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Review

Olfactory Dysfunction in Huntington's Disease

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Abstract. Olfactory dysfunction is a common symptom in patients with neurodegenerative disorders, including Huntington's disease (HD). Understanding its pathophysiology is important in establishing a preventive and therapeutic plan. In this literature review, we cover the physiology of olfaction, its role in neurodegeneration, and its characteristics in patients with HD. In the general population, olfactory dysfunction is present in 3.8–5.8% and the prevalence increases significantly in those older than 80 years. For HD, data regarding prevalence rates are lacking and the scales used have been inconsistent or have been restructured due to concerns about cross-cultural understanding. Pathogenic huntingtin deposits have been found in the olfactory bulb of individuals with HD, although no studies have correlated this with the grade of olfactory impairment. Olfactory dysfunction is present in both premanifest and manifest patients with HD, showing a progressive decline over time with more severe deficits at advanced stages. No specific treatment for olfactory impairment in HD has been proposed; identifying and avoiding potential medications that cause olfactory dysfunction, as well as general safety recommendations remain the basis of the therapeutic strategy.

Keywords: Huntington's disease, olfaction disorders, smell, neurodegenerative diseases

INTRODUCTION

Huntington's disease (HD) is an inherited neurodegenerative condition characterized by a triad of motor, cognitive, and neuropsychiatric symptoms. The disease is caused by the expansion of a trinucleotide repeat (CAG) in the first exon of the huntingtin gene (HTT), which culminates in the translation of an elongated huntingtin protein (mHtt). The clinical symptoms of HD are thought to be a result of the neuronal toxicity induced by the presence of mHtt in various regions of the brain, including the striatum and neocortex [1]. The clinical diagnosis has historically been defined by the motor symptoms with most adult HTT pathogenic variant carriers becoming symptomatic during middle age; however, nonmotor symptoms including cognitive decline and neuropsychiatric disturbances may present even earlier [2] during the prodromal period. An additional, and relatively understudied, early nonmotor symptom of HD is olfactory dysfunction. Despite this association being known for several decades [3], there are a paucity of studies which explore the relationship between olfactory dysfunction and the other major symptomatic domains of HD.

Currently, there are no disease-modifying therapies approved for HD and available treatment options are purely symptomatic [4]. Age of motor onset is

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inversely correlated with CAG repeat length; however, considerable variation exists and only recently have additional genes been identified and implicated in contributing to this variance [5]. Additionally, there can be marked phenotypic variability amongst individuals with HD [6]. Given the uncertainty this poses on HTT pathogenic variant carriers, improved biomarkers are needed to better predict symptomatic onset and track clinical progression. Evaluation of olfactory function is a potential clinical parameter that could be useful in achieving this goal. Furthermore, closer scrutiny of olfactory dysfunction in HD could lead to clues into the pathophysiology of the disease, which remains incompletely understood. Herein, we review what is known, both clinically and pathophysiologically, regarding olfactory dysfunction in HD and discuss the prospect of gaining a more thorough understanding in hopes of possibly using this symptom as a surrogate measure of disease onset and progression.

METHODS OF SEARCH

The literature search included observational studies and reviews including both human and mouse studies published up to September 2021. PubMed and Google Scholar databases were searched. The terms ((Huntington's disease OR Huntington disease) AND (olfaction OR olfactory OR odor)) AND (dysfunction OR impairment)) were used, as well as those related with neurodegeneration. On the initial search, 506 results were retrieved, and their abstracts were reviewed to determine their suitability for the manuscript. Briefly, articles were selected if they were written in English and presented information regarding olfactory dysfunction in patients with HD, including studies on epidemiology, pathophysiology, diagnosis, or treatment. The list of references from all selected manuscripts was also checked in order to identify studies that could have been missed in the first searching stage, with a final result of 62 articles.

