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# Underestimated olfactory domains in Huntington's disease: odour discrimination and threshold

E Amini[1,2], M Rohani[2,3], S A H Habibi[2], Z Azad[3], N Yazdi[2], E Cubo[4], T Hummel[5] and M Jalessi[3,6]

[1]ENT and Head and Neck Research Center, The Five Senses Health Institute, Rasoul Akram Hospital, Iran University of Medical Sciences, Tehran, Iran, [2]Department of Neurology, Rasoul Akram Hospital, School of Medicine, Iran University of Medical Sciences, Tehran, Iran, [3]Skull Base Research Center, The Five Senses Health Institute, Rasoul Akram Hospital, Iran University of Medical Sciences, Tehran, Iran, [4]Neurology Department, Hospital Universitario Burgos, University of Burgos, Burgos, Spain, [5]Smell and Taste Clinic, Department of Otorhinolaryngology, TU Dresden, Dresden, Germany and [6]Department of Otorhinolaryngology, Head and Neck Surgery, Rasoul Akram Hospital, School of Medicine, Iran University of Medical Sciences, Tehran, Iran

## Abstract

**Background.** Olfaction has recently found clinical value in prediction, discrimination and prognosis of some neurodegenerative disorders. However, data originating from standard tests on olfactory dysfunction in Huntington's disease are limited to odour identification, which is only one domain of olfactory perceptual space.

**Method.** Twenty-five patients and 25 age- and gender-matched controls were evaluated by the Sniffin' Sticks test in three domains of odour threshold, odour discrimination, odour identification and the sum score of them. Patients' motor function was assessed based on the Unified Huntington's Disease Rating Scale.

**Results.** Compared with controls, patients' scores of all olfactory domains and their sum were significantly lower. Besides, our patients' odour threshold and odour discrimination impairments were more frequently impaired than odour identification impairment (86 per cent and 81 per cent *vs* 34 per cent, respectively).

**Conclusion.** Olfactory impairment is a common finding in patients with Huntington's disease; it is not limited to odour identification but is more pronounced in odour discrimination and odour threshold.

## Main Article

Maryam Jalessi takes responsibility for the integrity of the content of the paper

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**Corresponding author:**
Maryam Jalessi;
Email: dr.jalessi@googlemail.com

## Introduction

Huntington's disease is an autosomal dominant neurodegenerative disorder with progressive cognition and psychomotor function deterioration as the main presentations.[1] The reported prevalence of Huntington's disease is 6–14 per 100,000 people, and the expanded cytosine-adenine-guanine triplet repeats on the short arm of chromosome 4 and is known as the genetic basis.[1,2] The disease onset is clinically defined as the development of a motor sign that is strongly related to Huntington's disease, which usually appears at 30 to 50 years old.[3] The more cytosine-adenine-guanine repeats, the earlier the disease onset.[3] A subsequent progressive course with no available curative or disease-modifying treatments leads to enormous morbidity and dependency for the patient.[3]

Olfactory impairment has been recently suggested as a potential early diagnostic, discriminative and prognostic biomarker in some neurodegenerative diseases.[4–7] It has been hypothesised that the propagation pattern of the aggregated protein in peripheral and central olfactory structures might lead to the development of the disease.[8] Closer examination of olfactory function in neurodegenerative diseases may be worthwhile in patient categorisation to determine the best intervention time with the future advent of disease-modifying treatments.[9] The prevalence of olfactory impairment has been reported to be 45 per cent to 90 per cent in Parkinson's disease and 100 per cent in Alzheimer's disease, while the exact prevalence has remained unknown in Huntington's disease.[9–11]

Olfactory impairment in Huntington's disease has been reported in some studies with limited olfactory assessment tools.[12–21] In a clinical and research setting, the assessment tool should ideally include tests of odour threshold, odour discrimination and odour identification (or at least threshold and one of the supra-threshold tests).[22] Moreover, the thorough combination of odour threshold and supra-threshold olfactory tests increases the diagnostic value and the accuracy of the assessment in Huntington's disease patients.[22,23] There is evidence suggesting that the pattern of olfactory dysfunction can help to find the possible aetiologies; peripheral pathologies are more represented by the odour threshold test, and central or cognitive underlying pathologies are better shown in the supra-threshold tests of odour discrimination and odour identification.[23–25]

