Olfaction in migraine and its psychiatric comorbidities: a narrative review

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Abstract

Objective

Migraine is a primary headache with a constellation of neurovegetative and sensory-related symptoms, comprehending auditory, visual, somatosensorial and olfactory dysfunctions, in both ictal and interictal phases. Olfactory phenomena in migraine patients consist in ictal osmophobia, interictal olfactory hypersensitivity and an increased sensitivity to olfactory trigger factors. However, osmophobia is not listed as an associated symptom for migraine diagnosis in ICHD-3.

Design

We reviewed the literature about the anatomical circuits and the clinical characteristics of olfactory phenomena in migraine patients, and highlighted also the common comorbidities with psychiatric disorders.

Discussion

The evidence suggests a potential role of the olfactory dysfunctions as diagnostic, prognostic and risk biomarker of migraine in clinical practice. Olfactory assessment could be useful in reducing the overlap between migraine and other primary headaches - especially the tension type one - or secondary headaches (ictal osmophobia, olfactory trigger factors), and in predicting migraine onset and its chronic transformation (ictal osmophobia). Furthermore, ictal osmophobia and olfactory hypersensitivity showed to be related with an increased risk of psychiatric comorbidities and suicidality, probably beacause of the sharing of anatomical circuits (in particular the limbic system).

Conclusion

In conclusion, the assessment during clinical interviews of olfactory phenomena, with the validation of scales or scores to measure olfactory dysfunctions, surpassing the binary presence/absence paradigm, could improve the diagnostic and prognostic possibilities, especially in tertiary headache centers.

KEYWORDS: OSMOPHOBIA; OLFACTORY HYPERSENSITIVITY; MIGRAINE; PSYCHIATRIC DISORDERS; SOMATOSENSORY HYPERSENSITIVITY

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Introduction

Visual, auditory and olfactory hypersensitivity in general are frequently reported by patients during migraine attacks and, less prominently, also during interictal periods[1], leading to photophobia (i.e. intolerance to light), phonophobia (i.e. intolerance to sound) and osmophobia (O-P), the latter is defined as intolerance to odors experienced during migraine attacks, those odors are usually perceived by other people not suffering from migraine as neutral or pleasant.[2] Olfactory hypersensitivity (O-HS), on the other hand, is reported as a perception of distress in being exposed to olfactory stimuli between attacks.[3] Nonetheless, during the interictal phase, some patients indicate olfactory stimuli as possible migraine trigger factors (O-TFs).[4] The relationship between odors and migraine was described for the first time in the second century AD by Aretaeus of Cappadocia, over the years this interconnection has been continuously and widely reported and discussed.[5] Nevertheless, olfactory symptoms were never enlisted in the diagnostic criteria of International Headache Society (HIS) for migraine as well as in the last version of the International Classification of Headache Disorders (ICHD-3).[6]

It is noteworthy that odors are the result of the interaction between volatile molecules and specific receptors, from which olfactory impulses are transmitted to rhinencephalon (orbitofrontal, entorinal and perirhinal), and, therefore, processed by a complex network of brain structures involved in emotional and hedonic salience as well as in cognitive functions such as learning and memory.[7] Consequently, olfactory stimuli are characterized by their quality (by which a person recognizes a specific odor as familiar or not and can categorize it), intensity (representing the strength of the induced perception) and hedonic tone (defining the pleasantness of odors).[8]

Quantitative olfactory dysfunctional changes have been described in various neurological diseases.[9, 10] In particular, among headache syndromes, olfactory impairment has been identified as a clinical feature of idiopathic intracranial hypertension and the lowering of increased intracranial pressure is able to improve hyposmia. Nonetheless, in migraine, also quality characterization, as the ability to identify specific odors, has shown to be affected.[3, 12, 13] Olfactory modifications in migraine have been studied with both subjective and objective (e.g. electrophysiological) tests.[14-17] However, due to the high prevalence of hyposmic and anosmic patients in the general population (almost 20%)[18] specific migraine-related olfactory changes are difficult to identify.

