Taste dysfunction after COVID-19: Analysis with functional near-infrared spectroscopy

Karolina Jezierska1ABCDE, Danuta Lietz-Kijak1DE, Helena Gronwald1DE, Barbara Oleksy1E, Barbara Janina Gronwald1E, Wojciech Podraza1ABCDE

1Pomeranian Medical University, Department of Medical Physics, Szczecin, Poland
2Pomeranian Medical University, Department of Propaedeutics, Physical Diagnostics and Dental Physiotherapy, Szczecin, Poland
3Paediatric Neurology Clinic, Institute of Mother and Child in Warsaw, Poland
4Doctoral Study at the Department of Propaedeutics, Physical Diagnostics and Dental Physiotherapy, Szczecin, Poland
5Pomeranian Medical University, Department of Medical Physics, Szczecin, Poland

ABSTRACT:

Introduction: According to official data, COVID-19 emerged in China in December 2019 and has spread worldwide since then.

Aim: The aim of this study was to investigate differences in functional near-infrared spectroscopy (fNIRS) recordings between convalescent COVID-19 patients and a healthy control group, which could help to clarify the pathomechanism of dysgeusia in COVID-19.

Material and methods: The study included 16 participants, comprised of 8 convalescent COVID-19 patients and 8 healthy controls. All participants were examined with fNIRS. The amplitude of changes in oxyhemoglobin (oxyHb) concentration in the cerebral cortex was analyzed statistically (for the test and control groups after stimulation with a taste stimulus – citric acid solution).

Results: The differences in the amplitude of changes in oxyHb concentration in the cerebral cortex were not statistically significant between the groups.

Discussion: Using fNIRS, a strong stimulation of the visual cortex was discovered in response to the taste stimulus, consisting of large, repetitive changes in oxyHb concentration occurring in parallel with stimulation of areas of the taste cortex. This phenomenon has not, to our knowledge, been described previously in the scientific literature. The exact location of the primary taste cortex is controversial, but to date the occipital cortex has not been considered to be involved.

Conclusions: No difference was observed in the dynamics of changes in oxyHb in the examined areas of the cerebral cortex between convalescent COVID-19 patients and healthy controls. However, the determination of the role of the occipital cortex in the perception of taste requires further research.

KEYWORDS: brain cortex, COVID-19, functional near-infrared spectroscopy, taste

ABBREVIATIONS

ACE2 – angiotensin-converting enzyme 2
fNIRS – functional near-infrared spectroscopy
oxyHb – oxyhemoglobin

INTRODUCTION

According to official data, COVID-19, an acute respiratory disease caused by the novel SARS-CoV-2 coronavirus, emerged in China in December 2019 and has since spread worldwide [1–4]. The situation became so serious that on March 11, 2020, the World Health Organization officially announced the COVID-19 pandemic. COVID-19 now occurs worldwide, causing loss of health and life for many people [2, 3].

Severe pneumonia was the main symptom of the first COVID-19 cases that caught the attention of physicians. However, the available observations indicate that the disease may take different courses in individual patients and that the percentage of people who have a completely asymptomatic form of the disease is still unknown. The most frequently reported clinical symptoms include cough, fever, sore throat, upper respiratory rhinitis, overall fatigue, and gastrointestinal symptoms [1, 3–6]. Smell and taste dysfunctions are relatively common and characteristic symptoms of COVID-19 [2, 7–16].

The aim of this study was to investigate differences in functional near-infrared spectroscopy (fNIRS) recordings between convalescent COVID-19 patients and a healthy control group, which could help to clarify the pathomechanism of dysgeusia in COVID-19.

MATERIALS AND METHODS

The study included 16 right-handed participants (8 women and 8 men), comprised of 8 convalescent COVID-19 patients (test group) and 8 healthy controls. The mean age was 40 years (18–61).
COVID-19 diagnosis was based on PCR assay (n = 6) or clinical symptoms (n = 2). All patients presented with typical COVID-19 symptoms: loss of taste and smell, cough, shortness of breath, fever, muscle pain, fatigue, and gastrointestinal symptoms. In the control group, taste dysfunctions lasted an average of 9 days (2–25) and occurred in all but 1 person. Examinations were performed an average of 58 days after the diagnosis of SARS-CoV-2 infection. All tests were approved by the Bioethics Committee of the Pomeranian Medical University in Szczecin, Poland (KB-0012/77/18). The participants were informed about the purpose and the course of the study and provided their written consent.

