The Pitfalls and Perspectives of Assessing Olfactory Function via Optical Brain Imaging

Systematic Review

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Abstract

Olfaction is critical for maintaining daily life activities. It is crucial to measure olfactory performance for the diagnosis and treatment of certain neurodegenerative diseases. Moreover, impairments and a lack of quality in the olfactory system may indicate the early diagnosis of some diseases such as Parkinson's. In this context, there are several imaging methods available for evaluating olfactory function. In addition to the conventional methods used in measuring the brain's responsiveness to olfactory stimuli, this article presents a systematic review of the current applicability of optical brain imaging (i.e., functional near-infrared spectroscopy) in the evaluation of olfactory function. A database literature search was conducted in PubMed, Scopus, the Web of Science, and ScienceDirect. This review excluded animal studies, clinical studies, pathology- or neurodegenerative disease-related studies, newborn-related studies, cross-modal- and dual-task-related studies, and non-original research studies. Thus, seven studies were examined to discuss the pitfalls and perspectives of the use of optical brain imaging under olfactory stimulation. As for this conclusion, they can be used to evaluate olfactory performance in healthy individuals through the interpretation of hemodynamic changes. Further studies are needed to standardize the applicability of these optical imaging techniques.

Keywords: Near-infrared spectroscopy, olfaction, prefrontal cortex, hemodynamic brain response

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Cite this article as: *Akın Öztürk G, Ermiş G, Eskicioğlu E, Güdücü Ç. The Pitfalls and Perspectives of Assessing Olfactory Function via Optical Brain Imaging. Turk Arch Otorhinolaryngol 2023; 61(1): 37-42*

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Received Date: 18.01.2023
Accepted Date: 02.03.2023

DOI: 10.4274/tao.2023.2023-1-6

Introduction

Optical imaging technologies have gained a key role in the field of brain research in the last decade. These technologies involve non-invasive vascular-based neuroimaging methods such as functional near infrared spectroscopy (fNIRS) or near infrared spectroscopy (NIRS), and functional magnetic resonance imaging (fMRI). The basis of these methods is to map the changes in blood flow and blood hemoglobin changes in activated cortical regions (1, 2). When a particular cortical region is activated, cerebral blood flow transiently increases. The concentrations of oxyhemoglobin (Oxy-Hb), deoxyhemoglobin (HbR), or the summed total hemoglobin (HbT) in the activated region can be indicative of the changes in blood flow (3). This condition is related to neuronal activity at the cortical capillary level over the scalp and can be measured with fNIRS and NIRS (4, 5). fNIRS is an effective and reliable imaging method for examining the relationship between hemodynamic changes and neural activity, providing consistent and parallel results with other hemodynamic imaging techniques such as fMRI and positron emission tomography (PET) (5, 6). Research with the fNIRS method has expanded rapidly as the fNIRS system has some advantages (compared to fMRI), such as relatively high temporal resolution, portability, and insensitivity to electrical or magnetic devices (e.g., hearing aids, pacemakers, or cochlear implants) (7, 8).

In the last decade, with the development of its technology, the fNIRS method was used by multiple disciplines in various experimental designs to investigate cognitive functions as well as sensory systems under different conditions (4, 9). In addition to these studies, fNIRS was used in studies evaluating olfactory performance. Olfaction is one of the crucial perceptions for humans to avoid spoiled food or gas leaks and adds to the awareness of personal hygiene and provides the ability to enjoy the taste of food and beverages (10, 11). Impairment in the sense of smell has been associated with eating disorders (overeating or avoiding food), decreased quality of life, developing moderate to severe depression and resulting anxiety problems, social isolation, physical health problems, and increased mortality rate (12, 13). Olfactory dysfunction can occur due to various clinical reasons such as chronic sinusitis, viruses, nasal polyps, intranasal tumors, allergic rhinitis, pathological or congenital conditions (hypogonadotropic hypogonadism known as Kallmann syndrome) or presbyosmia (2, 11, 14). Idiopathic loss of smell can be a precursor symptom of Parkinson's disease. Patients with idiopathic olfactory loss have a high rate of getting Parkinson's disease in the following decade (10, 15).

