorhinolaryngology, TU Dresden, Dresden, Germany; Center for Rhinology and Allergology, Wiesbaden, Germany; Department of Otolaryngology, Head and Neck Surgery, Munich Clinic Schwabing, Academic Teaching Hospital, Ludwig-Maximilians University, Munich, Germany; and Department of Otolaryngology, University of Foggia, Foggia, Italy.

Inclusion was during the time from April 2020 to October 2020 and were studied prospectively. The group consisted of 52 females, 59 males. All patients had an RT-PCR confirmed COVID-19 infection. The participants had a mean age of 44.5 years (standard deviation 15.0) ranging from 18 to 77 years. None of the patients had previously been diagnosed with olfactory- or gustatory dysfunction.

This prospective study was conducted at various sites in accordance with the Helsinki Declaration and was approved by the ethics committee at various sites. Informed consent was obtained from all the participants.

Procedures

Testing of the participants was performed in quiet and well-ventilated rooms. All participants were told not to eat, drink, smoke, or brush their teeth up to 1 hour before participation in the test, but they could drink water.

All sites examined the participants during infection and re-tested once after the infection. Testing was done within 3 days of diagnosis of COVID-19. Retesting was performed for the sites at different time points, following the sites usual follow-up schedule: 28 days after infection (Center of Rhinology and Allergology, Wiesbaden, Germany), 45 days after infection (Department of Otolaryngology, University of Foggia, Foggia, Italy), 77 to 162 days after infection (Smell and Taste Clinic, Department of Otorhinolaryngology, TU Dresden, Dresden, Germany), and 98 to 165 days after infection (Head and Neck Surgery, Munich Clinic Schwabing, Academic Teaching Hospital, Ludwig-Maximilians University, Munich, Germany). The mean days of testing after the infection was 62.9 days (SD 45.8).

Gustatory Testing

Two methods of gustatory testing were used at various study sites, as available on site. A simple testing tool: Taste Sprays and a more detailed tool: Taste Strips. For screening of taste function the Taste Sprays were used.¹⁹ The Taste Strips were used at the Department of Otolaryngology, University of Foggia, Foggia, Italy. The Taste Sprays were used at the Head and Neck Surgery, Munich Clinic Schwabing, Academic Teaching

Hospital, Ludwig-Maximilians University, Munich, Germany and Smell and Taste Clinic, Department of Otorhinolaryngology, TU Dresden, Dresden, Germany. The taste sprays comprises sweet, sour, salty, and bitter taste qualities in concentrations above threshold: sucrose (1 g in 10 ml water), citric acid (0.5 g in 10 ml water), sodium chloride (0.75 g in 10 ml water), and quinine hydrochloride (0.005 g in 10 ml water). The different sprays are sprayed in a pseudo-randomized order on the tongue of the participant. Then a forced-choice paradigm is used by asking the participant if the spray was sweet, sour, salty, or bitter. The participants could try the sprays up to three times. Gustatory dysfunction was assumed if participants failed to correctly identify two (or more) of the four sprays. If the participants failed to identify only one of the sprays, this was not regarded as dysfunction, due to the common taste quality confusion in the general population.^{20,21} The Taste Strips (Burghart Messtechnik, Germany) is a more extensive test of gustatory function.¹⁸ The Taste Strips is a gustatory test tool validated for testing identification and quasi-threshold abilities for the four basic taste qualities of sweet, salty, bitter, and sour. The strips are presented to the participant in a pre-defined pseudo-randomized order for four different concentrations of each taste quality.¹⁸ This test provides results for gustatory thresholds and identification abilities with a maximum score of 16. A higher score corresponds to a better gustatory function. Cut-off values used in this study were for hypogeusia a score ≤ 9 and for normogeusia a score ≥ 10 . No cut-off values are available for ageusia, as this condition is extremely rare.