PHYSIOLOGY OF OLFACTION

Despite the suggestion that the acuity of human olfaction has regressed over evolutionary time [7], some empirical studies have shown that humans can distinguish odors that vary by a single molecular component and possess comparatively lower olfactory detection thresholds relative to primates and rodents [8, 9]. Conversely, other studies have demonstrated that humans can differentiate smaller odor concentration changes compared to rats, with rats and dogs having a 2.5 log unit lower absolute odor detection threshold than humans [10]. This sensitivity is achieved by the nasal mucosa, which is composed of the olfactory epithelium and an overlying mucus layer. The olfactory epithelium has different cell types including basal cells, sustentacular cells, and olfactory receptor neurons—the latter of which is responsible for the function of chemosensation [11]. Anatomically, the olfactory epithelium overlies the cribriform plate and is found posteriorly and superiorly within the nasal cavity [12]. While there is variation in the olfactory epithelium between individuals, this specialized sensory mucosa can extend to the middle turbinates and the middle and posterior nasal septum [12, 13].

Once a specific odor enters through the nostrils, it will come into contact with the olfactory epithelium retronasally via the choanae, which plays a particularly important role in flavor perception [12]. Odorants, which are typically not very large molecules [14], are then deposited upon the mucus-lined olfactory epithelium and contact the apical dendrites of bipolar olfactory receptor neurons, which possess elongations called olfactory cilia that enhance the exposure of these neurons to odorous compounds [11, 12].

Olfactory receptors (ORs), first discovered as a distinct gene family in 1991, are G-protein-coupled receptors (GPCRs) that bind to and are activated by a vast array of molecular species. There are a wide range of genes that encode ORs within the class *Mammalia*, with rodents having ~1000 functional genes and humans having only ~400 [15]. Interestingly, an individual olfactory receptor neuron only expresses a single allele of one OR gene, presumably rendering the neuron with only the ability to detect odorants recognized by a specific OR [16]. Thus, the combinatorial pattern of OR activation represents the molecular correlate of the perception of a particular odor [14]. When an odorant is recognized by an OR, a signaling transduction cascade using a second messenger system is elicited which finally alters the concentration of cations. The influx of Na+ and Ca^{2+} depolarizes the neuron and produces a graded receptor potential [11].

On the circuit level, olfactory receptor neurons project unmyelinated axons through the cribriform plate, where they form synapses with secondary neurons in the olfactory bulb. These initial synapses are made in the glomeruli, which exist towards the

surface of the olfactory bulb, and are thought to be the functional unit of olfactory information processing [17, 18]. Each glomerulus receives input from only a single type of olfactory receptor neuron. Thus, olfactory receptor neurons expressing a single OR gene project to only a few congruous glomeruli [18, 19]. Once the axons of a given type of olfactory receptor neuron converge on a corresponding glomerulus, they form glutamatergic synapses with three types of secondary cells - mitral cells, external tufted cells, and periglomerular cells [18]. Mitral cells, which are excitatory neurons that are only associated with a single glomerulus, project their axons via the olfactory tract to the piriform cortex, a region of paleocortex primarily associated with higher olfactory processing [17, 20]. Excitatory tufted cells also carry outgoing signals, but project instead to the anterior olfactory nucleus, and synapse with short-axon neurons, which project to other glomeruli within the olfactory bulb [17, 18, 21]. These cells send projections to other structures associated with the olfactory system such as the olfactory tubercle [22]. Both mitral and tufted cells synapse with periglomerular cells and in turn, receive reciprocal inhibitory input from these interneurons, which innervate several glomeruli in a given region of the olfactory bulb. Finally, mitral and tufted cells also synapse with extraglomerular interneurons called granule cells [17].

OLFACTORY DEFICITS IN NEURODEGENERATION

In the general population, the greatest predictor for olfactory dysfunction is advancing age, with a general prevalence between 3.8% and 5.8% and predominance in males [23, 24]. While approximately 2% of the population under 65 years report olfactory loss, its prevalence dramatically increases with age and reaches approximately 75% in those older than 80 years [25]. In addition to aging, other factors that have been associated with olfactory impairment in individuals without dementia are vocations in manufacturing, history of cardiovascular disease, cerebrovascular disease, and diabetes mellitus, decreased ambulatory speed, use of many pharmaceuticals, and presence of the apolipoprotein E4 (*APOE* ε4) allele [26]. Recently, an association between SARS-CoV-2 infection and olfactory dysfunction has been found [27].