The frequently applied psychophysiological tests for evaluating olfaction in Huntington's disease patients are the University of Pennsylvania Smell Identification

Test and its national variants, the Brief-Smell Identification Test.[13,14,17,19,20] These two olfactory tests only evaluate impairment in odour identification.[9,26] The scant available data on odour discrimination and odour threshold in Huntington's disease are not based on appropriate standard tests. A well-validated and highly reliable test for quantitative assessment of olfactory function is the Sniffin' Sticks test, which is widely used to measure odour threshold, odour discrimination and odour identification.[26] Because olfactory function weakens along with ageing and is also affected by gender, the cut-off scores for discriminating normosmia, hyposmia and anosmia are considered within predefined age groups, separately for men and women.[27–29] This study aims to describe olfactory function in Huntington's disease patients in the three domains of odour identification, odour discrimination and odour threshold and to examine correlations with genetics, disease duration and severity of Huntington's disease motor dysfunction.

## Materials and methods

This study was performed between November 2019 and March 2023 in a clinic for movement disorders at a tertiary hospital. Twenty-five genetically confirmed Huntington's disease patients and 25 healthy sex- and age-matched volunteers were evaluated. The control participants were recruited from the hospital personnel and were enrolled only if they had no olfactory complaints. Participants with chronic rhinosinusitis, history of nasal or paranasal sinus surgery, recent respiratory tract infection and olfactory disorders following coronavirus disease 2019, or previous head trauma were excluded. Patients with cognitive decline (Mini-Mental State Examination score below 24) were excluded.[30] Patients' age, disease duration and gene expansion repeats were extracted from their electronic medical records. Cytosine-adenine-guanine age-product score was calculated as defined by Ross *et al.* (i.e. $100 \times \text{age} \times (\text{genetic} - 30 \div 627)$).[31] The study protocol was explained to the participants, and written informed consent was obtained. All the procedures contributing to this work were in accordance with the ethical standards of the relevant national and institutional review board guidelines on human experimentation at the Iran University of Medical Sciences (IR.IUMS.FMD.REC.1399.350) and were compliant with the Helsinki Declaration of 1975, as revised in 2008.

The cognitive evaluation was performed using adapted Mini-Mental State Examination by a single expert neurologist,[30] and the total score was calculated. The highest possible score is 30, and a score less than 24 is considered a cognitive impairment.[30] The motor score of the Unified Huntington's Disease Rating Scale was assessed by an expert neurologist in movement disorders for each patient. A higher score correlates with more severe motor dysfunction. The sum of the scores was finally calculated. The olfactory function of the Huntington's disease patients and healthy individuals was evaluated using the Sniffin' Sticks test, which includes three domains to measure odour threshold, odour discrimination and odour identification.[32]

The N-butanol odour threshold was assessed by a single-staircase, three-alternative forced-choice procedure. Three pens were presented to the patient in a randomised order; two contained an odourless solvent (propylene glycol), and the other an odorant in specific dilutions. The participants were asked to identify the pen with the odorant. The odour threshold score is the average of the last four turning points and it ranges from 1 to 16.

For odour discrimination, participants were offered 16 triplets of pens, each including two identical odours and one different odour. Then, patients were instructed to choose the distinct odour. The odour discrimination was the sum of correct responses ranging from 0 to 16.

To evaluate odour identification, 16 pens that included common odours were offered. The participants had to identify each odorant from a list of four descriptors. The odour identification score was the sum of correct responses ranging from 0 to 16. The sum of the scores of all three domains resulted in the threshold, discrimination and identification score, which had a maximum of 48 points.