Olfactory Testing

For testing of olfactory function, the present study used two methods for evaluating olfactory function by Sniffin' Sticks (Burghart Messtechnik, Germany), as available on site. The Sniffin' Sticks pens are felt-tip pens, containing odors as previously described by Hummel et al.²² In the threshold and discrimination subtests participants are presented with three pens in a randomized order. In the identification test the participant identifies the correct odor by a forced multiple-choice paradigm of four written odor descriptors. For all sub-tests, a forced multiple-choice regime was used. The Sniffin' Sticks are presented in front of both nostrils with intervals of at least 30 seconds and approximately 3 seconds per individual pen. Most sites used the Sniffin' Sticks test consisting of three subtests, which provides scores for odor threshold (1–16), discrimination (0–16), and identification (0–16). The three scores are combined to a global olfactory function score consisting of threshold, discrimination and identification combined (TDI-score: 1–48). All sites except one used the TDI-test ($n = 95$). TDI-score cut-off value for anosmia (≤ 16), hyposmia (≤ 30.5), and normosmia (>30.5) were used.^{22–24} One site (Head and Neck Surgery, Munich Clinic Schwabing, Academic Teaching Hospital, Ludwig-Maximilians University, Munich, Germany) used the Sniffin' Sticks 12 Identification set (SIT-12) ($n = 16$). For this test the cut-off values for anosmia (≤ 6), hyposmia ($7 \leq \text{and} \leq 10$), and normosmia (score ≥ 11) were used in the present study.²⁵

COVID-19 Testing

All patients were confirmed positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and COVID-19 infection by laboratory testing of RT-PCR analysis from swabs of the throat and/or nasopharynx.

Statistical Analysis

The statistical analyses were conducted by means of STATA/IC 16.1 for Mac (StataCorp, TX). Means, percentage,

standard deviation, and 95% confidence intervals are detailed, when appropriate. The Fischer's exact test was used for the comparison of recovery rates according to patient characteristics. For testing differences in mean scores independent samples *t*-test was used. Alpha level of significance used was .05 for *P* values.

RESULTS

Olfactory Function

There was a significant difference in olfactory function during infection and after infection for all olfactory tests and sub-tests (see Table I).

The difference during and after infection in TDI-score in COVID-19 patients with olfactory dysfunction was a mean of 10.5 ($P < .001$). The difference in TDI-score in COVID-19 patients without olfactory dysfunction was 0.12 during and after infection ($P = .9$). In patients with olfactory dysfunction there was a decline in function in all of the subtests (threshold, discrimination, and identification) almost equally ranging from a mean of 3.1 in threshold score, to a mean of 3.69 in discrimination score, and to a mean of 3.75 in identification score.

For the patients from the site that used SIT-12 for testing the score was a mean of 8.2 during infection and 11.1 after infection ($P = .01$) (see Table I).

During infection 21% ($n = 23$) were anosmic, 49% ($n = 56$) hyposmic, and 30% ($n = 31$) normosmic. After infection only 1% ($n = 1$) were anosmic, 25% ($n = 23$) hyposmic, and 74% ($n = 69$) normosmic. The difference was significant (Fisher's exact, $P = .003$). See Table II for more details.

Out of the 23 anosmics during infection, one was still anosmic after infection, four hyposmic, and 18 normosmic. Out of the 44 hyposmics (during infection), after infection

none were anosmic, 17 still hyposmic, and 27 normosmic. Out of the 26 normosmics during infection, two were hyposmic after infection and 24 were still normosmic. See Figure 1 for more details.

Eleven patients were lost to follow-up with the TDI test (N changed from 94 to 83). Six patients were lost to follow-up with the SIT-12 test (N changed from 16 to 10).

Gustatory Function

For extensive testing of gustatory function with the Taste Strips there was also a difference during and after infection for all taste qualities, but especially for sour, bitter, and total score, which was statistically significant (see Table III). For gustatory screening with the Taste Sprays, there were no statistically significant differences in function during ($n = 46$) and after infection ($n = 27$) with a mean of 2.73 and 2.88, respectively ($P = .11$). However, when combining both gustatory test methods, there were 16 patients (26%) with gustatory dysfunction during infection and 45 with normal function. After infection only two (6.5%) had gustatory dysfunction and 29 had normal gustatory function.