In this review, we elaborated on the anatomical and functional substrates of olfaction and the olfactory phenomena characterizing migraine, with particular focus on ictal O-P, interictal O-HS and olfactory stimuli as O-TFs. Moreover, we investigated changes observed in migraine psychiatric comorbidities. To review the role of olfactory phenomena in migraine, we performed a Pubmed-based literature search until April 2020 using the keywords "Olfactory", "Osmophobia", "Sensory hypersensitivity", "Headache" and "Migraine". A total number of 135 articles written in English were found. To remove outdated content we selected 118 articles excluding papers written before the 1995. Among them we also excluded clinical case reports, studies where the keywords referred to different and unrelated subjects (e.g. drug delivery, other diseases, biochemical receptors studies, etc)

to select 55 core articles that explored the olfactory dysfunction related to migraine and headaches.

We guess that olfactory changes may represent potential clinical biomarkers useful in migraine-related diagnostic and prognostic processes, able to identify specific migraine subgroups. Therefore, the detection of olfactory phenomena could also play a role in identifying the most effective treatment in the different clinical phenotypes of migraine.

Anatomical and functional substrates of olfaction in migraine

Environmental olfactory stimuli are substantially constituted by pure odorants activating the olfactory system or chemical compounds able to trigger the trigeminal system stimulating the free nerve endings of trigeminal nerve located within the mucosa of the nasal vestibule.[17]

For this reason, many olfactory stimuli (the so-called "trigeminal odors") can reproduce various sensations such as irritation, pain, and burning which are not experienced with the purely olfactory compound such as vanillin (the so-called "olfactory odors").[19]

Signals from pure olfactory stimuli are normally transduced by the olfactory epithelium via the olfactory bulb (OB), both tract and tubercle (the latter is also connected with the mediodorsal nucleus of the thalamus), to the olfactory cortex encompassing anterior olfactory nucleus, amygdaloid, periamygdaloid, entorhinal, and piriform cortices. The olfactory cortex and amygdala project to orbitofrontal and insular cortices, subiculum, thalamus, hypothalamus, brainstem and caudate nucleus.[16] On the other hand, information from trigeminal olfactory stimuli converges to the rostral part of the spinal trigeminal nucleus and, via the ventral posterior medial nucleus of the thalamus, to the anterior and central insula, claustrum, primary somatosensory cortex and posterior portion of the anterior cingulate cortex. Interestingly, painful stimuli activate similar pathways.[3, 20]

While olfactory and trigeminal pathways have been widely characterized, their specific role into the intricate migraine pathophysiology still shows some gaps that might be partly bridged by advanced neuroimaging techniques conducted by using resting brain and event-related experimental paradigms in the course of headache attacks (e.g.: the so-called ictal phases of migraine) as well as in the period that occurs between them.

By employing analysis of functional connectivity with functional magnetic resonance imaging (fMRI), the brain functional organization is investigated basing on temporal correlations in blood oxygenation level-dependent (BOLD) signal fluctuations between and within different brain regions, mostly in pain-processing regions.[14, 21, 22]

Advanced neuroimaging studies, aimed to explore functional connections and the strength of such functional connections in migraine, have consistently shown aberrant functional connectivity in brain regions involved in sensory-discriminative processing of pain (e.g.: somatosensory cortex, posterior insula), affective-emotional processing (e.g.: anterior insula, anterior cingulate cortex, and amygdala), cognitive processing (e.g.: hippocampus, parahippocampal gyrus, and orbitofrontal cortex) and pain modulation (e.g.: periaqueductal grey, nucleus cuneiformis).[14, 21, 22] Furthermore, atypical functional connectivity of several resting-state networks (such as the default mode one, the central-executive one, the salience network, the somatosensory and motors network and the frontoparietal attention network) seems to characterize migraine patients.[21]

Among advanced neuroimaging studies using event-related approaches through different tasks, trigeminal nociceptive stimulations such as cutaneous noxious thermal stimulation or trigeminal nociceptive activation by intranasal ammonia have been employed in migraine patients.[23-25] These studies have enhanced our understanding of hypersensitivity in migraine, including the identification of brain regions contributing to the atypical processing of sensory stimuli.[26] This abnormal processing is a key feature of the migraine brain, leading to increased sensitivity to pain as well as to non-painful stimuli, enabling non-noxious environmental visual or olfactory inputs (e.g. flashing lights and odors) to trigger migraine attacks.