A threshold, discrimination and identification score below 30.75 was considered hyposmia.[27] Their threshold, discrimination, identification and olfactory scores in each domain were compared with their related age and gender subgroups based on the most recent available normative data.[27]

For data analysis, SPSS® (version 22.0) statistical analysis software was used to analyse the statistical variables. The Kolmogorov–Smirnov test assessed the normal distribution, and non-parametric tests were performed accordingly. Data were presented as mean and standard deviation for quantitative variables and as percentage for qualitative variables. The Spearman correlation test assessed the correlation between the variables. The Mann–Whitney U test was applied to compare quantitative variables. The receiver operating characteristics curve was used to detect the olfactory subtests with the largest area under the curve that could discriminate patients from healthy controls. *P*-values less than 0.05 were set as a statistically significant level.

## Results

Twenty-one eligible patients with Huntington's disease were enrolled in the final analysis. Based on Mini-Mental State Examination scores, four patients were not included because of their cognitive impairment. The mean age of Huntington's disease patients was 50.8 ± 12.2 years (range from 32 to 72) and 48 per cent (10 patients) were women. These were not significantly different from the control group, with a mean age of 44.3 ± 12.3 years and 52 per cent (11 participants) being women. On average, disease duration was 5.1 ± 5.0 years (ranging from 1 to 15 years). The mean age at disease onset was 45.0 ± 12.3 years (ranging from 21 to 64 years). The mean gene expansion repeat was 44 ± 5.9 (median, 41).

Patients had a mean total Mini-Mental State Examination score of 26.23 ± 1.89 (ranging from 24 to 30). The mean Unified Huntington's Disease Rating Scale score was 25.19 ± 15.68 (ranging from 6 to 52). The detailed scores of the Unified Huntington's Disease Rating Scale-motor part are shown in Table 1 in the supplementary material, available on *The Journal of Laryngology & Otology* website. The average cytosine-adenine-guanine age-product score was 109.3 ± 44.3 (ranging from 52.6 to 186).

The Huntington's disease group's mean threshold, discrimination and identification score was significantly lower than the control group. Furthermore, compared with the control group, patients had significantly lower odour threshold, odour discrimination and odour identification scores (Table 1).

All the Huntington's disease patients showed olfactory dysfunction according to the cut-off value of 30.75 for the threshold, discrimination and identification score, whereas all the participants in the control group had normal threshold, discrimination and identification scores.

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**Table 1.** The average of olfactory assessment scores and the hyposmia and normosmia number and frequency of the participants

| Olfactory subtests | Patients* | Controls† | *P*-value |
|---|---|---|---|
| Odour identification | | | |
| – Score (mean (SD)) | 11.90 (2.52) | 14.16 (2.03) | <0.001 |
| – Hyposmic (*n* (%)) | 7 (33.3) | 1 (4) | 0.009 |
| – Normosmic (*n* (%)) | 14 (66.7) | 24 (96) | |
| Odour discrimination | | | |
| – Score (mean (SD)) | 6.66 (2.49) | 12.76 (1.39) | <0.001 |
| – Hyposmic (*n* (%)) | 17 (81) | 1 (4) | <0.001 |
| – Normosmic (*n* (%)) | 4 (19) | 24 (96) | |
| Odour threshold | | | |
| – Score (mean (SD)) | 2.17 (2.58) | 7.23 (3.49) | <0.001 |
| – Hyposmic (*n* (%)) | 18 (85.7) | 4 (16) | <0.001 |
| – Normosmic (*n* (%)) | 3 (14.3) | 21 (84) | |
| Total (TDI) | | | |
| – Score (mean (SD)) | 20.75 (4.75) | 34.15 (3.15) | <0.001 |
| – Hyposmic (*n* (%)) | 18 (85.7) | 0 | <0.001 |
| – Normosmic (*n* (%)) | 3 (14.3) | 25 (100) | |

*$n = 21$; †$n = 25$. SD = standard deviation; TDI = sum of threshold, discrimination and identification scores

The number and frequency of hyposmic and normosmic participants based on the normative data of the specific age and gender subgroups are shown in Table 1. The frequency of hyposmic patients was significantly higher in all three Sniffin' Sticks domains and threshold, discrimination and identification scores compared with the control group (Table 1).

