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# Smell status in functional movement disorders: New clues for diagnosis and underlying mechanisms

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ABSTRACT

*Objective:* Functional movement disorders (FMDs) mimic a range of movements, neuropsychiatric and neurodegenerative disorders known to have smell dysfunction, which has been neglected in terms of its application to FMD. We aim to determine the smell status in FMD patients tested by a non-invasive, reliable and validated olfactory test.

*Patients and methods:* We quantitatively assessed in thirty-five FMD patients their smell status and compared it to that of healthy age- and sex-matched controls, and of patients with Parkinson's disease (PD). All participants were administered the Brief Smell Identification Test (B-SIT), a standardized short version of the University of Pennsylvania Smell Identification Test (UPSIT). The Picture Identification Test (PIT), a visual test analogous in content and form to the UPSIT designed to control for non-olfactory cognitive confounds, was also administered.

*Results:* The B-SIT scores of the FMD patients were higher than those from PD patients [respective means (standard deviations: SDs) = FMD, 9.54 (1.57); PD, 4.64 (1.05), $p < 0.01$)] but similar to the smell scores from healthy controls [9.97 (1.77), $p = 0.35$]. Gender, age, time of disease onset, smoking status, and phenotypic expression did not influence the test scores. Fourteen FMD patients who mentioned having olfactory dysfunction before smell testing have their test results within normal range. PIT scores from patients and healthy controls were within normal range.

*Conclusions:* These findings indicate that FMD patients have normal olfactory function. Olfactory testing may be helpful in identifying and differentiating FMD from other movement, neurodegenerative and neuropsychiatric diseases for which smell function is altered.

## 1. Introduction

Functional movement disorders (FMDs) are disorders characterized by abnormal movements that cannot be attributed to any known structural abnormality [1]. Psychiatric comorbidities are often present [2]. Patients with FMD account for about half of patients with functional neurological symptoms [3]. Depending upon case definition and setting of the clinic FMD prevalence ranges from 2 to 20% of patients seen at movement disorder clinics [3]. FMD can present tremor, dystonia, parkinsonism, gait disturbances, speech disorders, and diverse hyperkinetic movements [4]. Hypokinetic and sometimes paralytic conditions have also been reported [5]. Furthermore, FMD mimics a full range of involuntary and abnormal movements of known origin (IAMOK), adding to difficulties in correctly diagnosing psychogenic movement disorders [6]. Such diagnostic confusions have resulted in inappropriate pharmacological and non-pharmacological interventions, complicating the course of the disorder [3]. Clearly, there is an urgent need to identify FMDs upon initial clinical presentation so that appropriate, focused and timely therapies can be initiated.

It is now generally appreciated that a number of IAMOKs are accompanied by a number of non-motor alterations, some of which are diagnosed by costly, and sometimes invasive, tests such as positron

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emission tomography or molecular biology studies [7,8]. Alterations in olfactory function are of particular value, since such non-motor dysfunction can be detected by non-invasive and cheaper tests, have been proposed as disease biomarkers and can aid in differential diagnosis of a number of movement, neuropsychiatric and neurodegenerative disorders. Indeed, smell status is useful in differentiating Parkinson's disease (PD) from progressive supranuclear palsy (PSP) and essential tremor [9–11], and Alzheimer's disease (AD) from depression [12]. Objective olfactory testing has also been useful in detecting a number of psychiatric disorders, as well as malingering [13]. Similarly, different degrees of smell dysfunction have also been unveiled in focal and generalized dystonia [14,15], hyperkinetic disorders [16], and gait-associated movement disorders [17]. While smell testing has become part of the diagnostic armamentarium in some countries in regard to several of the aforementioned disorders, it has been neglected in terms of its application to FMD.

The aim of this study was to determine the smell status in patients with FMD tested by a non-invasive, worldwide validated and cheap olfactory test. Since the forebrain, a key brain area that modulates smell, is usually spared in FMD but altered in a number of neural disorders showing olfactory dysfunction-associated cholinergic circuits such as PD, dystonia, tremor, and hyperkinetic disorders we hypothesized that smell function should be preserved or minimally altered in FMD. If this proves true, then smell testing may be useful as a supportive diagnostic test for FMD, and would be useful in differentiating FMD from a number of IAMOKs. Alternatively, if smell dysfunction is present, this would raise new questions on the mechanisms involved in functional (psychogenic) movement disorders. Our novel and robust results on the smell status in FMD may open new avenues about disease pathophysiology, and will help to improve diagnostic assessment.