Similarly, several nuclear medicine studies of functional neuroimaging have been conducted to investigate the pathophysiological mechanisms underlying olfactory phenomena in migraine patients. Among these, Demarquay and colleagues showed, thanks to a $H_2{}^{15}O$ PET study, abnormal cerebral activation pattern during olfactory

stimulation with rose odor, probably reflecting either an altered functional response to olfactory stimulation or an abnormal top-down regulation processes related to underlying migraine pathophysiological mechanisms.[27]

Conversely, few structural neuroimaging observations have been conducted to explore olfactory phenomena in migraine patients, specifically to examine the volume of OBs, already widely investigated in other disorders with olfactory changes such as neurodegenerative [9, 28, 29] and autoimmune diseases.[30, 31]

A bilateral OB atrophy, correlated with O-P, has been found in these patients[32, 33] probably subtended by maladaptive plasticity related to antinociceptive mechanisms[33] (similarly to the retinal thinning found in migraine patients experiencing photophobia).[34] The left OBs were mainly involved, reflecting the predominant multisensorial associative role of the left brain areas in integrating the perception of olfactory as well as auditory and visual stimuli with their processing and codification.[35]

Taken together, functional ad structural neuroimaging findings suggest that brain areas, which are activated by painful trigeminal stimulations, are involved in functional activation due to olfactory stimuli in migraine patients and altered olfactory processing characterizes migraineur's brains during the ictal period.[3, 20, 24, 25] These data support the functional link between olfactory and trigeminal nociceptive pathways, probably explaining the mechanism by which odors could trigger migraine attacks.

Notably, all the brain areas known to be involved in the processing of olfactory stimuli such as the amygdala, insula, anterior cingulate and orbitofrontal cortices show abnormal activity other than in migraine patients also in psychiatric diseases such as major depression.[36]

Ictal osmophobia

The term O-P refers to the aversion to odors (commonly considered pleasant or neutral) during the pain phase of migraine. Migraine patients are osmophobic especially for perfumes, followed by cleaning products, cigarette smoke, oil derivatives, and certain foods (e.g. coffee, fried food, onions, meat, etc.).[8, 37] The prevalence of O-P during a migraine attack ranges from 20% to 81.7% depending on the studies[8, 15, 38], with a higher value in migraine patients without aura compared with migraine patients with aura.[8, 15] Considering the predominance of perfumes and pleasant odors in migraine olfactory phenomena, it could be subject of further studies to investigate the pathways involved in the hedonic assessment and migraine pain.[8, 37]

Notably, it was shown that the specific migraine subset with O-P seems to present the lowest odor discriminatory score compared with the whole migraine group.[39]

The O-P, previously reported in the appendix of ICHD-2[40], has been definitively eliminated from the migraine diagnostic criteria in the final version of ICHD-3. However, some diagnostic overlap between primary headaches[41] led to explore clinical features that can allow more precise and correct identification of patients, focusing on olfactory phenomena and, specifically, on the O-P.[42] In this frame, O-P prevalence has been reported in 43% of migraine patients without aura, 39% in migraine patients with aura and 7% of cluster headache patients in a study conducted on 775 subjects.[43] Several reports documented the high specificity of O-P for migraine, quite rare in TTH or other primary headaches[44, 45] (less than 10% of O-P prevalence in TTH).[46] However, though the O-P is characterized by a low sensitivity, it appears more specific than photophobia and phonophobia in the differential diagnosis between migraine and TTH.[38, 44, 47] Moreover, O-P could be useful to differentiate migraine from secondary headaches as suggested by large studies and recent tests in the field of diagnostic criteria.[44, 48]

Interestingly, O-P assessment in headache patients could have various utilities that are not limited to its diagnostic value. In fact, O-P, which is more prevalent in adult women and pediatric men[49], seems to identify a specific clinical subtype of migraine, characterized by early-onset, persistent course, more intense and lasting attacks, higher frequency of triggered-attacks and affective symptoms.[15] Moreover, O-P would seem to characterize a subgroup of patients with a higher likelihood to develop chronic migraine, thus representing also a risk marker of the disease.[47, 50] A positive association between O-P and migraine history has been described and patients with a long headache history would be more likely osmophobic.[2] In the pediatric population the presence of O-P as well as cyclic vomiting syndrome (CVS) seems to

increase the risk to develop migraine in adulthood[47, 51] and the presence of either OP or O-TFs may increase the probability (up to 39%) of migraine development[47] with a more disabling phenotype.[52]