All participants were examined with fNIRS using a NIRScout instrument (NIRx Medical Technologies LLC, Glen Head, NY, USA). The light emitted by 16 LED sources (wavelengths 760 nm and 850 nm) was captured by 16 detectors located approximately 3 cm from the emitter. The location of emitters, detectors, and channels (blue lines between the detectors and emitters) is shown in Fig. 1. This setting covered the entire left hemisphere of the brain. All measurements were recorded with NIRStar 15.0 software, using a 0.2 Hz low-pass filter. The signal intensity was calibrated and verified for each channel before data collection.

After a preliminary visual analysis, the highest signals were recorded for two groups of channels: channels 14, 21, 28, 29, and 30, and channels 45, 46, 47, 48, and 49. The first group corresponds to the location of the cortical taste center, covering Brodmann area 43, the subcentral area, the postcentral gyrus, and the inferior frontal gyrus, including the pars opercularis, pars triangularis, and pars orbitalis. The second group (45, 46, 47, 48, and 49) is comprised of occipital channels covering the visual cortex, including part of the primary visual cortex (striate cortex or Brodmann area 17), the secondary visual cortex (Brodmann area 18), and the tertiary visual cortex (Brodmann area 19). The optodes were located with the use of fOLD v2.2 software [17].

Mean values were calculated for each group of channels across five replications and the amplitude of changes in oxyhemoglobin (oxyHb) concentration in the cerebral cortex after stimulation with a taste stimulus (citric acid solution) was analyzed statistically. The same methods were applied for each group of participants (test and control) and each protocol. Two protocols were used: a “rest” protocol and a “taste” protocol. In the rest protocol, the participants remained at rest with their eyes open in a darkened room during the entire examination. The study was carried out according to the scheme below, which shows the relevant timepoints for data analysis:

\[ \text{rest 5 s} \rightarrow 5 \times \text{rest 40 s} \rightarrow \text{rest 20 s} \]

In the taste protocol, 0.5 mL of a 1% citric acid solution was pipetted directly into the participant’s oral cavity, as shown in the scheme below. A period of 10 seconds was arbitrarily used as the duration of the taste stimulus.

\[ \text{rest 5 s} \rightarrow 5 \times \text{stimulus 10 s} \rightarrow \text{rest 40 s} \rightarrow \text{rest 20 s} \]

All data were analyzed with NIRSLab 15.0 software, which is based on MATLAB. A bandpass filter with an upper frequency limit of 0.2 Hz and a lower frequency limit of 0.01 Hz was used for all recordings. The absorption spectra of oxyHb and deoxyhemoglobin (deoxyHb) were used for the analysis and data transformations, according to the software manufacturer’s recommendations.

The main aim of the study was to determine whether there is a difference in the oxyHb signal amplitude (the difference between the maximum and minimum oxyHb concentration; ΔoxyHb) between healthy controls and convalescent COVID-19 patients. Another aim was to identify the location of these changes.

To assess the influence of COVID-19 on ΔoxyHb in the cerebral cortex, the results of examinations for the control group and the test group were compared, both at rest and after the administration of citric acid. To assess the effect of the taste stimulus on ΔoxyHb, the recordings from the “rest” measurements were compared with those from the “taste” measurements for both the control and test groups. After the initial analysis, the two groups of channels (i.e. the areas of the taste cortex and visual cortex) were additionally compared.

The distribution of data was verified with the Shapiro–Wilk test. For normally distributed data, Student’s t-test was used; otherwise, the Mann–Whitney U test was applied. Dell Statistica version 13 (Dell Inc., 2016) was used for the statistical analysis. Differences were considered statistically significant for p-values of <0.05.

RESULTS

The maximum and minimum values of oxyHb (ΔoxyHb [μmol/L]) for the control and test groups for both the rest and taste protocols are presented in Tab. I., and the statistical comparison of the control and test groups for each protocol is presented in Tab. II.–III.
presents the statistical comparison of ΔoxyHb between the taste cortex and the visual cortex during simultaneous measurements.

