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Comparing the accuracy and neuroanatomical correlates of the UPSIT-40 and the Sniffin' Sticks test in REM sleep behavior disorder

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ABSTRACT

Background: Olfactory impairment increases the risk of developing neurodegenerative diseases in patients with idiopathic REM sleep behavior disorder (IRBD). Knowing the test properties of distinct olfactory measures could contribute to their selection for clinical or research purposes.

Objective: To compare the accuracy in distinguishing IRBD patients from controls with the University of Pennsylvania Smell Identification Test (UPSIT-40) and Sniffin' Sticks Extended test, and to assess the gray-matter volume correlates of these tests.

Method: Twenty-one patients with IRBD and 27 healthy controls were assessed using both olfactory tests. Independent logistic regressions were computed with diagnosis as a dependent variable and olfactory measures as predictive variables. Receiver operating characteristic curves were computed for each olfactory subtest. Diagnostic accuracy for IRBD was calculated according to the resulting optimal cut-off score. Structural MRI data, acquired with a 3T scanner, were analyzed with voxel-based morphometry.

Results: Patients differed from controls in all olfactory measures. The Sniffin-Identification correctly classified 89.1% of cases; the UPSIT-40, 85.4%; the Sniffin-Discrimination, 82.6%; the Sniffin-Total, 81.8%; and the Sniffin-Threshold, 77.3%. Respective AUROC, optimal cut-off, sensitivity, and specificity for each test were: 0.902, ≤26, 85.7%, and 85.2% for the UPSIT-40; 0.884, ≤29, 89.5%, and 76.0% for the Sniffin-Total; 0.922, ≤11, 90.5%, and 88.0% for the Sniffin-Identification; 0.739, ≤4, 73.7%, and 76.0% for the Sniffin-Threshold; and 0.838, ≤11, 85.7%, and 76.0% for the Sniffin-Discrimination. UPSIT-40 scores correlated with gray-matter volumes in orbitofrontal regions in anosmic patients.

Conclusions: UPSIT-40 and Sniffin' Identification showed similar discrimination accuracy, but only the UPSIT-40 showed structural correlates ($p \leq .05$ FDR-corrected).

1. Introduction

Rapid eye movement (REM) sleep behavior disorder (RBD) is a parasomnia characterized by abnormal motor and vocal behaviors associated with unpleasant dreams and increased electromyographic activity during REM sleep [1]. The idiopathic form of RBD (IRBD) is diagnosed when RBD symptomatology occurs in the absence of associated comorbidities or known causing factors. Patients with IRBD are at high risk of eventually developing a neurodegenerative disease, such as dementia with Lewy bodies (DLB), Parkinson's disease (PD), or multiple system atrophy [2,3]. In this setting, IRBD has been described as the strongest and most specific clinical predictor of neurodegenerative disease available [4]. Therefore, there is a growing interest in finding clinical biomarkers of neurodegeneration in this prodromal disorder.

Since olfactory loss has also been recognized as a premotor symptom of PD [5,6], it has been widely studied as a possible biomarker of neurodegeneration in IRBD [7]. In this sense, olfactory impairment in RBD has been reported in 35.7–97.0% of patients compared with

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2.5–16.6% of healthy control subjects [7]. Furthermore, previous works have found RBD patients with olfactory dysfunction to have an increased short-term risk of developing manifested PD and DLB [3,8]. Therefore, improving the accuracy of olfactory clinical testing in IRBD could help identify patients at a higher risk of conversion to a neurodegenerative disease, and thus define target populations for disease-prevention trials.

The University of Pennsylvania Smell Identification Test (UPSIT-40) and the Sniffin' Stick test are the most frequently used tests to evaluate olfaction worldwide. Both tests have been traditionally used as diagnostic complementary tools in PD [9,10] and their accuracy for this disease is high [11–14]. Furthermore, methods have been proposed to convert between UPSIT-40 and Sniffin' Stick test scores with meta-analytic purposes [15]. Nevertheless, as far as we know, no previous published works have compared in the same study neither the accuracy of UPSIT-40 and Sniffin' Stick tests in distinguishing IRBD patients from controls, nor the neuroanatomical correlates of these tests in IRBD patients.