Outside the context of normal aging, loss of olfactory function has been recognized as a prodromal manifestation of multiple neurodegenerative diseases since at least the 1970s. In Parkinson's disease (PD), a neurodegenerative disease in which olfactory dysfunction has been extensively characterized, 90% of afflicted individuals have olfactory deficits that are independent of disease severity and duration. Furthermore, this dysfunction is generally bilateral and is not affected by treatment [28]. Olfactory dysfunction has been recognized as an early manifestation of Alzheimer's disease (AD) and has been correlated with disease progression, therefore, olfactory decline serves as an early diagnostic marker. Although some studies have found a higher risk of dementia in *APOE* ε4 positive patients with olfactory impairment [29, 30], recent reports with longer follow-up periods have suggested that such compromise is independent of the *APOE* ε4 carrier status. Dintica et al. provided evidence of an association between cognitive decline and progressive olfactory dysfunction, with MRI studies showing lower brain volumes in the fusiform gyrus and the middle temporal cortex. Additionally, this study confirmed previous reports of episodic memory compromise in patients who develop olfactory dysfunction [24].

Interestingly, inflammatory signals emanating from the olfactory bulb may serve as a proxy for an inflammatory or degenerative process occurring in deeper regions of the brain. In mice subjected to cerebral ischemia, Toll-like receptor 2, which is upregulated by inflammatory states and serves as a marker of microglial activation, was first induced in olfactory microglia, despite the location of the infarct being remote from the olfactory bulb [31, 32]. A similar finding was observed in mice exposed to the pathogenic stimulus of lipopolysaccharide [31]. At the molecular level, Toll-like receptor 2 is continuously expressed in olfactory microglia, which is a unique characteristic of this particular population of microglia and may explain the sensitivity of the olfactory bulb to certain types of pathology within the brain [31, 32]. Therefore, it is believed that olfactory bulb microglia could serve as sensors or modulators of brain inflammation in general [32].

Integrating the prion theory of neurodegeneration with disease-associated olfactory dysfunction, some have postulated that the olfactory bulb serves as a site of entry for pathogens and other environmental insults, which induce pathological changes via olfactory pathways involving the prion-like spread of protein aggregates [33, 34]. However, neuropathological studies in post-mortem human tissues have not been conclusive regarding the role of

neurodegeneration-associated protein deposits such as tau, amyloid-β, or α-synuclein in olfactory dysfunction [32, 35, 36], suggesting the lack of a direct linkage. Alternatively, other hypotheses point towards a potentially increased susceptibility to external factors, such as viral infections or environmental agents, in patients with neurodegenerative diseases, specifically AD, which could lead to inflammation of the blood-brain barrier and damage to the olfactory bulb [32, 33, 37, 38]. These various hypotheses highlight the need for additional studies that can provide a comprehensive explanation for olfactory dysfunction in neurodegenerative diseases.

Multiple studies have been done regarding olfactory dysfunction in HD. Mice have served as an important animal model for the characterization of olfactory deficits in HD. A study by Menalled et al. in 2003 described mHtt deposits in the olfactory system of a chimeric mouse/human exon 1 containing 140 CAG repeats [39]. Another study using a Q175 knock-in model showed decreased blood oxygen level dependent (BOLD) imaging signal intensity in the olfactory bulb of the mice, suggesting a deficit in olfactory sensitivity [40]. Structural abnormalities in the olfactory bulb and pyriform cortex were also identified in YAC128 mice [41]. The most studied N-terminal transgenic models R6/1 and R6/2 have shown signs of reduced neurogenesis and inflammation associated with the olfactory system, respectively [42–44].