Based on the Taste Strips, eight patients had hypogeusia and seven had normogeusia during COVID-19 infection. Unfortunately, seven patients were lost to follow-up. After the infection no patients had hypogeusia and eight had normal gustatory function. Out of these eight patients, three had hypogeusia during infection and five had normal gustatory function during infection.

When combining both taste tests 12 patients (22%) had combined olfactory- and gustatory dysfunction during infection (out of 16 patients with gustatory dysfunction). After infection none of the followed-up patients had

TABLE I.
Olfactory Function of the Study Population During and After COVID-19.

	Olfactory Function During COVID-19 Mean (SD) [95% CI]	Olfactory Function After COVID-19 Mean (SD) [95% CI]	<i>P</i> Value
Threshold (1-16)	6.5 (3.8) [5.7, 7.2] ($n = 95$)	8.5 (3.6) [7.8, 9.2] ($n = 84$)	<.001*
Discrimination (0-16)	9.3 (3.4) [8.6, 10.0] ($n = 94$)	11.9 (2.3) [11.4, 12.4] ($n = 83$)	<.001*
Identification (SIT-16) (0-16)	9.7 (4.0) [8.8, 10.5] ($n = 95$)	12.3 (2.6) [11.7, 12.8] ($n = 83$)	<.001*
TDI (1-48) ($n = 94$)	25.2 (9.0) [23.4, 27.0] ($n = 94$)	32.7 (6.9) [31.2, 34.2] ($n = 83$)	<.001*
SIT-12 (0-12)	8.2 (2.7) [6.3, 10.1] ($n = 16$)	11.1 (1.3) [10.2, 12.0] ($n = 10$)	.01*

*Statistically significant.

CI = confidence interval; SD = standard deviation; TDI = threshold, discrimination, and identification; SIT = Sniffin' Sticks identification test.

TABLE II.
Olfactory Function According to the Number of Patients with Anosmia, Hyposmia, and Normosmia During and After Infection with COVID-19.

		Olfactory Function After Infection			Total During Infection	<i>P</i> Value
		Anosmia	Hyposmia	Normosmia		
Olfactory function during infection	Anosmia	1	4	18	23	0.003
	Hyposmia	0	17	25		
	Normosmia	0	2	26		
	Total after infection	1	23	69		

The *P* value is calculated with Fisher's exact test.

Olfactory function during infection (N=110) Olfactory function after infection (N=93)