Receiver operating characteristic analysis showed that the area under the curve was 0.93 for odour threshold, 0.99 for odour discrimination, 0.78 for odour identification and 0.97 for threshold, discrimination and identification. Figure 1 shows that the Sniffin' Sticks test domains and threshold, discrimination and identification could significantly discriminate Huntington's disease patients from healthy individuals ($p \leq 0.001$ for all).

There was no significant relationship between the olfactory test results, Mini-Mental State Examination, Unified Huntington's Disease Rating Scale, disease duration, age and gene expansion repeats. Gene expansion repeat was negatively correlated with age ($r = -0.44$, $p = 0.04$) and age at disease onset ($r = -0.55$, $p = 0.01$).

Unified Huntington's Disease Rating Scale total motor score was inversely correlated with threshold, discrimination and identification ($r = -0.43$, $p = 0.04$) but not with any of its components separately. Cytosine-adenine-guanine age-product score was positively correlated with gene expansion repeats ($r = -0.80$, $p < 0.001$). Cytosine-adenine-guanine age-product score was not correlated with either the Sniffin' Sticks domains or the threshold, discrimination and identification score.

## Discussion

This study evaluated the comprehensive olfactory function (odour discrimination, odour threshold and odour identification) in manifest Huntington's disease patients using a standard olfactory test (Sniffin' Sticks) that showed a highly significant decrease in all subtests in Huntington's disease patients compared with the control group. The most prominent finding of this study was that odour discrimination and odour threshold were significantly impaired compared with the control group. This study is the first study evaluating odour threshold and odour discrimination by a reliable, validated and highly standardised olfactory test. The total of the threshold, discrimination and identification score has a cut-off value of 30.75 points, which is used to define the normosmic group and was calculated in a reference group of young adults.[27] According to this cut-off, all of our patients showed olfactory impairment. However, based on the most recently available normative data by Oleszkiewicz *et al.*[27] for specific sex and age subgroups for this test, olfactory impairment was detected in 86 per cent of the patients when considering the threshold, discrimination and identification score (86 per cent, 81 per cent and 34 per cent of the patients in the odour threshold, odour discrimination and odour identification domains, respectively). Receiver operating characteristics analysis indicated that among Sniffin' Sticks domains, odour identification had the lowest capacity to discriminate our Huntington's disease patients from healthy individuals (area under the curve = 0.78). In contrast, odour discrimination (area under the curve = 0.99) and odour threshold (area under the curve = 0.93) appeared to have higher capacities in this study. Besides, our patients' odour threshold and odour discrimination were more frequently impaired than odour identification.

Olfactory involvement is a presentation of some neurodegenerative diseases, including Parkinson's disease, Alzheimer's disease and dementia with Lewy bodies.[8] Olfactory dysfunction has been evaluated in Huntington's disease patients mainly with odour identification. However, according to the odour identification domain of Sniffin' Sticks, only one-third of the patients were detected to be olfactory impaired. Therefore, a thorough evaluation of olfaction in all three domains might be valuable to identify patients with olfactory impairment in order to inform clinicians, patients and their caregivers to be aware of the potential related health risks and to apply protective measures, such as the use of a gas alarm, specific attention to food expiration dates, keeping weight and appetite in balance and special attention to the role of olfactory loss in psychiatric presentations of Huntington's disease.[33,34]

Although the exact mechanism of olfactory dysfunction in this group of diseases has not yet been comprehensively clarified, the reported pathological changes vary from olfactory receptors to the olfactory cortex and between structures.[8] Earlier Huntington's disease studies have shown inclusions of the mutated huntingtin protein, and consequent neuropathological changes occur markedly in the midbrain, cortex, brainstem, amygdala and cerebellum.[35,36] A recent study on 13 post-mortem Huntington's disease cases showed huntingtin aggregation, especially in the anterior olfactory nucleus in the olfactory bulb.[37] Some evidence regarding odour threshold preservation in Alzheimer's disease and Parkinson's disease patients suggests that the peripheral sensory organ is intact.[38,39] Although the most peripheral structure of the olfactory system, olfactory neuroepithelium, has not yet been evaluated in Huntington's disease patients, decreased odour threshold in our patients may represent a peripheral pathology whereas impaired odour identification and odour discrimination support involvement of the central olfactory system. Therefore, a thorough olfactory tract pathohistological study, including the olfactory epithelium of Huntington's disease