Various olfaction modalities have been evaluated in patients with HD and include detection, intensity discrimination, quality discrimination, emotional valence, and recognition memory. Previous studies have shown that, while patients with HD are able to recognize odors, they may present with impaired odor memory and identification [45–47], as well as altered strength and quality discrimination. Regarding memory, initial studies hypothesized that because individuals with HD may present with manifestations of subcortical pathology as opposed to other cognitive disorders (i.e., AD), olfactory recognition memory would be affected more than the visual or verbal paradigms [3]. Their results were consistent with their hypothesis, however criticized later since they were potentially attributed to lexical difficulties or inattention [48]. More recent evaluations have again reported odor recognition memory deficits in individuals with HD compared to controls using the odor discrimination and memory test (ODMT), which has also been seen in murine models [41].

Importantly, the results have indicated that the aforementioned deficits are due to a primary olfactory impairment rather than a difficulty understanding the assessment tasks [48]. A small study by Mitchell et al. showed interesting results regarding a selective difficulty rating the unpleasantness of odors and cited previous evidence that individuals with HD were specifically impaired with respect to perception of disgust [49], which might indicate a difference in the emotional valence triggered by olfactory stimuli. Although additional studies are needed to replicate these results, they are already of high importance given that individuals with HD-associated olfactory dysfunction may be at risk of harm if they are unable to identify odors associated with potentially dangerous substances.

PREVALENCE OF OLFACTORY DYSFUNCTION IN HD

While less thoroughly described than in other neurodegenerative diseases, HD is known to be associated with hyposmia [50], with several previous studies identifying impairments in odor discrimination, identification, and detection [39, 45, 48]. Although cross-sectional and longitudinal studies have reported data regarding olfactory impairment in HD, these reports have focused on comparisons with other factors in multivariate models, without reporting the number of individuals who present with olfactory dysfunction. One limitation in such studies that prevents an exact measure of the prevalence of HD-associated olfactory dysfunction is the use of different instruments to evaluate this impairment. For example, initial studies utilized preparations of alcohol dilutions [51], while later research conducted standardized tests such as the University of Pennsylvania Smell Identification Test (UPSIT), the Brief Smell Identification Test (B-SIT), and their respective abbreviated versions to assess olfaction [52]. Identifying and using a standard methodology to calculate the prevalence of olfactory dysfunction in patients with HD will aid the identification and management of this specific symptom.

Though widely used in research, the UPSIT has been criticized because of cross-cultural differences which limit its applicability in countries outside of North America [53]. Several efforts have been made to implement and adapt the instrument, including odors that are identifiable by subjects in non-North American countries [54, 55]. Additionally, a study

focused on subjects with PD successfully equated the scores of a variety of different olfactory scales, which allowed for analyses that are more sensitive to different cultural backgrounds [56].

Given that data collected with the UPSIT may be confounded by ethnicity, the B-SIT—an assessment with validity in cross-cultural settings—was introduced in an attempt to overcome this problem [28, 57]. Indeed, recent studies have found that B-SIT scores are relatively resistant to sociodemographic factors such as ethnicity and language [58], and it has been validated for olfactory evaluation in patients who suffer from chronic rhinosinusitis [59]. Furthermore, given that the B-SIT is a brief test, its application in clinical practice may be more feasible. Consequently, this measure can be used for research of olfactory impairment in culturally diverse populations who are at risk or are diagnosed with neurodegenerative disorders, including HD.

NEUROPATHOLOGY OF OLFACTORY DYSFUNCTION IN HD

The deep brain structures known to have the greatest impact on olfaction, as identified by imaging techniques used to find deterioration correlated with olfactory deficits, are the entorhinal cortex, thalamus, parahippocampal gyrus, and caudate nucleus [60]. These structures are of importance since they share connections with the olfactory system. For example, the caudate nucleus and thalamus participate processing olfactory information [61]. It has been found that alterations of the orbitofrontal cortex and hippocampus contribute to deficits in olfactory identification [62]. The striatum relays information to the prefrontal cortex, specifically the lateral orbitofrontal cortex [45, 46]. Studies suggest that olfactory performances may be associated with the lateral orbitofrontal circuit, which receives inputs from the temporal prepyriform cortex, an area also known to be involved in olfaction [63]. In individuals with HD, the neuronal loss in the entorhinal cortex, which has been identified in post-mortem analyses [64], causes disruptions in the connections with the prefrontal cortex, ventral striatum, and the hippocampal formation. This pathologic cell loss leads to disruptions in olfactory information sent to and from olfactory areas of the prefrontal cortex, such as the lateral orbitofrontal cortex [46]. A study evaluating the olfactory event-related potential (OERP) in patients with HD showed that, compared to controls, they had a delay in the P3 component of the OERP, which was also correlated with worse outcomes in various neuropsychological measures [65].