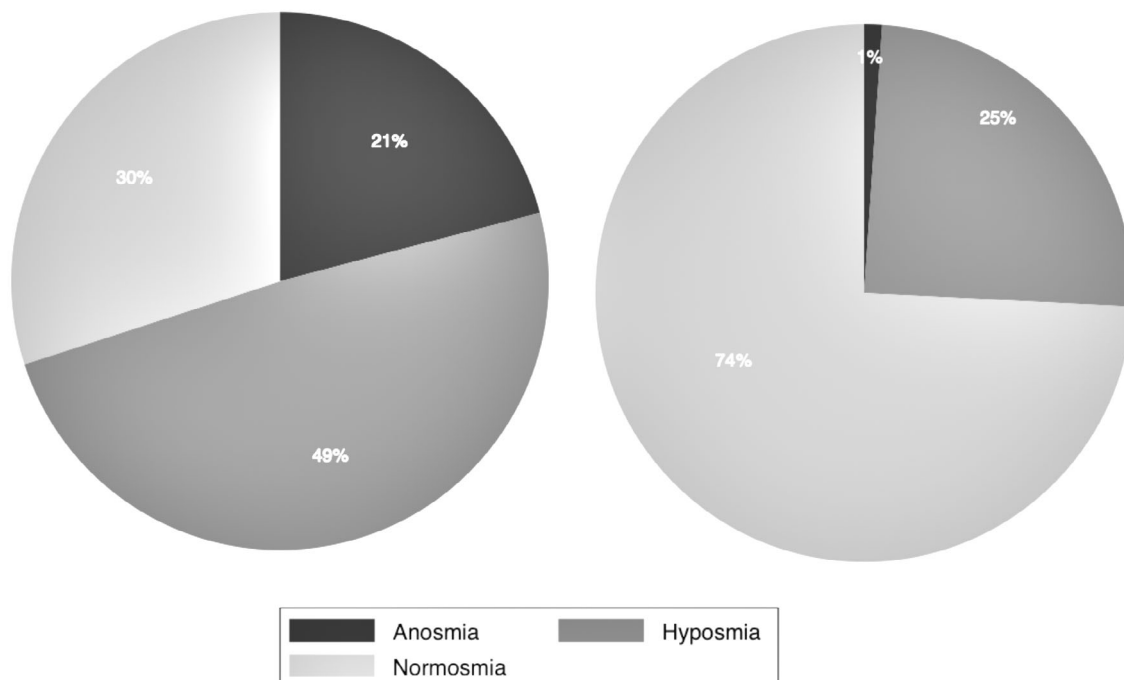


Fig. 1. Olfactory function of the pooled study population during and after COVID-19 infection in percent. The mean days of testing after infection was 62.9 days (SD 45.8).

TABLE III.

Gustatory Function of the Study Population During and After COVID-19 Obtained with the Taste Strips Gustatory Test.

	Gustatory Function During COVID-19 Mean (SD) [95% CI] n = 15	Gustatory Function After COVID-19 Mean (SD) [95% CI] n = 8	P Value
Sweet	2.9 (0.8) [2.4, 3.4]	3.6 (0.5) [3.2, 4.1]	.056
Salty	2.7 (0.8) [2.2, 3.1]	3.4 (0.7) [2.8, 4.0]	.054
Sour	2.0 (0.7) [1.6, 2.4]	2.6 (0.7) [2.0, 3.2]	.049*
Bitter	2.1 (1.1) [1.5, 2.7]	3.0 (0.5) [2.6, 3.4]	.043*
Total score	9.7 (2.7) [8.2, 11.2]	12.5 (1.5) [11.2, 13.8]	.01*

*Statistically significant.

CI = confidence interval; SD = standard deviation.

combined dysfunction. Out of the 15 patients that were tested with extended gustatory and olfactory methods 53% (n = 8) had a combined olfactory and gustatory dysfunction during infection. After infection, none of the followed-up patients had combined olfactory and gustatory dysfunction.

Nineteen participants were not retested with the Taste Sprays (N changed from 46 to 27). Seven Participants were not retested with the Taste Strips (N changed from 15 to 8).

Effect of Age and Sex

No statistically significant differences were found between men and women for any of the chemosensory

function during (N = 111 for olfactory function; N = 61 for gustatory function) or after infection (N = 93 for olfactory function; N = 35 for gustatory function) or for the rate of recovery for any of the tests and sub-tests.

The effect of age between groups of ages 18 to 39 (N = 45), 40 to 69 (N = 61), and 70+ (N = 5) years old produced no statistically significant differences between the groups in terms of any of the chemosensory functions during or after infection or for the rate of recovery for any of the tests and sub-tests.

Effect of Time on Olfactory Recovery

For the population tested after 28 days (N = 46; Weisbaden, Germany), one patient was anosmic, seven patients were hyposmic, and 38 patients were normosmic. After 45 days (N = 14; Foggia, Italy) no patients were anosmic, 10 patients hyposmic, and four normosmic. After 75–169 days (N = 33; Dresden, Germany and Munich, Germany) no patients were anosmic, 6 were hyposmic, and the rest normosmic (27 patients).

DISCUSSION

The pandemic of SARS-CoV-2 has spread to virtually every country in the world. To date, almost 38 million patients have been affected by COVID-19, and more than one million have lost their lives.²⁶ Various symptoms have been described for the disease, and it has been