## 2. Materials and methods

### 2.1. FMD patients

Thirty-five consecutive patients seen in a specialized FMD clinic [17] [10 men, 25 women; mean (SD) age = 49.0 (13.2)] were studied. All patients fulfilled the clinical criteria for FMD as defined by Fahn and Williams [18]. Symptom duration ranged from 3 months to 20 years; mean = 5.53 years. The diagnosis of FMD was confirmed by a neurologist with fellowship training in movement disorders (KL). Information on demographics (i.e., gender, age, disease duration, mode of disease onset, family history), lifestyle (i.e., smoking habits), and general health status was obtained via face-to-face interviews as part of the clinical visits. Patients were also asked whether they were aware of any olfactory dysfunction. Patients who had a history of other neurological disorders, apparent cognitive disorder, traumatic brain injury, viral infections, or sinonasal diseases were excluded. Data from patients were obtained as part of a comprehensive evaluation done in a specialized FMD clinic [19], and retrospectively analyzed (Supplementary material). The study was approved by the ethics committee of the University of Louisville.

### 2.2. Controls

We included as controls selected individuals with PD who had phenotypes similar to some of those found in our group of FMD patients (e.g., hand tremor, foot tremor, gait disturbances), and healthy participants. This approach is more accurate than testing smell status in patients only [11,14,15], or using normative data [20].

17 patients with a diagnosis of PD based on UK brain bank criteria were studied [21,22]. The starting symptom in these PD patients was resting hand tremor in 12, resting foot tremor in 3, and gait disturbances (e.g., unsteadiness and arrhythmicity of stepping) in 2. PD motor symptoms were present for 4.2 ± 2.3 years. The mean ( ± standard deviation) of the Hoehn &Yahr scale was 1.4 (0.5), of the UPDRS motor score was 21.9 (12.4), and of the Minimental state examination was 28 (1.1). Two PD patients were past smokers. Medications were carbidopa/levodopa 25/100 (n = 9), pramipexole (n = 6), or ropinirole (n = 2).

Thirty-five healthy participants (HP) [10 men, 25 women; 49.8 (12.5) without neurological deficits were also studied. These participants were matched to FMD patients with respect to age and gender. All controls provided written informed consent after receiving a thorough explanation of the study. This study protocol was reviewed and approved by the ethics committee of the Mediciencias Research Group and of the University of Louisville. All participants were studied in accordance with the ethical principles of the Declaration of Helsinki (1964) and its later amendments.

### 2.3. Olfactory function

Olfaction was assessed using the Brief Smell Identification Test (B-SIT), a forced choice test comprised of twelve odorant items presented on microencapsulated pads (scratch and sniff). Also known as the Cross-Cultural Smell Identification Test [23], the B-SIT is a standardized shorter version of the widely used University of Pennsylvania Smell Identification Test or UPSIT [24]. Six of its odorants are food related (lemon, banana, pineapple, chocolate, cinnamon, and onion) and six nonfood related (rose, gasoline, smoke, turpentine, soap, and paint thinner). Each microencapsulated scent was released in a standardized manner by scratching the odorized strip using a pencil tip. Although the B-SIT is typically self-administered, in this study a trained technician individually administered it to each subject. The odor of the odorized strips was released under the subject's nose, and following sniffing the subject selected one of four possible multiple-choice answers. The response alternatives were read by the experimenter to the subject. The experimenter encouraged every subject to vigorously sniff each stimulus and visually confirmed that adequate sniffing occurred. The participant had to indicate which of the four response alternatives was most similar to the perceived odor. Participants were instructed to choose a response alternative even if no smell was perceived. The number of correctly identified odors served as the test score, with higher scores denoting better performance.

### 2.4. Cognitive studies

To be certain that the test measures were not meaningfully confounded by cognitive problems undetected during the medical exam at the clinic or the lack of knowledge of the concepts employed in the B-SIT, we administered the Picture Identification Test (PIT). This test, designed to control for non-olfactory cognitive confounds, is analogous in content and form to the UPSIT, but uses pictures rather than odors as test stimuli [25]. The PIT was administered after the application of the B-SIT in 33% of the patients pseudorandom selected, and in all controls.