In the current work, we aimed to compare the accuracy and brain correlates of two smell tests in IRBD patients and to describe its optimal cut-off scores for this disorder. It was hypothesized that: (1) IRBD patients will have worse performance than healthy controls in all olfactory measures; (2) Sensitivity and specificity of smell identification tests for IRBD will be comparable for the tests assessed in manifested PD; and (3) gray matter volume in olfactory regions will be related to the degree of olfactory function.

2. Methods

2.1. Participants

Twenty-one patients with IRBD were recruited from the multidisciplinary Sleep Unit at Hospital Clinic, Barcelona. Diagnosis of RBD required a history of dream-enacting behaviors, video-polysomnographic demonstration of REM sleep without atonia, associated with abnormal behaviors, absence of motor and cognitive complaints at the time of the recruitment, unremarkable neurological examination, normal brain magnetic resonance imaging and no temporal association between the estimated onset of RBD and the introduction or withdrawal of a medication [16,17]. Twenty-seven healthy subjects (HC) without cognitive, motor, or sleep complaints were recruited from the Institut de l'Envelliment (Barcelona, Spain).

Exclusion criteria consisted of [1]: Presence of psychiatric and/or neurologic comorbidity [2], MMSE score < 25 [3], claustrophobia [4], MRI artifacts [5], pathological MRI findings other than mild white matter hyperintensities, and [6] exclusion of HC with evidence of a clinical history suggestive of abnormal sleep behaviors and cognitive impairment. Specific exclusion criteria for the olfaction test were: (1) history of nasal bone fracture, (2) diagnosis of rhinitis or nasal polyps, and (3) upper respiratory tract infections in the two weeks prior to testing.

The study was approved by the Ethics Committee of the University of Barcelona (IRB00003099) and Hospital Clinic (HCB/2014/0224). All subjects provided written informed consent.

2.2. Olfactory and clinical assessment

Olfaction was assessed using the Spanish version of the UPSIT-40 [9] and the Sniffin' Sticks Extended Test [18]. The UPSIT-40 is a standardized multiple-choice scratch-and-sniff test consisting of four test booklets with 10 items each. In accordance with normative instructions, subjects scratch the impregnated area and are asked to select one of four possible answers for each item.

The Sniffin' Sticks Extended Test (www.burghart-mt.de) consists of three subtests [1]: the Threshold test (Sniffin-Thr) used to ascertain the patient's olfactory threshold. It has 48 Sniffin' Sticks (32 blanks and 16 dilutions of n-butanol) [2]; the Discrimination test (Sniffin-D), where the patient must differentiate between smells with varying degrees of similarity. It consists of 48 Sniffin' Sticks (48 Sniffin' Sticks = 16 pairs of odorants each with one individual smell); and [3] the Identification test (Sniffin-I) that consists of 16 Sniffin' Sticks with everyday smells which the patients have to identify using a selection card containing four choices. The results of all subtests are added up to get the total score (Sniffin-Total).

Presence of motor symptoms was evaluated using the International Parkinson and Movement Disorders Society Unified Parkinson's Disease Rating Scale motor section (MDS-UPDRS-III). Neurological examination based on the MDS-UPDRS-III frequently disclosed mild parkinsonian signs, that were, however, not sufficient to diagnose Parkinsonism according to standard criteria [19].

The Beck Depression Inventory II (BDI), the Starkstein's Apathy Scale (AS), and the Neuropsychiatric Inventory (NPI) were administered to all subjects to explore the presence of psychiatric symptoms. Finally, the Innsbruck REM Sleep Behavior Disorder Inventory (RBD-I) was used to study the presence RBD-like symptomatology in both patients and controls for comparisons.

2.3. MRI acquisition and analyses

MRI data were acquired with a 3T scanner (MAGNETOM Trio, Siemens, Germany). The scanning protocol included high-resolution 3-dimensional T1-weighted images acquired in the sagittal plane (TR = 2300 ms, TE = 2.98 ms, TI = 900 ms, 240 slices, FOV = 256 mm; 1 mm isotropic voxel) and an axial FLAIR sequence (TR = 9000 ms, TE = 96 ms).