established (mainly by subjective reports) that smell, and taste is affected by the disease—even mono-symptomatically. To our knowledge, this is the first study to objectively test chemosensory dysfunction in COVID-19 patients during infection and after infection with extensive testing of olfactory function for threshold, discrimination, and identification abilities. The prevalence of COVID-19-associated olfactory dysfunction ranges in the literature from 0% to 98%.⁷ Most of these reports are based on subjective ratings of olfactory function where the proportion ranges from 0% to 93%.⁷ Of note, patients have previously been shown to poorly account subjectively for chemosensory dysfunction—even before COVID-19.^{15,16} This makes it crucial to include psychophysical testing in studies of chemosensory function in relation to COVID-19. Based on a meta-analysis, the few objective studies to investigate olfactory function found proportions from 41% to 98%.⁷ The meta-analysis of subjective and objective reports of olfactory dysfunction found a combined proportion of 69% (95% CI: 61%–77%).⁷ This is in line with the current study that found olfactory dysfunction in 72% of patients during infection. We observed that olfactory dysfunction persisted in 27% during our follow-up period ranging from 28 to 169 days when combining the data from different sites. When only looking at patients re-tested from day 75 to 169 the prevalence of olfactory dysfunction was still 20.5%. This is higher than previously reported by Vaira et al., which only found olfactory dysfunction in 7.2% after 60 days.²⁷ However, it also has to be kept in mind, when assessing results from studies (including this) on hyposmia that hyposmia is frequent in the general population, ranging from 13.3% to 18%.^{1–3} This might over-estimate the prevalence of olfactory dysfunction in studies like this, if not taken into account. If we subtract the prevalence from the general population, then the persisting olfactory dysfunction would be closer to 11% in this study, which would be consistent with the finding of 7.2% by Vaira et al.²⁷ However, the patients in the present study is generally younger, and thus the background prevalence is lower, as age is one of the primary indicators of hyposmia in the general population.¹⁷ Adding to this, most of the participants noticed a sudden change in olfactory function, which might not have been noticed, were they previously hyposmic or anosmic. All in all this might indicate that the true prevalence could be the one without subtracting the prevalence of hyposmia in the general population, but the point should be taken into account by the reader when interpreting findings of studies of olfactory dysfunction. Most of our participants with persistent dysfunction only had hyposmia, while only a single patient persisted with functional anosmia (which was measured at day 28). Peculiarly, two patients (normosmic during infection) showed hyposmia after infection. None of the other patients exhibited a deteriorating olfactory function.

When looking at gustatory dysfunction, most regained their sense of taste, and only four patients still had hypogeusia at follow-up. No patients had combined gustatory- and olfactory dysfunction at follow-up. It may be speculated that the transient character of taste dysfunction was due to a missing interaction between taste and smell on a central nervous level, which relatively quickly resolved during the course of the disorder.^{28–30}

Most of the other objective studies mainly used a self-administered home-test kit.^{12,31} A few studies have used (previously) validated tools for testing olfactory function, but these studies have only applied the Sniffin' Sticks identification set with 12 or 16 odors^{14,32}—these test kits are commonly meant for the screening of olfactory dysfunction. A major advantage of the present study is the extensive evaluation of olfactory function in terms of threshold, discrimination, and identification abilities. The limitations of the study are that the number of participants for detailed gustatory function is quite limited, however, this is supplemented in the present study with more participants tested with the Taste Sprays. The study had a low dropout of 11 patients olfactory tested with the TDI and six with the SIT-12. It could be speculated that the participants did not show up for the follow-up due to the problem no longer being present, however, the patients were not contacted as to why they did not show up. There were 19 participants that were not re-tested at follow-up with the Taste Sprays, however, most of these 19 participants (except two) had a normal function at first test. Although the present study only used a single follow-up for each participant, and it should be interesting to see several follow-ups, however, as different sites used follow-up times varying from 28 to 169 days, this does give an overview of the chemosensory function at various timepoints after infection.

CONCLUSION

In conclusion, our results seem to indicate that most people with COVID-associated chemosensory dysfunction regain smell and taste within the first 28 days, which is in line with previous studies. However, up to a quarter of the patients seems to exhibit a longer-lasting dysfunction—higher than previously expected.²⁷ These patients should be referred to specialist smell and taste clinics for the rehabilitation of chemosensory function.³³

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AUTHOR CONTRIBUTIONS

A.N. drafted the article. C.H., J.D., C.H., L.K., E.T., S.B., T.H., S.L., and A.A. collected the data. A.N. and T.H. analyzed the data. All authors revised the article critically for intellectual content and approved the final version of the manuscript.

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