**DISCUSSION**

Many studies on the clinical aspects of COVID-19 describe smell and taste dysfunctions [2, 7–16], lasting from 7 days to 2 months [2, 8, 9, 18, 19]. The pathomechanism of these dysfunctions has not yet been fully elucidated and is the subject of many studies. Potential causes of taste impairment in COVID-19 include decreased sialic acid concentration in the saliva [20], retronasal olfactory dysfunction, high angiotensin-converting enzyme 2 (ACE2) expression on the oral cavity mucosa and epithelial cells of the tongue [2, 21, 22], interleukin-6 level [9], or changes in the expression of bitter taste receptor TAS2R38 [23–26]. The lack of a statistically significant difference in the response of specific cerebral cortex sites (measured as a change in oxyHb concentration in response to taste stimulation) between the control group and convalescent COVID-19 patients was not surprising. The measurement was performed more than 4 weeks after the onset of COVID-19 in each convalescent patient. All convalescent patients declared having taste sensation at the time of the study, although in 2 patients it was slightly less intense than normal. In these 2 participants, fNIRS did not show any characteristic aberrations in changes in oxyHb or deoxyHb. This is in line with multicenter data that confirm the return of taste within 28 days of COVID-19 infection [18]. Other studies indicate an average of 2 weeks of ageusia, although this can extend up to 2 months in individual cases [2, 8, 9, 19]. We were not able to test patients with active COVID-19 during the period in which they had a loss of taste. The results of our study seem to support the conclusions of other authors about the transient nature of taste damage in COVID-19.

Due to the limited number of optodes available in our instrument (16 emitters and 16 detectors), we decided to study only one; however, this covered the entire cerebral left hemisphere, including all external Brodmann areas. As a result of this procedure, we accidentally made a discovery which, to the best of our knowledge, has not been described in the literature so far. We found strong signals (i.e., changes in oxyHb and deoxyHb concentrations), not only in the taste cortex, but also in the occipital area of the cerebral cortex, corresponding to Brodmann areas 17, 18, and 19 (channels 45, 46, 47, 48, and 49).

When the neurons of the cerebral cortex are stimulated in a specific location, oxygen demand and consumption increase. This causes an increase in local cerebral blood flow, resulting in a higher level of oxyHb and a lower level of deoxyHb. This phenomenon is described as a hemodynamic response, neurovascular coupling, or...
rapidly and simultaneously with the first oxyHb peak, differing from the classic hemodynamic response. This seems to be related to the sudden, rapid inflow of blood in the area under analysis. These changes are several times greater under the influence of the taste stimulus than at rest, when these changes are Mayer wave-related [30]. The difference between oxyHb changes at rest and in response to the taste stimulus was statistically significant (Fig. 4–5.). The ΔoxyHb signal in the visual cortex in response to the taste stimulus, of which this is the first report, was very strong, with no statistical difference between this signal and the signal in the “traditional” taste area. This appears to “functional hyperemia”, and can be quantified using fNIRS [27–29]. The hemodynamic response to the taste stimulus is varied. In the taste areas of the cortex, we always observed a two-peak response: a sharp first peak and a milder second peak (Fig. 2.). The amplitude (ΔoxyHb) of the first peak was slightly higher than that of the second. The response did not always have two peaks in the occipital areas; however, when it did, the amplitude of the first peak was always noticeably higher than that of the second (Fig. 3.). ΔoxyHb was always higher than ΔdeoxyHb. Attention should be paid to the very characteristic changes in deoxyHb, which also increased rapidly and simultaneously with the first oxyHb peak, differing from the classic hemodynamic response. This seems to be related to the sudden, rapid inflow of blood in the area under analysis. These changes are several times greater under the influence of the taste stimulus than at rest, when these changes are Mayer wave-related [30]. The difference between oxyHb changes at rest and in response to the taste stimulus was statistically significant (Fig. 4–5.). The ΔoxyHb signal in the visual cortex in response to the taste stimulus, of which this is the first report, was very strong, with no statistical difference between this signal and the signal in the “traditional” taste area. This appears to