2.4. Definition of regions of interest

A mask that defined the olfactory system was created including the amygdalae; hippocampi; thalami; insular cortices; parahippocampal gyri; superior frontal gyrus, orbital part; middle frontal gyrus, orbital part; gyrus rectus; olfactory cortex; and the limbic subregion of the striatum (including the nucleus accumbens and the ventral portion of the caudate nucleus and putamen bilaterally). The Automated Anatomical Labeling atlas was used to create the corresponding masks, except the limbic striatum mask, which was obtained from the Oxford-GSK-Imanova striatal connectivity atlas (available in FSL).

2.5. Gray matter volume analysis: voxel-based morphometry

Structural data was analyzed with FSL-VBM (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLVBM), an optimized voxel-based morphometry (VBM) protocol [20] carried out with FSL tools [21]. First, structural images were brain-extracted and gray-matter-segmented before being registered to the MNI 152 standard space using non-linear registration. The resulting images were averaged to create a study-specific template, to which native gray matter images were non-linearly re-registered. Second, all native gray matter images were non-linearly registered to this study-specific template, resampled to a voxel size of 2x2x2 mm^3, and modulated to correct for local expansion or contraction due to the non-linear component of the spatial transformation. A mask encompassing the structures of interest (see *Definition of Regions of interests*) was created to define a search volume for subsequent statistical testing. A voxelwise general linear model with non-parametric permutation testing (5,000 permutations) was used alongside threshold-free cluster enhancement for statistical inference. False-discovery rate (FDR) correction was applied for multiple comparisons correction. Statistical significance was established at FDR-corrected p-values (q-values) < 0.05.

2.6. Statistical analyses of non-MRI analyses

Statistical analyses of demographic, clinical, and olfactory data were carried out using the statistical package SPSS-24 (2016; Armonk, NY: IBM Corp.). The Mann-Whitney *U* test was used to assess group differences between IRBD and healthy subjects in clinical and olfactory continuous variables, and Pearson's chi-squared test was applied to assess group differences in categorical variables. Correlations between olfactory measures and clinical scores in IRBD patients were analyzed using Spearman's rho correlation. Finally, stepwise independent binary logistic regressions were computed introducing the diagnosis (either healthy subject or IRBD) as a dependent variable and the olfactory measures as predictive variables. The Bonferroni method was used to correct for multiple comparisons.

A receiver operating characteristic (ROC) curve was computed for each olfactory measure. RStudio (2015; available online at: www.rstudio.com) was used to calculate statistical differences of area under the curve (AUC) values from ROC (AUROC) analysis. Sensitivity, specificity, diagnostic accuracy, positive predictive value, and negative predictive value for IRBD were calculated according to the resulting optimal cut-off. In this setting, altered test performances were considered as positive findings, whereas correct performance defined negatives. True positives (TP) were defined as the number of IRBD patients with altered performance in a certain test; true negatives (TN) as the number of HC with correct performance; false positives (FP) were calculated as the number of HC with altered performance; finally, false negatives (FN) were described as the number of IRBD patients who had scores greater than the optimal cut-off. The following diagnostic measures were calculated: (1) Sensitivity, defined as the probability of testing positive when IRBD is present: TP/(TP + FN); (2) Specificity, defined as the probability of testing negative when IRBD is absent: TN/(FP + TN); (3) Positive predictive value (PPV), calculated as the percentage of subjects with a positive test who actually have IRBD: TP/(TP + FP); (4) negative predictive value (NPV), defined as the percentage of subjects with a negative test who do not have IRBD: TN/(TN + FN); finally, (5) overall diagnostic accuracy was defined as the proportion of correctly classified subjects among all subjects: (TP + TN)/(TP + TN + FP + FN).

3. Results

3.1. Demographic and clinical characteristics

No significant differences between groups were found in age, years of education, sex, BDI, and AS. Intergroup differences were found in NPI (U = 418.000; p < .001) and RBD-I scores (U = 466.000; p < .001) (Table 1).

3.2. Comparison between healthy subjects and IRBD patients in olfactory performance

After adjusting for age, years of education, and sex, intergroup differences were found in UPSIT-40 total score (U = 64.000; p < .001), Sniffin-D (U = 82.000; P < .001), Sniffin-I (U = 48.000; p < .001) and Sniffin-Total (U = 65.000; p < .001) scores (Table 1).

Following the normative cut-offs of each test, the percentage of HC and IRBD patients identified as normosmic, hyposmic, and anosmic was calculated (Supplementary material 1).