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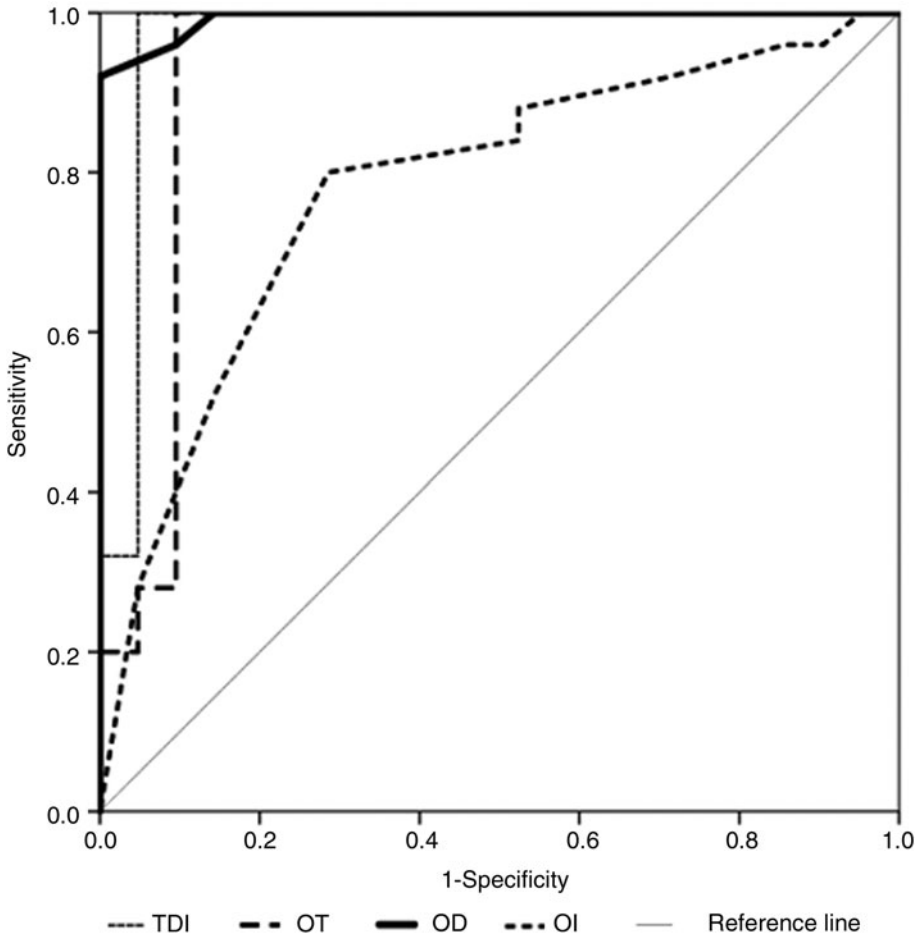


**Figure 1.** Receiver operating characteristics curve analysis of the Sniffin' Sticks test and its domains for discriminating patients with Huntington's disease from healthy controls. Area under the curve was 0.93 (95 per cent confidence interval (CI), 0.83–1.00) for odour threshold (OT), 0.99 (95 per cent CI, 0.98–1.00) for odour discrimination (OD), 0.78 (95 per cent CI, 0.64–92) for odour identification (OI) and 0.97 (95 per cent CI, 0.90–1.00) for the sum score of odour threshold, odour discrimination and odour identification (TDI) ($p \leq 0.001$ for all). Diagonal segments are produced by ties.

patients, is required to determine the exact mechanisms of the olfactory loss.