Studies in murine models of HD have shown mHtt deposits in the olfactory bulb, anterior olfactory nucleus, and olfactory tubercle; however, few studies have been conducted to correlate olfactory impairment in mice with HD with the presence of such deposits [39]. Nevertheless, the finding that pathologic protein aggregates are deposited in olfactory structures manifesting as early olfactory impairment as in other neurodegenerative diseases, lends credence to the hypothesis that a similar process may be occurring in HTT pathogenic variant carriers. Furthermore, a recent study comparing post-mortem brain tissue from individuals with HD who experienced olfactory dysfunction with healthy controls found mHtt deposits in the olfactory bulb. Additionally, mHtt deposits were found in the anterior olfactory nucleus, a structure commonly found to harbor disease-specific protein aggregations in other neurodegenerative diseases, suggesting a principal and general role for this structure in the development of olfactory dysfunction. Interestingly, these aggregates were not correlated with the Vonsattel grading system of neuropathology in HD, which focuses primarily on basal ganglia pathology, and no gradient was found along the olfactory bulb and tract, suggesting either the absence of aggregate progression or that deposition occurs earlier, and tissues are saturated in the later stages of disease. Demonstrating the specificity of protein aggregation, no α-synuclein, Lewy bodies, amyloid-β plaques (except for one patient), or phospho-TDP-43 were present in the anterior olfactory nucleus (AON) in these samples [66]. Despite such exciting progress, no studies explicitly correlating the concentration of mHtt protein deposits with olfactory status using a formal smell evaluation have been conducted.

The impact of mHtt deposits in the olfactory bulb of individuals with HD is yet to be fully understood. A study evaluating the presence of inflammatory markers in an R6/2 mice model showed increased glial fibrillary acidic protein (GFAP) expression in the corpus callosum, cerebellum, and olfactory bulb [42]. This might contribute to the olfactory dysfunction demonstrated in individuals with HD; however, further evaluation of mHtt levels and GFAP expression are needed to determine whether inflammation plays a role in the pathophysiology of olfactory dysfunction.

Recent studies have evaluated defective developmental processes that lead to olfactory dysfunction

in HD. Interestingly, a concept denominated *reactive neuroblastosis* has emerged and highlights the process by which migration of neuroblasts is directed towards the degenerating striatum at the expense of olfactory neurogenesis. However, evidence suggests that some of these neurons, which usually originate from the subventricular zone, fail to survive in the striatum and ultimately die [67]. It has been shown that neurogenic regions of the olfactory bulb, specifically the granular cell layer and glomerular layer, present with decreased survival of newly generated neurons in HD, possibly secondary to an altered environment in the presence of mHtt [68]. Decreased neural plasticity in the piriform cortex, a structured mentioned earlier to be involved in olfaction, was also associated with olfactory dysfunction in a study using R6/1 mice [43]. Improvements in molecular techniques are expected to better characterize how defects in neurogenesis correlate with olfactory dysfunction in HD.

Additionally, studies have evaluated altered signaling pathways that might be involved in striatal degeneration or malfunctioning [69]. Adenosine $A2_A$ receptors are known to be decreased in the early stages of HD and coincide with chorea symptoms. Interestingly, evidence in humans points towards degeneration of these receptors in the caudate nucleus, putamen, nucleus accumbens, globus pallidus, and olfactory tubercle [70]. Genetic studies also support this relation since deficiency of these receptors seems to alter DNA methylation and contribute to the pathophysiology of HD [71]. Studies in mice have shown that overexpression of these receptors lead to a decreased striatal lesion volume [72]. Additional studies should be done to better understand the association between this signaling pathway alteration and olfactory dysfunction.

