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Commentary Paper

Neurochemical Insights Into COVID-19-related Anosmia: A Commentary Study

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Running Title Persistent COVID Anosmia Alters Orbitofrontal Cortex Neurochemistry

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ABSTRACT

In the wake of the COVID-19 pandemic, anosmia, the loss of the sense of smell, has emerged as a curious and widespread symptom. While the sense of smell in many individuals has eventually recovered, some grapple with anosmia for extended periods. In our recent study entitled "magnetic resonance spectroscopy findings of brain olfactory areas in patients with COVID-19-related anosmia," we embarked on a journey to explore the neurochemical underpinnings of anosmia in COVID-19 patients. This commentary extends our original research, providing insights into the evolving landscape of COVID-19-related anosmia and its implications.

Keywords: COVID-19, Anosmia, Magnetic resonance spectroscopy, Anosmia, Central nervous system, Transcranial direct current stimulation

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Highlights

- COVID-19 anosmia linked to reduced OFC NAA levels, indicating neuronal dysfunction.
- Study suggests CNS dysfunction association with COVID-19, impacting neural pathways.
- Prospective magnetic resonance spectroscopy (MRS) studies offer promise for understanding long-term CNS impact of COVID-19 anosmia.

Introduction

As the COVID-19 pandemic expanded worldwide, its clinical manifestations became broader, including symptoms extending beyond the anticipated respiratory distress. Among these symptoms, anosmia, the loss of the sense of smell, emerged as a unique and intriguing characteristic of the illness. This sensory loss was frequently accompanied by a diminished sense of taste, known as ageusia, which left many people feeling confused and disoriented [1, 2].

Our research delved into this unknown realm, utilizing magnetic resonance spectroscopy (MRS), a non-invasive imaging technique known for its effectiveness in unraveling the complexities of the central nervous system [3, 4]. Focusing specifically on the brain's olfactory areas, we aimed to uncover the alterations of molecular neurometabolites that may underlie COVID-19-related anosmia [5].

The intricate interplay between the SARS-CoV-2 virus and the human olfactory system has raised compelling questions about the multifaceted nature of this sensory loss. As we explore the mysteries of COVID-19-related anosmia, we aspire to contribute to a deeper understanding of the virus's impact on the human body and, ultimately, to develop effective strategies for its diagnosis, management, and relief.

In the upcoming sections, we welcome you to accompany us on this expedition as we navigate the complex landscape of anosmia associated with COVID-19 and endeavor to illuminate the way toward its understanding and potential solutions.

Neural pathways of olfactory information processing and memory formation

Olfactory information processing is initiated in the sensory neurons in the nasal olfactory epithelium. These sensory signals travel through the olfactory tract, reaching the primary cortex. From there, they progress to secondary olfactory regions, which include the insular cortex (IC), orbitofrontal cortex (OFC), thalamus, hippocampus, and anterior cingulate cortex (ACC) [6-12]. Consequently, the central olfactory system establishes intricate connections with limbic structures, facilitating the processing of olfactory memories [7]. Furthermore, the limbic loop within the basal ganglia, which consists of the ACC, ventromedial prefrontal cortex (VMPFC), and dorsolateral prefrontal cortex (DLPFC), plays a crucial role in the processing of olfactory information [2, 8]. These cerebral regions are also significantly involved in the encoding and retrieving memories associated with olfaction [13]. Notably, existing literature underscores the predominant involvement of structures within the right hemisphere in the context of olfaction [12, 14-17].

Summary of previous research

Our study revealed a remarkable finding regarding COVID-19-related anosmia. Individuals suffering from this condition displayed decreased levels of N-acetylaspartate (NAA), creatine (Cr), and choline (Cho) in different brain regions. The most significant reduction was observed in the OFC. Notably, significant differences were observed in NAA and Cr levels within the OFC, as well as NAA levels within the VMPFC, between COVID-19-induced anosmia patients and the normal control group [5].

Intriguingly, the radiographic evaluation of post-infectious olfactory loss remains a topic with limited data and ongoing debate. Some prior research indicates structural changes in the brain, like gray matter volume reduction in the right OFC in patients with post-infectious olfactory loss, suggesting structural brain changes. Therefore, it is crucial to acknowledge that COVID-19-related anosmia differs from pre-pandemic cases of post-infectious olfactory loss, with less associations with rhinorrhea, inflammation, or obstructive mechanisms. Radiological studies, encompassing magnetic resonance imaging

(MRI) and diffusion tensor imaging (DTI), propose that the primary pathology in COVID-19-related olfactory dysfunction resides in CNS malfunction [16, 18, 19].