The value of O-P as a risk and prognostic marker was highlighted in a Turkish large population study where among the non classification symptoms (e.g. throbbing, severe pain and vomiting) O-P was the major predictor for receiving a confirmatory migraine diagnosis after five years.[53] In other words, photophobia and phonophobia are critical for migraine diagnosis, but they are not prognostic since they are not able to predict migraine persistency or severity.[53] Finally, migraine patients with O-P showed higher psychiatric comorbidity than non-osmophobic migraine patients, with higher rates of anxiety, depression, and suicidality.[54-56]

The complex relationship between the olfactory and limbic networks in migraine has been further supported by advanced neuroimaging studies using olfactory stimulation in patients experiencing migraine without aura and migraine with aura, both during ictal and interictal period.[26] Interestingly, migraine patients and healthy controls did not show any differences in both odor perception and neuroimaging findings during interictal phases, whilst a significantly increased activity in limbic areas (known to play a key role in both migraine pathophysiology and advanced olfactory processing) and in the rostral pons (a structure previously defined as "migraine generator") in response to olfactory stimuli was observed during spontaneous migraine attacks.[26]

Olfactory hypersensitivity

O-HS is defined as the perception of distress upon exposure to olfactory stimuli usually perceived as neutral or even pleasant and it could be often reported by migraine patients during the interictal period.[3]

Interestingly, migraine patients experiencing O-HS seem to have a higher frequency of attacks, a higher number of odor-induced migraine attacks, a higher degree of hedonic tone for odors (describing the pleasantness of odors) and visual hypersensitivity when compared with migraine patients without O-HS.[37] On the other hand, no association has been found between O-HS and other parameters of disease severity such as disease duration, age, gender or other symptoms of sensory hypersensitivities.[37]

In migraine patients O-HS could be subtended by cortical hyperexcitability, reflecting abnormalities of limbic and dopaminergic systems, two anatomic and functional strictly linked systems, involved in emotional response as well as in hedonic judgment of olfactory stimuli.[3]

Although migraine patients usually experience O-HS, no differences have been found in olfactory discrimination when compared with healthy controls.[37] Inversely, different thresholds have been reported in migraine patients when compared with healthy controls, depending on specific olfactory stimuli (e.g. lower threshold for vanillin, a higher threshold for pyridine odor).[19, 57] Apparently in contrast with O-HS, possibly due to distress and emotions affecting olfactory function[58], migraine patients report lower combinatory scores of threshold perception, discrimination and identification of odors.[39] This observation testifies that O-HS may be caused by an olfactory alteration, rather than a sensorial gain of function as well as it is observed in the early phases of pregnancy, during which about two-thirds of women report an increased sense of smell reacting to particular olfactory stimuli described as unpleasant.[59] Indeed, different odors such as spices, coffee, cigarettes smoke, perfumes and certain foods (fish or spoiled groceries) are reported much stronger than usual or disagreeable by both pregnant women and migraine patients, and therefore, a hormonal contribution has been suggested. On the other hand, it is noteworthy that the greater chance of developing migraine during the pubertal hormonal spurt may be related to the hormonal influences on peculiar brain areas in women.[60]

Moreover, different neuronal substrates between male and female children suffering from migraine have been supported by advanced neuroimaging observations using structural and functional approaches, demonstrating increased gray matter in the primary somatosensory cortex (S1), supplementary motor area, precuneus, basal ganglia and amygdala in women migraine patients as well as greater resting-state functional connectivity between precuneus and thalamus, amygdala and basal ganglia and between amygdala and thalamus, anterior midcingulate cortex and supplementary motor area. These data are further supported by sex and developmental differences observed in pediatric migraine patients in brain regions associated with sensory, motor and affective circuits, showing more gray matter in the S1, amygdala, and caudate

in women migraine adolescents compared with men migraine adolescents and healthy controls.[61]

Olfactory stimuli as migraine triggers

O-TFs are defined as exogenous or endogenous factors that, acting alone or in combination, may induce a migraine attack in predisposed individuals.[62] This field is controversial, here we resume the most relevant data found in literature, even if O-TFs are so far to be a consistent feature of the migraine disease itself. Frequently, migraine patients identify as trigger factors stress, ovarian hormone fluctuations, sleep modifications (e.g. in pattern, duration and/or quality), long fasting periods, consumption of alcohol or certain foods. Many headache attacks may also be triggered by sensorial stimulations such as light, noises or some types of odorants[15, 62] and migraine patients can identify very precisely their triggers reporting avoidance of specific situations putatively triggering attacks.