OLFACTORY DYSFUNCTION IN HD CLINICAL PHENOTYPES

Previous prospective, observational studies have highlighted the importance of recognizing early nonmotor manifestations of the disease and the impact such symptoms may have in diagnosis and treatment. Advances in various molecular techniques and the identification of the mHTT gene have allowed for the proper stratification of symptoms according to clinical stages of the disease. Overall, the evidence has pointed towards increasing olfactory dysfunction in individuals with HD, which progresses along the course of the disease.

Interestingly, although not thoroughly studied in HD, the mechanics of sniffing could be involved in an altered perception of odors. It could be expected that this alteration in the voluntary act of smelling was higher in those with more advanced symptoms. Studies in mice have shown that specific frequencies are required to prevent constant inhibition of feedback while sniffing [73], and that disruptions in dopaminergic systems can elicit changes in these frequencies [74]. Also, in juvenile HD sniffing tics have been reported [75] which highlights a potential contribution of altered smell mechanics to olfactory dysfunction.

Identification of olfactory impairment prior to symptom onset is common in other neurodegenerative diseases such as PD and AD and appears to be the case in individuals with premanifest HD. This is relevant as it can potentially allow for earlier recognition of motor symptom onset and could be used a diagnostic indicator along with additional nonmotor symptoms. Table 1 summarizes the available evidence in humans regarding olfactory dysfunction and different clinical phenotypes.

THERAPEUTIC STRATEGIES FOR OLFACTORY DYSFUNCTION IN HD

Identifying olfactory dysfunction in patients with neurodegenerative disorders is not only important for making an early diagnosis, but also for establishing a therapeutic plan in order to prevent adverse outcomes. Various drug classes have been associated with olfactory impairment including certain types of antibiotics, tricyclic antidepressants, antihistamines, antihypertensives, anticonvulsants, and antipsychotics among others [78]. Some medications used for the management of symptoms in patients with HD may amplify olfactory impairment, and the continuation of such agents should be carefully considered depending on the degree of distress it causes. For example, medications such as carbamazepine and clozapine (used to control neuropsychiatric symptoms), and baclofen (for the management of spasticity) have been associated with alterations in smell and taste [78, 79]. Also, patients with HD often present with other comorbidities, and a careful evaluation of other medications should be done to help decrease the severity of olfactory impairment [78].

Table 1
Studies evaluating olfactory dysfunction in individuals with HD according to clinical stages

Study	Number of Participants	Smell Test	Clinical Stage of HD	Results
Moberg et al. 1987 [3]	38 individuals with HD and 38 controls	Battery of 30 different odors developed by the authors	Motor manifest individuals with HD TFC I-II grouped as EHD ($n = 17$) TFC III-IV grouped as LHD ($n = 21$)	EHD had significant olfactory impairment compared to controls
Nordin et al. 1995 [48]	16 individuals with HD and 16 controls	Evaluation of absolute detection and intensity discrimination with butanol dilutions; quality discrimination with four isointensive odorants; recognition memory, and identification with UPSIT	Motor manifest individuals with HD	Motor manifest individuals with HD had deficits in detection and identification, as well as discrimination in quality and intensity. No deficits in recognition memory
Bylsma et al. 1997 [45]	20 individuals with HD and 20 controls	UPSIT	Motor manifest individuals with HD and premanifest HTT pathogenic variant carriers	Motor manifest individuals with HD scored worse compared to premanifest individuals. Increased age was associated with poor performance
Moore et al. 1999 [76]	11 individuals with HD and 40 controls	Odor threshold using butanol dilutions, and odor fluency	Motor manifest individuals with HD	Individuals with HD had poorer odor sensitivity and fluency compared to controls
Larsson et al. 2006 [51]	10 individuals with HD and 10 controls	Evaluation of intensity discrimination with butanol dilutions; quality discrimination with four isointensive odorants; recognition memory and identification	Premanifest HTT pathogenic variant carriers	Premanifest HTT pathogenic variant carriers presented with impaired odor quality discrimination compared to controls
Paulsen et al. 2007 [63]	438 individuals with HD	UPSIT	Premanifest HTT pathogenic variant carriers	Individuals with less estimated time-to-diagnosis had increased olfactory impairment
Pirogovsky et al. 2007 [47]	20 individuals with HD and 28 controls	Evaluation of odor detection with butanol dilutions; odor identification with the San Diego Odor Identification Test	Motor manifest individuals with HD ($n = 10$) Premanifest HTT pathogenic variant carriers ($n = 10$) Nongene carriers ($n = 8$)*	Manifest and premanifest individuals had impaired source memory, but only premanifest individuals had preserved visual stimuli source memory
Tabrizi et al. 2009 [77]	243 individuals with HD and 123 controls	Abbreviated version of UPSIT (20 items)	Motor manifest individuals with HD ($n = 123$) Premanifest HTT pathogenic variant carriers ($n = 120$)	Manifest and premanifest individuals scored worse than controls. There was a higher degree of dysfunction in manifest individuals compared to premanifest
Tabrizi et al. 2011 [52]	243 individuals with HD and 123 controls	Abbreviated version of UPSIT (20 items)	Motor manifest individuals with HD HD1 ($n = 77$) HD2 ($n = 46$) Premanifest HTT pathogenic variant carrier PreHD-A ($n = 62$) PreHD-B ($n = 58$)	Manifest individuals with HD with lower scores in TFC had significant differences in annualized rates of change in the abbreviated UPSIT