### 2.5. Statistical analyses

For descriptive statistics, percentage was used as the dependent measure for most categorical variables (e.g., relatives with an IAMOK). Variables with continuous measurements (e.g., age, B-SIT scores) were expressed as mean ± standard deviation. Frequency differences were analyzed using Fisher's exact probability test. Paired t-tests were used to compare continuous measures across matched subjects. Analysis of Covariance (ANCOVA) was employed to assess whether the B-SIT scores of patients and controls differed and covaried with age, gender, smoking habits, and mode of disease onset (sudden vs chronic). Another ANCOVA was run to dissect possible effects of pattern of disease progression; accordingly, the test scores were compared between subjects who have one and more than one symptom found at exam. The area under the receiver operating characteristic curve (AUC) was used to analyze the sensitivity and specificity of smell testing in FMD. The AUC

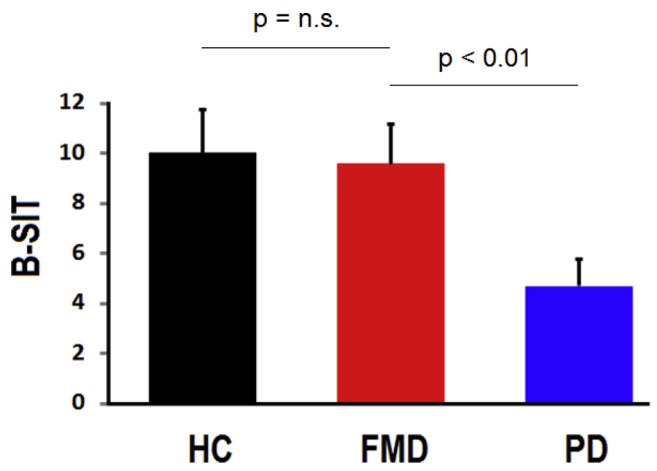


**Fig. 1.** Y-axis: B-SIT scores from participants (Mean + SD); X-axis: FMD: functional movement disorders; HC: healthy controls; PD: Parkinson's disease. n: not significant.

values ranges from 0 to 1, and have the ability to discriminate individuals with and without a disease [26]. Positive and negative likelihood ratio (LR) tests were calculated from the AUC data.

### 2.6. Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## 3. Results

The B-SIT score from FMD patients (9.54 ± 1.57) was significantly higher than that from PD patients (4.64 ± 1.05, $p < 0.01$), and similar to HP score (9.97 ± 1.77, $p = 0.35$) (Fig. 1). The AUC was 0.983 (95% confidence interval: 0.946 - 1.0**)**. The optimal cutoff value was found to be 6.5. This value had a sensitivity of 1.0 and a specificity of 0.667. Negative LR test was zero whereas positive LR test was 1.5 (Fig. 2).

Neither gender nor cigarette smoking significantly influenced the B-SIT scores in either the FMD or control groups (ps ranging from 0.18 to 0.36) (Table 1).

Smell function was unaffected by disease duration ($p = 0.53$). Five of the FMD patients mentioned experiencing olfactory dysfunction prior to testing. However, their test scores were within normal limits and did not differ from the test scores of the other FMD subjects ($p = 0.34$). 20% of FMD patients reported having a relative with IAMOK whereas it was found in 3% of the controls only ($p = 0.05$). FMD Patients who complained about subjective smell abnormalities were not among those who reported relatives with IAMOK ($p = 0.56$). FMD pattern distribution (one versus more than one symptom) was unrelated to the B-SIT scores ($p = 0.87$). PIT scores did not differ significantly between FMD patients and controls (FMD: 38 ± 0.06, PD: 39.8 ± 0.33 and HP 39.8 ± 0.10, $p = 0.1$).

## 4. Discussion

The present study demonstrates that olfactory function is unimpaired in patients with FMD. Further, these patients were cognitively intact enough to understand the concepts involved in the identification task. These findings imply that a brief olfactory test such as the B-SIT provides a rapid and practical way of differentiating FMD from a number of neurodegenerative, movement, and neuropsychiatric disorders known to have smell dysfunction, which in some cases precedes disease diagnosis by years [27]. For instance, low smell scores have been found in patients with clinical and laboratory proven PD [27],