An early diagnosis of olfactory dysfunction helps with successful treatment and opens the door to identifying the neurodegenerative disease before motor symptoms occur (16). Given the importance of olfaction, routine clinical evaluation of olfactory performance is essential. In clinical evaluation, MRI, fMRI, electroencephalography (EEG), and computed tomography are used to identify the structural and functional changes of the brain and to determine the etiology of olfactory disorders (16). In recent years, fNIRS/NIRS has become an alternative imaging technique for assessing olfactory performance. Despite the limited number of studies, optical imaging can offer promising techniques as they offer rapid evaluation of blood flow changes in the prefrontal cortex (PFC), and Oxy-Hb, HbR, and HbT parameters can be used to assess olfactory performance in healthy individuals and in patient groups (3).

With the aforementioned information, a question has arisen in recent years: can fNIRS be used as a reliable neuroimaging method to track olfactory changes? There are limited number of studies in the literature that have already shown that fNIRS is a useful technique in the evaluation of olfactory performance. In this review, we attempted to elucidate the current and potential applications of fNIRS and NIRS in olfaction-related studies.

Methods

Search Strategy and Resources

A systematic literature search in four databases (PubMed, Scopus, Web of Science, and ScienceDirect) was conducted in June 2022. All relevant studies using fNIRS/NIRS techniques for monitoring hemodynamic activity to assess olfactory performance are reviewed. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram was used to choose articles. The following terms were used to search the three databases:

- NIR OR fNIRS OR "functional near-infrared spectroscopy" OR "near-infrared spectroscopy" OR "functional near-infrared spectroscopic" OR "optical imaging system".

- Olfaction OR smell OR olfactory perception OR sense of smell.

Inclusion and Exclusion Criteria

The relevant studies were selected for the PICOS [Participant(s), Intervention(s), Comparison(s), Outcome(s), and Study design] principle (17). The studies written in English and involving healthy subjects to measure hemodynamics with fNIRS/NIRS were included. The exclusion criteria were defined as follows: animal studies, clinical studies, pathology, or neurodegenerative diseases-related studies, newborns-related studies, cross-modal and dual-task studies, editorial letters, books, and book chapters.

Data Extraction

All potentially relevant studies (n=105) were retrieved. Their titles and abstracts were recorded in an Excel file, and duplicates (n=53) were removed by manual review. Articles that did not meet the inclusion criteria were excluded (n=40). Then, the full articles (n=12) were reviewed to identify whether the study met the eligibility criteria. Seven of the 12 eligible studies were used for this systematic review (Figure 1).

Results

Information (authors, title, methodology, and results) about the articles of seven studies are provided in Table 1. We analyzed the results section of all included articles by searching evaluating the Oxy-Hb, HbR, and HbT parameters. In these studies various odors such as Β-phenyl ethyl alcohol, iso-valeric acid, γ-undecalactone, vanilla, strawberry, scatol, kyara, sumatra, samora, rakoku, managa, manaban, citral, human body odors and garlic were used to observe the hemodynamic changes in the prefrontal area of the brain. There were also mixed group characteristics in the evaluated studies, such as mothers, healthy subjects, and "koh-do experts". In five studies, NIRS were used while the other two studies employed the fNIRS as the monitoring tool. In four studies, Oxy-Hb, HbR and total Hb parameters were evaluated, while three studies evaluated general PFC without giving any details about the hemoglobin parameters.

In a study conducted with "koh-do" experts and non-experts, there was a significant difference in the right and left PFC during the discrimination odor task (18). Ishimaru et al. (19) conducted the study via NIRS, B-phenyl ethyl alcohol and iso-valeric acid exposure altered Oxy-Hb and HbT levels. Oxy-Hb correlated positively with odorant concentration. Oxy-Hb responses differed between odor and placebo stimulations (19). In another study using vanilla, scatol and strawberry odor as stimuli, found that scatol odor increased Oxy-Hb concentrations, notably in the frontal (orbitofrontal) region. During vanilla exposure, both frontal sides plateaued at 12–15 seconds. on the same time span, the strawberry odor changed somewhat but not statistically on either frontal side. These findings shed light on how different scents affect frontal brain regions, which may help us comprehend olfactory processing and sensory perception (20). An additional NIRS experiment conducted