*Nongene carriers as individuals who have a parent with HD but who do not carry the genetic mutation for HD. HD, Huntington disease; TFC, Total Functional Capacity; EHD, early HD; LHD, late HD; UPSIT, University of Pennsylvania Smell Identification Test; PreHD-A, further from predicted diagnosis; PreHD-B, nearer from predicted diagnosis; HD1, higher TFC; HD2, lower TFC.

If medications are proven to be the etiology of olfactory dysfunction or bear a temporal association with symptom onset or exacerbation, they should be altered or discontinued, if possible. However, when a neurodegenerative disorder such as HD is the sole cause of olfactory impairment, it is very important to educate patients and caregivers about safety measures regarding the use of smoke and gas alarms, as well as

the need to pay close attention to the expiration date of food. Various techniques and procedures for the treatment of olfactory dysfunction in patients with pathologies such as chronic rhinosinusitis and post-infectious smell impairment have been studied. For example, olfactory training, which relies on repetitive exposure to different odors to increase sensitivity towards them, has shown to be helpful in this subset of patients with an improvement in 25% compared to 7% in the control group [80]. To increase its impact, different modalities to improve adherence [81] and longer periods of training [82] have shown to be more effective. There is no evidence for the use of olfactory training in individuals with HD [83, 84].

CONCLUSIONS

While progress has been made to integrate olfactory dysfunction into the larger understanding of HD pathophysiology and related clinical symptomatology, more research is required to fully characterize this aspect of the disease. In addition to filling multiple gaps in our knowledge regarding HD, there are practical benefits to this line of inquiry as well. Particularly, ascertaining the prognostic utility of monitoring olfactory status in individuals with premanifest HD is a worthwhile endeavor. A definitive answer to this question could have immediate relevance to the management of HD and could be adopted to clinical practice relatively easily. Studying olfactory dysfunction in HD could help in uncovering the role olfactory pathways might play in disease pathogenesis, such as the hypothesis that protein aggregates originating in the olfactory bulb influence pathological deposition elsewhere in the brain, or that inflammation and neurogenesis are among the initiating events that lead to impairments in olfaction. Thus, an opportunity exists to determine whether there are any correlations between loss of olfactory function and the motor, cognitive, and neuropsychiatric manifestations of HD. There is also an opportunity to obtain more evidence regarding the applicability of therapies such as olfactory training to improve olfaction in individuals with HD. In conclusion, continued efforts should be made to enhance our understanding of the role olfactory dysfunction plays in HD. Olfactory function is fairly easy to evaluate clinically and should be considered as an important tool in further developing diagnostic and therapeutic strategies in HD.

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CONFLICT OF INTEREST

The authors have no conflict of interest to report.

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