Our results demonstrated an association between threshold, discrimination and identification and motor score in Huntington's disease with the evaluation of Unified Huntington's Disease Rating Scale-motor part score as a clue to the severity of the disease. According to the results, the worse the olfactory impairment, the worse the motor function. This correlation has not been reported in Huntington's disease patients previously. Furthermore, olfactory impairment is correlated with motor impairment in some neurodegenerative diseases, such as Parkinson's disease.[40,41] In a recent longitudinal study, it was shown that despite the high prevalence of olfactory impairment among three subgroups of patients with Parkinson's disease (i.e. tremor dominant, postural instability and gait difficulty), it was only in the tremor dominant subgroup that the olfactory dysfunction was correlated with motor impairment.[41] Structural connections and dopaminergic and cholinergic neurotransmitter dysregulation are responsible for different central pathways that have explained these correlations between olfactory impairment and motor deficit.[40,42,43] The connection between the substantia nigra and olfactory structures may explain relevant motor symptoms and anosmia in Parkinson's disease.[44] These findings point towards the potential utility of olfactory dysfunction for tracking the progression of Parkinson's disease. Further studies with an appropriate sample size are also required to confirm this finding in Huntington's disease.

In this study, we also considered the association between olfactory impairment and cytosine-adenine-guanine age-product score, an index of the exposure chronicity to the pathogenic mechanisms of Huntington's disease. We were not able to detect any association between cytosine-adenine-guanine age-product and olfactory scores. However, in a recent study, an association between odour identification impairment and cytosine-adenine-guanine age-product score was reported in Huntington's disease patients.[21] A possible explanation for this discrepancy may be the limited sample size of both studies.

This study has some limitations besides the limited sample size. We did not evaluate other parts of the Unified Huntington's Disease Rating Scale. These assessments, especially behavioural function and total functional capacity, may also be associated with olfactory function. However, we evaluated the cognitive status of the patients with a separate test (Mini-Mental State Examination) and included only the patients with normal cognition. Moreover, using the cut-offs based on the European population normative data may have affected our results because of using a culturally adapted Sniffin' Sticks identification subtest. In order to overcome this shortcoming, we also compared the results with a sex- and age-matched control group.

There are studies trying to find a biomarker capable of determining the progression of Huntington's disease.[17,20,45] Although extensive longitudinal Huntington's disease studies have been combined and analysed to track Huntington's disease progression with the best possible model among imaging markers and various models of clinical presentation (e.g. motor and cognition) as potential biomarkers, olfactory dysfunction could not be taken into account.[46] In this study, we showed that olfactory impairment is quite prevalent in Huntington's disease, especially in patients without clinically detectable cognitive presentations and has a significant

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relationship with motor function in these patients. Olfactory dysfunction may be necessary for tracking disease severity and chronicity. Therefore, a longitudinal study is needed, including a thorough Unified Huntington's Disease Rating Scale examination for a complete evaluation of the disease severity along with a comprehensive olfactory assessment) to evaluate the capability of olfactory status as a prognostic biomarker in Huntington's disease.

- Available data on Huntington's disease originating from standard tests on olfactory dysfunction are limited to odour identification, which is only one domain of olfactory perceptual space
- All three domains of olfaction are impaired in patients with Huntington's disease
- Odour threshold and odour discrimination were more frequently impaired than odour identification in patients with Huntington's disease
- A total of 86 per cent of patients with Huntington's disease were hyposmic based on the normative data specific for the age and gender subgroups
- Odour identification had the lowest capacity to discriminate Huntington's disease patients from healthy individuals
- Unified Huntington's Disease Rating Scale score was inversely correlated with the Sniffin' Sticks score

## Conclusion

Olfactory impairment is a common finding in Huntington's disease patients, even in those with normal cognitive function, which is not limited to odour identification but is more pronounced in odour discrimination and odour threshold. Longitudinal studies with proportionate sample size and a thorough olfaction assessment are needed to determine the pattern of olfactory involvement from pre-symptomatic Huntington's disease to the end stage of the disease.

**Supplementary material.** The supplementary material for this article can be found at https://doi.org/10.1017/S002221512300124X.

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**Competing interests.** None declared

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