However, our findings differ from those reported by Ho et al. Based on their functional near-infrared spectroscopy (fNIRS) study, they suggested that COVID-19 infection might not substantially affect the function of the frontotemporal cortex. We argue that normal oxyhemoglobin levels, as detected by fNIRS, do not necessarily rule out biochemical changes indicative of neuronal damage [20].

Discussion

This commentary study uses MRS findings based on the study entitled "magnetic resonance spectroscopy findings of brain olfactory areas in patients with COVID-19-related Anosmia: A preliminary comparative study" to focus on the brain's olfactory regions and explore changes in neurometabolites that might be linked to anosmia in COVID-19 patients. The findings shed light on the consequences of anosmia and provide clues about how COVID-19 might affect the body. The study looks at the OFC and finds that neurochemical changes in this area are strongly connected to persistent anosmia in COVID-19 patients. Reduced levels of NAA in the OFC distinguish COVID-19-related anosmia patients from healthy individuals, suggesting regional damage to neurons in the OFC. This finding emphasizes the role of the central nervous system (CNS) in anosmia following COVID-19 infection [5].

The study suggests an association between COVID-19 and CNS dysfunction, indicating the virus's ability to affect the brain. By focusing on the central olfactory system, the study enriches our understanding of how the virus travels through neural pathways and potentially causes neurological complications. However, it is essential to note that the study has a small sample size (common in preliminary investigations), and the exact cause-and-effect relationship between OFC neurometabolites and COVID-19-related anosmia remains unclear. Anosmia occurs when the nose-to-brain sensory connection is disrupted, resulting in reduced activation, neuronal plasticity, functional reorganization, and even structural changes in the brain's olfactory areas. The brain can adapt to sensory shifts, and the duration and cause of anosmia can impact the extent of these changes [5].

Current developments and future directions

Understanding how anosmia affects the brain is crucial for diagnosis and potential interventions. Researchers are exploring the intricate relationship between anosmia and brain changes to develop effective treatments. Expanding the study to include more anosmia groups with different causes could provide a comprehensive understanding of the neurobiological aspects of this condition.

Anosmia highlights the virus's ability to affect neural pathways associated with our senses. Interestingly, the study's findings could suggest potential therapeutic effects of innovative therapeutic interventions, such as transcranial direct current stimulation (tDCS), as a possible treatment for COVID-19-induced anosmia [21].

tDCS is a non-invasive technique that applies a low electrical current to specific brain regions. It shows promise in enhancing neural activity and promoting neuronal plasticity. The study suggests tDCS as a targeted approach to stimulate and potentially rehabilitate the OFC [5, 21]. Studies show that traditional treatments targeting the nasal epithelium, such as intranasal steroids or oral steroids combined with nasal irrigation, may not fully address the neurological aspects of COVID-19-induced anosmia [5, 22]. Given the significant association between neurometabolic alterations within the OFC and COVID-19-induced anosmia observed in our previous study [5], tDCS could offer a targeted approach to stimulate and potentially rehabilitate the OFC. Using tDCS to stimulate the OFC could influence neuronal excitability and synaptic plasticity and may correct neurometabolic balances within the OFC, including an increase in NAA levels. This neuromodulatory effect could help reverse or mitigate the neurometabolic dysfunction observed in anosmia patients [21].

It should be noted that a prospective interventional cohort with a single group has currently introduced intranasal insulin for the treatment of persistent post-COVID-19 olfactory dysfunction. The results show that intranasal NPH (neutral protamine Hagedorn) insulin into the olfactory cleft rapidly improves patients' sense of smell from persistent post-COVID-19 olfactory dysfunction [23]. However, randomized clinical trials are needed to compare the potentially useful treatments mentioned above.

Clinical relevance

Prospective MRS studies have the potential to unlock the long-term impact of COVID-19-induced anosmia on the central nervous system, providing a dynamic view of neurometabolic changes and their correlation with olfactory recovery. As we await findings, these studies offer a promising approach to guide clinical interventions and inform treatment strategies.

Conclusion

To understand COVID-19-induced anosmia and develop effective treatments, a promising hypothesis would be investigating using tDCS to stimulate the orbitofrontal cortex. This approach takes a proactive stance in addressing the potential direct brain injury hypothesis and holds promises for individuals with this challenging condition. As research advances, tDCS may become a valuable addition to the arsenal of therapeutic options, moving us closer to recovering olfactory function and enhancing the lives of those enduring COVID-19-induced anosmia.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors contributions

All authors equally contributed to this commentary.

Conflict of interest

The authors declared no conflict of interest.

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