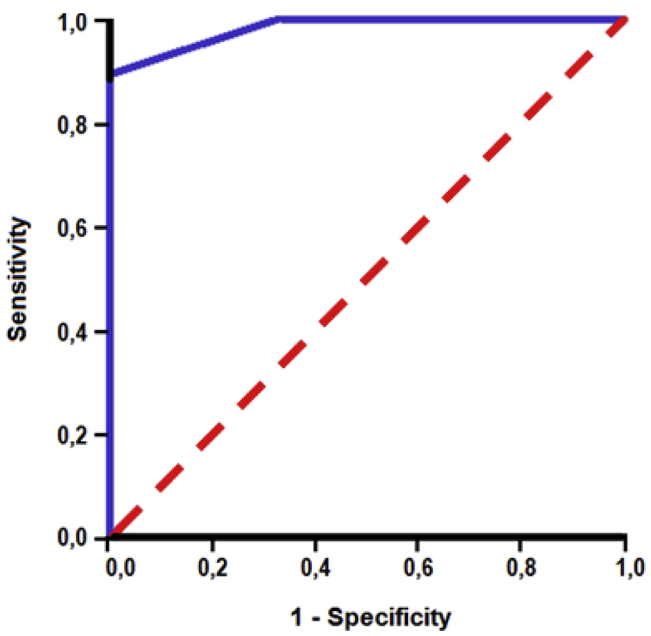


**Fig. 2.** Receiver operator characteristics for B-SIT in FMD. Blue line: our study. Red dotted line: random results. See the text for AUC value. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

**Table 1**
B-SIT scores in FMD patients and healthy controls. The smell scores were itemized by factors with possible impact on smell function. Complain: Participants who mentioned to have (+) and not to have (-) altered smell during clinical evaluation. Participants who had (+) and had not (-) a relative with IAMOK.

| | | FMD (n) | Controls (n) |
|---|---|---|---|
| Total participants | | 9.54 ± 1.57 (35) | 9.97 ± 1.77 (35) |
| Gender | | | |
| | Male | 9.2 ± 1.98 (10) | 9.4 ± 1.64 (10) |
| | Female | 9.68 ± 1.4 (25) | 10.2 ± 1.8 (25) |
| Smoking status | | | |
| | Past | 9.8 ± 1.36 (13) | 9.8 ± 1.6 (6) |
| | Current | 8.25 ± 2.06 (3) | 9.2 ± 2.38 (5) |
| | Never | 9.6 ± 1.56 (19) | 10.3 ± 1.7 (24) |
| Disease onset | | | |
| | Abrupt | 9.65 ± 1.72 (9) | – |
| | Gradual | 9.22 ± 1.64 (26) | – |
| Smell complain | | | |
| | Complain + | 10.1 ± 1.22 (5) | – |
| | Complain - | 9.46 ± 1.63 (30) | – |
| Relative with IAMOK | | | |
| | Relative + | 10.2 ± 0.9 (7) | – |
| | Relative - | 9.35 ± 1.66 (28) | – |
| Number of symptoms | | | |
| | One | 9.42 ± 1.8 (19) | – |
| | More than one | 9.68 ± 1.3 (16) | – |

essential tremor [11], dystonia-parkinsonism [14], dystonia [15], and hyperkinetic disorders [16] to name several of the most often clinical presentations observed in FMD. In our study, low scores in the PD group but normal scores in HP reinforced the aforementioned statements. More importantly, the AUC value obtained in our study as well as the LR tests indicated that smell testing had an excellent prediction [28] to diagnose FMD and to rule out IAMOK. It can be concluded that a normal smell score makes a diagnosis of an IAMOK unlikely and strengthens a diagnosis of FMD when this illness is suspected. Additionally, olfactory testing may aid in differentiating FMD from malingering, which can also be of concern when assessing these patients [6,29].

It is noteworthy that 14% of the FMD patients reported subjective olfactory dysfunction prior to being tested. This percentage is similar to that reported for AD (8%), PD (13%), PDG (13%) and MG (15%) patients before they were tested, even though the vast majority of such individuals clearly have demonstrable olfactory dysfunction [30]. It is not clear why some FMD patients believed they experienced smell dysfunction. Although we did not clinically examine the patients' relatives who were mentioned to have an IAMOK, no significant association was found between subjective olfactory alterations and familial medical history of IAMOK in FMD patients. Hence, it would seem unlikely that the FMD patients attempted to "model" the smell loss known to be present in the disease they were "modeling". Another reason for the reported smell dysfunction could be misinterpretation of interoceptive information [31,32]; however, recent studies did not find altered interoception in FMD patients [32]. Whatever the reasons for these findings, it is mandatory to test olfactory function in patients complaining of smell dysfunction.

