



Personalized medicine in olfactory testing: perspectives to improve patient compliance to psychophysical tests

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The sense of smell plays a crucial role in the human daily-life, as it is essential in social interactions, in transforming eating from a simple vital function to a pleasant activity, and for detecting environmental hazards [1]. Population-based studies of olfactory disorders (OD) reported a prevalence ranging from 2.7 to 24.5% in the general population [1]. Despite the frequent occurrence of OD and its significant impact on quality of life (QoL), it has been demonstrated that there is a serious issue regarding awareness among medical professionals about this problem. A recent survey demonstrated a lack of awareness towards OD of 64%, 76% and 47% of general practitioners, general otolaryngologists, and neurologists, respectively [2]. The lack of understanding and attention to OD can lead to inadequate diagnosis and management, repeated ineffective treatments, and mental health problems in 60% of patients [2].

The coronavirus disease 2019 (COVID-19) pandemic and the high prevalence of OD linked to the infection [3], particularly during the first wave, brought to light the importance of the sense of smell. To date, 5.2% to 30% of COVID-19 patients kept OD at 2- and 3-year post-infection [4], which mainly consists of anosmia, hyposmia, parosmia, or

phantosmia. The persistence of OD over the long term may be associated with severe QoL impairments [5]. According to the WHO statistics, it is estimated that 45 to 90 million of COVID-19-infected individuals still suffer from persistent olfactory or gustatory dysfunctions worldwide [6].

Currently, psychophysical tests (PT) are considered as the gold standard for evaluating olfaction due to their reliability, high test–retest consistency, and relative speed of administration, which makes them suitable for large-scale application. Despite these advantages, their use in daily clinical practice may remain infrequent [7]. Moreover, they are not still reimbursed in many countries [8], while they significantly improve the documentation and the monitoring of the OD, especially when a treatment is proposed [8, 9]. Most of PT include standardized quantitative and qualitative orthonasal and/or retronasal evaluations combining threshold, discrimination, and/or identification of some odors [8]. The use of standardized testing is important to define normative data and to properly compare results from several patient populations.

However, in our daily practice we observed that PT are not always adjusted to the patient OD complaints and wishes. First, patients with OD often experience qualitative as well as quantitative impairments. PT are not reliable in

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evaluating patients with qualitative OD, as these individuals may have a normal olfactory threshold or discriminative abilities. Furthermore, over time, these patients might memorize the meaning of the distorted odor and correctly identify it during identification tests [10]. Second, some odors tested in the PT may be rarely perceived in daily life from some patients who cannot properly answer to the testing. For instance, turpentine, which is included in the identification component of the Sniffin' Sticks test, is a substance that has fallen out of common use, being replaced by other types of solvents. It was included in the test because it was commonly used in Western Europe in the 1990s. This inclusion may suggest how the odors used in tests can become less reliable in different nations or over time.

In clinical practice, many patients suffer from the inability to smell the odors from their daily (for example, the perfumes or some specific foods/beverages) or the odors associated with unsafe situation (gas or smoke). Some of these odors are not tested in PT, while they are important in the patient daily-life. The addition of some specific odors from the patient daily life, (e.g. perfumes, gas, or dangerous odors) could be an interesting way of improvement of accuracy of PT, while maintaining standardized evaluation of PT to allow population comparisons. On the one hand, the PT results should theoretically better represent the daily-life smell function of the patient and the OD impact on its daily-life activities. On the other hand, the addition of daily-life important odors of patients in the olfactory testing could improve the patient compliance to the olfactory testing from the initial to the follow-up consultation. Indeed, it remains difficult to reach a high compliance rate from patients in the olfactory training or medication-based management of OD because many patients do not adhere to the need to perform PT in addition to the subjective self-assessment. In a recent prospective controlled study dedicated to the effectiveness of platelet-rich plasma in COVID-19 patients with a persistent OD, we observed that approximately 30% of patients did not complete the follow-up PT [9]. When we interrogated patients, most of them reported a lack of trust in PT due to the lack of daily-life odors and the ability to detect some distorted odors. Importantly, the patient comments were not associated with the success of treatment because half patients reported having satisfactory smell improvement. In the same vein, patients who do not feel smell improvement may not complete the follow-up, while they should have significant improvement at the PT, observing their own recovery process of some odor during the PT.

Considering the current prevalence of OD due to the COVID-19 pandemic, a discussion around the issue of “*how to improve the management of OD*” should be started. The personalization of some parts of PTs could match with the development of some artificial intelligence (AI) software used in the management/follow-up of patients. Indeed, some

AI-based software could be developed to help the patient in the olfactory training. The patient would select the most important odors of the daily-life and the software could organize the daily training with the related odors using a grading system of odor perception by patients. The involvement of AI-based software in the olfactory training process of patients could improve the adherence to training while collecting important data for research dedicated to the smell recovery process. A multicenter survey of patients who benefit from PTs could be conducted.

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