<table>
<thead>
<tr>
<th>Channel 46 (s15–d15)</th>
<th>OxyHb &amp; DeoxyHb</th>
<th>10^2</th>
<th>Fig. 4. Example of oxyhemoglobin changes under the influence of the taste stimulus.</th>
<th>Fig. 5. Example of oxyhemoglobin changes at rest, which are Mayer wave-related.</th>
</tr>
</thead>
</table>

### Tab. I. Statistical data on oxyhemoglobin amplitude (ΔoxyHb [μmol/L]) in the control and test groups for the “rest” and “taste” protocols, for channels 14, 21, 28, 29, and 30 and for channels 45, 46, 47, 48, and 49.  

<table>
<thead>
<tr>
<th>ΔOXYHB [μMOL/L]</th>
<th>Normal distribution</th>
<th>Mean or median*</th>
<th>Standard deviation or 25th/75th percentiles*</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>Rest 14, 21, 28, 29, 30 Yes</td>
<td>0.220</td>
<td>0.077</td>
<td>0.105</td>
<td>0.331</td>
</tr>
<tr>
<td>Taste 14, 21, 28, 29, 30 No</td>
<td>1.073*</td>
<td>0.968/1.918*</td>
<td>0.822</td>
<td>4.318</td>
<td></td>
</tr>
<tr>
<td>Rest 45, 46, 47, 48, 49 Yes</td>
<td>0.223</td>
<td>0.098</td>
<td>0.119</td>
<td>0.363</td>
<td></td>
</tr>
<tr>
<td>Taste 45, 46, 47, 48, 49 No</td>
<td>1.084*</td>
<td>0.895/3.605*</td>
<td>0.527</td>
<td>8.536</td>
<td></td>
</tr>
<tr>
<td>Test group</td>
<td>Rest 14, 21, 28, 29, 30 Yes</td>
<td>0.182</td>
<td>0.078</td>
<td>0.063</td>
<td>0.286</td>
</tr>
<tr>
<td>Taste 14, 21, 28, 29, 30 Yes</td>
<td>1.299</td>
<td>0.626</td>
<td>0.338</td>
<td>2.286</td>
<td></td>
</tr>
<tr>
<td>Rest 45, 46, 47, 48, 49 Yes</td>
<td>0.309</td>
<td>0.200</td>
<td>0.057</td>
<td>0.089</td>
<td></td>
</tr>
<tr>
<td>Taste 45, 46, 47, 48, 49 Yes</td>
<td>1.429</td>
<td>1.106</td>
<td>0.391</td>
<td>3.779</td>
<td></td>
</tr>
</tbody>
</table>
be the primary, direct response of this part of the visual cortex to the taste stimulus. Previous studies on taste using fNIRS [31–35], fMRI [36–39], or PET [39] did not focus on the occipital cortex. The exact location of the primary taste cortex is controversial [40], but to date the occipital cortex has not been considered to be involved.

The small sample should be indicated as a limitation of the research.

**CONCLUSIONS**

1. We observed no difference in the dynamics of changes in oxyHb in the examined areas of the cerebral cortex between convalescent COVID-19 patients and healthy controls.

2. Using fNIRS, we discovered a strong stimulation of the visual cortex in response to the taste stimulus, consisting of large, repetitive changes in oxyHb concentration and occurring in parallel with stimulation of areas of the taste cortex. This phenomenon has not, to our knowledge, yet been described in the scientific literature.

**DATA AVAILABILITY STATEMENT**

The datasets for this study can be found in the [HARVARD DAT-AVERSE] [https://doi.org/10.7910/DVN/VAEBXJ].

<table>
<thead>
<tr>
<th>CHANNELS</th>
<th>P-VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest, control group vs. rest test group</td>
<td>0.340</td>
</tr>
<tr>
<td>Taste, control group vs. taste test group</td>
<td>0.292</td>
</tr>
<tr>
<td>Rest, control group vs. taste control group</td>
<td>0.001</td>
</tr>
<tr>
<td>Rest, test group vs. taste test group</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**REFERENCES**