The potential ability for olfactory tests to differentiate disorders such as FMD from neurological disorders known to have smell dysfunction likely reflects differences in pathophysiology impacting the complexity of the circuitries involved with olfactory system. Such complex circuits were not the focus of this study; however, some pathomechanisms can be gleaned from current results and from reports published elsewhere. For instance, functional magnetic resonance imaging shows abnormal increases in regional cerebral blood flow in the primary motor cortex and thalamus of patients with focal dystonia [33]. This is not the case in patients with FMD [33,34], nor for olfactory brain circuits [35]. Amygdala hyperactivity found in conversion disorders [36] would not explain our findings either since conversion downregulated smell function [37] via midbrain dopaminergic neurons [38]. These neurons and associated neurotransmitter are not primarily involved in altered human olfaction. As outlined elsewhere [27], the degree of olfactory dysfunction in a range of neurodegenerative and movement disorders is strongly associated with the degree of forebrain decrements in acetylcholine [30]. It is important to note that olfactory stimulation leads to a significant activation of the orbitofrontal cortex [35], much of which may be modulated through cholinergic pathways [30,32,39,40]. For instance, scopolamine, a muscarinic acetylcholine receptor antagonist, modulates odor memory and discrimination in rats [41], and humans with altered cholinergic neural transmission, including ones with myasthenia gravis, show profound smell dysfunction [32,40]. In light of these observations, the preserved smell function of FMD patients as demonstrated here, regardless of phenotypic expression, suggest that forebrain cholinergic circuits associated with smell dysfunction are unlikely altered in FMD.

The concept that cholinergic involvement is preserved in FMD is supported by studies employing short afferent inhibition (SAI). This electrophysiological measure, studied using transcranial magnetic stimulation, reflects the integration of brain sensory and motor cortices [42]. Current evidence supports a significant role of acetylcholine in the generation of SAI [43]. For instance, scopolamine reduces SAI [43] and acetylcholinesterase inhibitors increase SAI [44]. SAI is also enhanced in chronic smokers, and following nicotine administration in non-smoking individuals [45]. Importantly, SAI is altered in disorders characterized by smell loss (i.e., AD, Down's syndrome, PD, and mild cognitive impairment), but preserved in disorders with little or no olfactory dysfunction such as progressive supranuclear palsy [27]. Germane to our findings, SAI has been found to be normal in patients with FMD [46,47], implying the lack of a cholinergic deficit in this disorder.

### 4.1. Limitations

We did not studied here patients with all classical movement, neuropsychiatric or neurodegenerative disorders (see introduction) known to have smell dysfunction. However, we anticipated that testing a larger sample of patients with IAMOK did not improve our research aims. As an example of this statement, the olfactory testing we made in PD patients confirmed the smell dysfunction reported in this disorder since decades ago. Another limitation might be that the number of FMD patients tested did not meet the power to detect subtle effects. However, the sample size tested in this research as well as our findings are more robust than data reported elsewhere in a number of studies done in FMD using more expensive technology [47]. Knowing that females have higher smell scores than men [48], a female predominance in our study might be viewed as biasing the findings. However, we saw no sex differences in smell function and matched patients and controls on age and gender. Importantly, the patient population studied here reflects the age and gender predominance reported for FMD [3].

## 5. Conclusion

The present research indicates that FMD patients have normal olfactory function. This study suggests that a brief and inexpensive non-invasive olfactory test may be of value in detecting and differentiating FMD from a range of neural disorders known to have structural abnormalities. Further chemosensory research that includes taste and chemestesis status, among other investigations, in a larger sample of individuals with movement and neurodegenerative disorders with known structural lesions at early stage of the disease compared to FMD patients is worth doing to fully assess this hypothesis. In the meantime, olfactory testing may be used as additional laboratory procedure for helping in the identification of FMD patients, thereby averting misdiagnoses that can result in inappropriate interventions that may complicate the course of the disorder.

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## Conflict of interest

RLD is a consultant to Acorda Therapeutics, Eisai Co, Ltd, and Johnson & Johnson and receives royalties from Cambridge University Press, Johns Hopkins University Press, and John Wiley & Sons, Inc. He is president of, and a major shareholder in, Sensonics International, a manufacturer and distributor of smell and taste tests. KL receives speakers' bureau fees from TEVA. All remaining authors report no conflicts of interest.

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.clineuro.2018.12.017.

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