Perfumes and odors may act as migraine trigger factors in percentages ranging from 18% to 70% of migraine patients,[8, 45, 62] (more frequently in chronic migraine)[3, 62] as demonstrated by clinical interview studies based on self-reported questionnaires.

Nevertheless, clinical interviews may be misleading, due to self-reporting data and supporting the legitimate anthropological bias of the *post hoc ergo propter hoc*.[63] Indeed, the conflicting or wide-ranging results, provided by clinical studies, have been mostly based on the complete entrusting to unreliable patient reports.

The experimental design, using olfactory stimulation (through a controlled administration of O-TFs) could partly overcome the bias. The experimental olfactory stimulation was performed in 158 patients (72 with migraine, 86 with other primary headaches) and it demonstrated that at least 35% of migraine patients had an odor-triggered attack after a mean latency of approximatively two hours.[4]

Notably, olfactory-triggered attacks showed high specificity, since they were referred almost exclusively by migraine patients and very rarely by other primary headaches patients[4] such as cluster headache[64] and seldom in the course of secondary headaches.[65] Moreover, the experience of olfactory triggered migraine attacks seems to characterize specific subsets of migraine patients. For example, patients with susceptibility to O-TFs when compared with non-triggered migraine attacks may exhibit a lower age of migraine onset[3] and slightly different pain characteristics, showing a significant prevalence of bilateral localization and a trend for associated nausea.[4]

The role of proven triggers for migraine, including neuropeptides with an emergent role in migraine pathophysiology, is unclear. Speculations based on epidemiological observations indicate that a series of volatile agents, as the umbellulone, the major volatile constituent of the "headache tree" Umbellularia californica, may trigger migraine attacks by the release of calcitonin gene-related peptide (CGRP), by activation of some members of the transient receptor potential (TRP) family of channels, and the mustard oil-sensitive ankyrin 1 (TRPA1) channel, expressed on dural sensory afferents.[66] CGRP revolution in migraine studies demonstrated that the understanding of disease pathophysiology could lead to experimental induction of migraine-like attacks.[67, 68] However, these attacks lack many of the typical prodromal characteristics and the olfactory pathway has never been assessed.[69] Interestingly, the induction of migraine attacks with the pituitary adenylate cyclase-activating polypeptides (PACAP) showed a higher percentage of prodromal symptoms, with the particular engagement of the dopaminergic system (fatigue, nausea and yawning).[69]

Interestingly, the susceptibility in experiencing olfactory triggered migraine attacks is not necessarily associated with another olfactory phenomenon such as O-P, since less than 10% of migraine attacks characterized by O-P are induced by O-TFs.[44] This high specificity and low sensitivity make the susceptibility to O-TFs a poor diagnostic criterion although potentially relevant to understand underlying migraine pathophysiological mechanisms.[44]

Olfactory changes in migraine psychiatric comorbidities

Olfactory dysfunction has been studied in different psychiatric conditions and it has proved to be common among psychiatric disorders, most frequently comorbid with migraine.[70] In particular, an altered olfactory function was prominent in affective disorders[71], although with conflicting results probably due to unstandardized methods of measurement.[72]

Depressive disorder showed a significant bidirectional association with migraine and odds for depression increased two- to fourfold in migraine patients in comparison to general population.[68, 69] Noteworthy, depression is commonly recognized as one of the major predictive factors for migraine chronic transformation [73, 74] as well as O-P.[51] Studies on patients affected by BD (both type I and II) reported migraine rates until 24.8% of all cases (versus a general population rate of 10.3%).[73]

Certain studies examined olfactory function in BD patients.[71] Some of these found no olfactory dysfunctions; others reported significant perceptual anomalies in BD subjects (olfactory, identification, sensitivity, intensity, discrimination and hedonic rating). In particular, depressive and mania symptoms were related to increased and decreased olfactory sensitivity respectively.[74] Therefore, odor acuity could be an indicator of disease status in BD patients, with increasing acuity predicting depression phases and decreasing acuity predicting mania episodes. Since the olfactory identification deficit can persist in BD subjects during the eutymic state, alternatively, olfactory acuity could be a trait marker, which identifies specific subtypes within the spectrum of bipolar syndromes.[75] However, the association between social performance and olfaction alterations was described also for other psychiatric disorders[76], suggesting that olfactory dyfunctions could be a marker of social performances, independently of the affective status.[71]