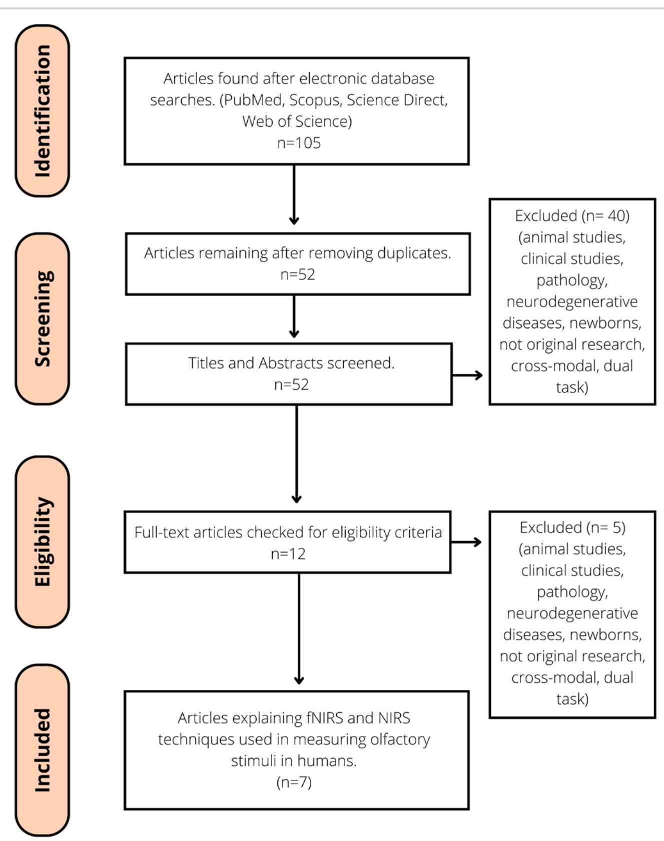

Figure 1. PRISMA flow diagram of the selection process of the studies

PRISMA: The Preferred Reporting Items for Systematic Reviews and Meta-Analyses, fNIRS: Functional near infrared spectroscopy, NIRS: Near infrared spectroscopy

by Kokan et al. (21), Participants correctly identified citral in six out of seven instances and rose in four out of seven throughout the olfactory identification task. Notably, participants who correctly recognized the odorant and those who did not, showed changes in HbT concentration in the left orbitofrontal cortex (OFC). However, neither between the groups exposed to citral and rose odorants nor between those exposed to pleasant and disagreeable odorants, there were any appreciable differences (21).

In another investigation employing fNIRS approach, researchers utilized strawberry odor stimulation to represent a pleasant odor, whereas garlic odor stimulation was employed to represent an unpleasant odor. The study's findings indicate that sessions using odors, as opposed to sessions without odors, resulted in a significant reduction in PFC activation in both the left and right channels after exposure to olfactory stimulation (22). The findings of the study that used fNIRS method demonstrated a significant rise in Oxy-Hb concentrations following to the delivery of isovaleric acid. However, no significant changes in HbR levels were observed. It is notable that isovaleric acid demonstrated a significant increase in HbT levels in comparison to the control saline condition. The results of this study indicate that isovaleric acid produces unique changes in hemodynamic responses, particularly in terms of oxygenated hemoglobin levels (23).

In a study conducted with new mothers, a significant increase was detected in the PFCs of mothers compared to non-mother participants. It was thought that mothers who gave birth to a newborn may have an increased ability to recognize newborn odor compared to mothers who did not give birth to a newborn (24). The findings obtained from the reviewed studies reflect that different odor stimuli can cause a significant change in PFC activation and this activation can be captured by the fNIRS and NIRS methods.

Discussion

This review concluded that the fNIRS approach could be used to estimate hemodynamic changes in the brain in response to olfactory inputs. We provided evidence from the literature that fNIRS is an applicable method for measuring olfactory function in adults with no history of neurodegenerative disorders or any other pathological conditions. The scientific papers used for this review addressed various limitations and advantages.

Blood flow alterations in the PFC in response to olfactory stimuli are observable with fNIRS, the leading method for non-invasive optical imaging techniques. Because of the unique characteristics of olfaction, olfactory perception is not unidirectional. When a signal created by an odor molecule travels from the nose to the brain, activities such as identifying the odor, determining its intensity, recalling memories triggered by the odorant, and perceiving the odorant occur simultaneously. Even if we cannot witness all these processes independently with fNIRS, it is crucial to be able to observe the hemodynamic changes in the brain generated by olfactory stimulation. Considering the seven articles that we selected based on our criteria, we discussed the results achieved using the fNIRS technique.

Fujii et al. (18) revealed that increased activation was observed in the PFC when distinguishing odor stimuli and representing multidimensional symbols of odor. Although there were differences in the responses of the right and left prefrontal regions, both hemispheres were involved in the odor-related reasoning process, and this universal effect could be demonstrated with NIRS. Different activations were observed in the right and left PFC, depending on

Table 1. A brief description of seven studies that used the fNIRS/NIRS method to evaluate olfactory performance

Studies	Optical imaging method	Sample	The type of stimuli	Results
Ishimaru et al. (19), 2004	NIRS	Twelve healthy subjects (eight males) with normal olfaction	- β-phenyl ethyl alcohol - Iso-valeric acid - γ-undecalactone	- Oxyhemoglobin (Oxy-Hb) and total hemoglobin (HbT) increased after the presentation of β-phenyl ethyl alcohol and iso-valeric acid. - Oxy-Hb increased in correlation with the odorant concentration. - The difference in Oxy-Hb responses between odor and placebo stimulation were significant (p<0.05). - Significant periods of olfactory responses on the left side were shorter than on the right side.
Harada et al. (20), 2006	NIRS	Thirteen healthy subjects (seven men) with normal olfaction	- Vanilla - Strawberry - Scatol - Distilled water (negative control)	- Oxy-Hb concentration was increased in scatol odor in the frontal (orbitofrontal area). -A plateau is seen in 12–15 seconds on both frontal sides in vanilla odor. -There is a minor change seen in 12–15 s in strawberry odor but no significant changes on both frontal sides.
Fujii et al. (18), 2007	NIRS	Twenty healthy subjects (experts and beginners)	- Kyara - Sumatra - Samora - Rakoku - Managa - Manaban	- There is a significant difference between the right and left prefrontal cortexes (PFCs) of "koh-do" experts and beginners during the discrimination task.
Kobayashi et al. (23), 2007	fNIRS	Eight healthy subjects (four females)	- Isovaleric acid (cheesy odor) - Saline (as control)	- There is a significant increment in Oxy-Hb for isovaleric acid. - Besides, there are no significant changes in deoxyhemoglobin (HbR). - In HbT, isovaleric acid showed a significant increase compared to the saline.
Kokan et al. (21), 2011	NIRS	Four female college students with normal olfaction	- β-phenyl ethyl alcohol (rose-like odor) - Citral (lemon-like odor)	- Citral was detected correctly 6/7. - Rose was detected correctly 4/7. - HbT concentration in the left orbitofrontal cortex (OFC). - There are significant differences in HbT signal on the right OFC between participants who correctly identified the odorant or not. - The is no significant difference between the pleasant and unpleasant groups or citral or rose groups.
Nishitani et al. (24), 2014	NIRS	Thirty eight healthy female subjects (19 mothers and 19 non-mothers)	Human body odor: - Newborn infant odor - Adult male odor	- Mother subjects have significantly different PFC activation compared to non-mother subjects.
Moein et al. (22), 2020	fNIRS	Seventeen healthy subjects (seven males) with normal olfaction	- Strawberry - Garlic - Placebo (odorless)	- In odor sessions compared with odorless sessions, there was significantly decreased PFC activation in both left and right channels after odor stimulation.

fNIRS: Functional near infrared spectroscopy, NIRS: Near infrared spectroscopy whether the subjects were expert or not. An increase was observed in the right PFC when discriminating and shaping symbols in the mind. An increase was also observed in the left PFC.