Also, disorders belonging to the anxiety spectrum - according to the DSM-IV classification (generalized anxiety disorder (GAD), obsessive-compulsive disorder (OCD), and panic attack disorder) - are often in comorbidity with migraine, with a prevalence of two to five times higher in migraine patients than in the general population and even more in chronic migraine.[77, 78] Notably, patients with anxiety disorders reported a longer headache history, phonophobia and a significantly higher prevalence of O-P.[2] Anxiety state or trait have been associated with decreased olfactory perception, maybe due to altered activity of common brain structures.[58, 79] In a hospital-based Asiatic population migraine patients with O-P had higher levels of anxiety and depression in comparison to non-osmophobic ones.[80] Similarly, another study found a higher percentage of O-P in patients with moderate and severe allodynia compared with individuals without or only mild allodynia[81], a condition frequently associated with depressive symptoms and a negative prognostic factor for migraine chronic transformation.[82]

Finally, both young and adult patients with migraine showed an increased risk of suicide attempt or ideation.[55, 83] The significant risk factors associated were female sex, unmarried state, migraine with aura, higher pain intensity, headache frequency and perceived disability.[55] Recently, both O-P and allodynia were found to be major risk factors for suicidality in migraine patients even after clinical controls for major depression, GAD, and chronic migraine pattern.[56] O-P especially was the major contributor in this multivariate model [adjusted Odds Ratio (AOR) 3.12; 95% confidence interval (CI) 1.57 - 6.21; p = 0.001], while allodynia showed, as expected, a lower contribution than anxiety and depression.[56] Eventually, a relevant contribution of olfactory pathway modifications to suicidality is plausible. The tight association of O-P with mood changes and suicidality probably relies on a common anatomic and functional network connecting smell perception and limbic system. However, other studies have evidenced that baseline severity in both migraine and non-migraine headaches remains the major risk factor for suicidality also after clinical controls for depression.[83, 84] Furthermore, since O-P is tightly associated with migraine severity and persistence, it might be considered only indirectly related to suicidality. The evidence described above raises the question of whether the olfactory modifications are related to migraine severity or combined with affective disorders.

The precise mechanism connecting mood disorders and migraine is far to be understood, however clarifying the direct/indirect contribution of olfaction could aid the process.

Antidepressants such as SSRIs and SNRIs can be used as second-line anti-migraine preventive drug.[88-90] On the other hand, a hypersensitivity of the dopaminergic system has been recently demonstrated in migraine patients[91] and dopaminergic symptoms such as nausea/vomiting and yawning are frequently reported both in the prodromal and pain phase of the migraine attack.

Conclusion

Among olfactory phenomena, the ictal O-P (e.g. the avoidance to odors, usually perceived as neutral or pleasant, during migraine attacks), the interictal O-HS (e.g. perception

of discomfort upon odor exposure between migraine attacks) and the existence of olfactory migraine trigger factors (e.g. olfactory exogenous volatile molecules able to induce migraine attacks) are well-identified migraine clinical features. Serotonergic and dopaminergic dysfunction influence the pathophysiology of both migraine and mood disorders.

In particular, based on their high specificity, O-TF[4] and O-P[38, 44, 47] could be considered as a diagnostic biomarker useful to improve the differential diagnosis between migraine and other primary headaches such as TTH as well as secondary headaches. Moreover, O-P might play a role as both risk and predictive/prognostic factor when identified in the pediatric population, since it is associated with a higher probability of developing migraine and its possible chronic evolution.[47, 51] Furthermore, both O-P and O-HS seem related to a higher risk of psychiatric comorbidity and suicidality in migraine patients.[54-56] Therefore, despite further studies are mandatory, we speculate that the migraine phenotype with olfactory abnormalities may better respond to migraine prophylaxis therapy with antidepressants and mood stabilizers. From this perspective, olfactory dysfunctions could be evaluated also as therapeutic response biomarkers.

Nevertheless, since olfactory dysfunctions are also present in the general population[92], a mere dichotomous classification of olfactory anomalies (yes vs no) might be inadequate as a clinical biomarker. Therefore, quantitative clinical scales able to score olfactory dysfunctions along a continuous distribution, combined with large sample studies, are necessary.

In conclusion, despite its exclusion from the diagnostic criteria of migraine, olfactory abnormalities should be recognized as pivotal features for diagnostic/prognostic evaluation and psychiatric comorbidity assessment.

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