Ishimaru et al. (19) reported a significant increase in the right prefrontal region Oxy-Hb responses when comparing the olfactory stimulus (gamma-undecalactone) to placebo to assess olfactory performance. In another study, odor stimulation and water stimulus hemodynamic responses were observed to show no significant change against water stimulus, but an increase in Oxy-Hb was observed in the orbitofrontal region against the odor stimulus scatol. The increase observed in the orbitofrontal could be interpreted as increased blood flow and neural activation in this region. The increase in Oxy-Hb concentration only occurred against the olfactory stimulus, and no significant difference was observed in placebo and water stimulation (20). Moreover, hemodynamic changes to olfactory stimulation were observed in the left orbitofrontal region. When olfactory familiarity tasks were present, the right orbitofrontal region was activated beside the left OFC (21). Considering the aforementioned studies, fNIRS/NIRS technique can be used to show how olfactory stimulus changes blood flow in the prefrontal/orbitofrontal area.

In another study, hemodynamic changes were evaluated under the olfactory stimulus with a button press task. Participants were asked to press a button as soon as they detected any odor. The results showed a significant difference between odorless and odor-containing trials. The authors suggested that fNIRS could be a potentially useful technique for assessing olfactory performance (22). The study used saline (as control) and isovaleric acid (cheesy odor) and spotted a significant increment in Oxy-Hb for isovaleric acid odor. Besides, there were no significant changes in HbR. In HbT, isovaleric acid showed a significant increase compared to saline. The authors also suggested that multichannel near-infrared spectroscopy could provide the hemodynamic changes for odor stimulation (23). In another study, infant odor, which is known as a baby odor, significantly increased the bilateral prefrontal activity of female subjects who recently gave birth. In the same study, another interesting result was that male odors increased the prefrontal activity of female (both mother and non-mother) subjects similarly, but this increase was not significant (24). Based on the mentioned studies, it can be claimed that the hemodynamic activation of the OFC can be evaluated via the fNIRS system.

To understand the physiological effects of odor modulation on specific tasks, it is important to distinguish between simple olfactory stimulation and the effects of odor modulation on blood flow. Although finger-tapping was considered a control clue, whether the hemodynamic increase observed in the prefrontal regions of the participants who were instructed to press the button when they perceived an odor was due to the odor stimulation or the decision-making process had to be determined (22). The activation of the PFC is accompanied by increased hemodynamic responses when stress is present. According to the researchers' findings, during mental arithmetic tasks that induce mental stress, the higher PFC activation and the stress factor shifted the activity of the PFC from the right to the left. Further research is required to determine whether the hemodynamic response observed with fNIRS is due to olfactory stimulus, cognitive function/cognitive load, or other emotional factors. Future studies should address questions such as: What distinguishes a pure odor stimulation from the hemodynamic changes caused by performing various tasks under odor modulation? Is the fNIRS-observed hemodynamic response due to olfactory stimulation or cognitive function/cognitive load? Are the hemodynamic responses to various odors (edible, unpleasant) identical? Which regions do we observe activation?

Conclusion

In this review, we compiled and summarized seven articles employing the fNIRS/NIRS techniques to measure olfaction-related activities. In the evaluation of olfactory performance, the fNIRS method appears more advantageous and promising than other neuroimaging techniques (EEG, PET, fMRI) based on the information presented in this review. Each method has its advantages and disadvantages, and we have detailed the disadvantages and limitations of the fNIRS method in the introduction and limitations sections. With further studies, it will be possible to complete the deficiencies in the literature fNIRS may establish itself as a standard procedure and become a reliable and valid technique. We hope that this review can encourage further studies that use the fNIRS method to investigate olfactory function. Considering the critical role of olfactory perception in human life, an early diagnosis of olfactory dysfunction will help successful treatment and open the door to identifying neurodegenerative diseases before motor or other symptoms occur. The fNIRS technique is expected to improve standard clinical assessments for early detection owing to its ease of use, portability, and lack of potential adverse effects.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: G.A.Ö., G.E., E.E., Ç.G., Design: G.A.Ö., G.E., E.E., Ç.G., Analysis and/or Interpretation: E.E., Ç.G., Literature Search: G.A.Ö., G.E., E.E., Writing: G.A.Ö., G.E., E.E., Ç.G.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Main Points

- This review investigates the possible and reliable usage of the non-invasive optical brain imaging method for assessing olfactory function.
- Optical brain imaging methods can be used to evaluate the olfactory performance in healthy individuals.
- Change in various parameters, such as oxyhemoglobin, deoxyhemoglobin, and total hemoglobin can be monitored in the prefrontal region via olfactory stimulation.

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