3.3. Correlation with clinical measures

No correlations were found in the IRBD group between olfactory measures and age, years of education, disease duration, NPI, AS, and BDI. The RBD-I was the only clinical measure that correlated with olfactory measures in IRBD patients, specifically with Sniffin-I scores (r = −.550; P = .012).

3.4. Discrimination between HC and IRBD by means of olfactory testing

Stepwise independent logistic regressions were performed to ascertain the effects of each single test on IRBD identification. The logistic regression model was statistically significant for UPSIT-40 (X^2 = 29.563; P = < .001), the Sniffin-I (X^2 = 34.326; P < .001), the Sniffin-Thr (X^2 = 5.312; P = .021), the Sniffin-D (X^2 = 19.842; P = < .001), and the Sniffin-Total (X^2 = 23.755; P < .001). The Sniffin-I model explained 70.3% of the variance in IRBD and correctly classified 89.1% of cases; the UPSIT-40 model explained 61.6% of the variance and correctly classified 85.4%; the Sniffin-Total model explained 56.0% of the variance and correctly classified 81.8%; the Sniffin-D model explained 46.8% of the variance and correctly classified 82.6%; finally, the Sniffin-Thr model explained 15.3% and correctly classified 77.3% of the cases (Table 2).

3.5. Optimal cut-off scores and their accuracy measures for the olfactory tests in IRBD

The ROC curve showed that the optimal cut-off score for the UPSIT-40 (AUROC = .902) was ≤26 with a sensitivity of 85.7% and a specificity of 85.2%. For the Sniffin-Total (AUROC = .884) the optimal cut-off was ≤29 with 89.5% sensitivity and 76.0% specificity. For the Sniffin' subtests the respective optimal cut-off scores, sensitivity, and specificity were: ≤11, 90.5%, and 88.0% for the Sniffin-I (AUROC = .922); ≤4, 73.7%, and 76.0% for the Sniffin-Thr (AUROC = .739); and ≤11, 85.7%, and 76.0% for the Sniffin-D (AUROC = .838) (Fig. 1, Supplementary material 2 and 3). AUROC values comparisons only showed significant differences between UPSIT-40 and Sniffin-Thr (t = 2.082; P = .037).

3.6. MRI correlates of olfactory test

In IRBD patients with anosmia, the UPSIT-40 test correlated positively with a cluster involving the right medial frontal cortex, right frontal orbital cortex, and left subcallosal cortex (2222 voxels; coordinates of cluster maximum: X = 12, Y = 40, Z = −22) (Fig. 2). No significant correlations were found either for Sniffin' total score or for Sniffin' subtests.

4. Discussion

To our knowledge, this is the first work comparing the UPSIT-40 and the Sniffin' Sticks test in the same sample of IRBD patients. In line with evidence from the literature, IRBD patients showed impaired olfactory identification and discrimination when compared with matched healthy subjects. We found that olfactory identification measures are the best smell predictor of IRBD; in particular, Sniffin' Identification scores had the highest classification accuracy. On the other hand, worse UPSIT-40 performance was related to gray matter reduction in orbitofrontal cortex regions in anosmic IRBD patients, whereas Sniffin' subtests did not show significant structural brain correlates.

We found that IRBD patients had impaired performance in both UPSIT-40 and Sniffin' Sticks total scores, as well as in Sniffin' Identification and Sniffin' Discrimination subtests. Previous studies have reported impaired smell identification in IRBD patients in comparison with HC using the Sniffin' Identification [3,22,23], the UPSIT short version (B-SIT-12) [24,25], the UPSIT-40 [26,27], the Sniffin' Sticks screening 12 test [28], and the Odor Stick Identification Test for Japanese [23]. Smell discrimination impairment has been also reported [3,23], as well as smell threshold increment [3,23,27]. As expected, these results highlight the presence of olfactory impairment in IRBD patients assessed with different smell tests. Otherwise, for clinical purposes it may be interesting to study the ability of tests to identify olfactory deficits in IRBD patients.

Our results showed that smell identification was the olfactory

Table 1
Inter-group comparisons of demographic, clinical, and olfactory measures.

Demographic and clinical characteristics					
	HC (n = 27)		IRBD (n = 21)		T stat/p
Age	66.4(9.9)		71.8(7.9)		69.500/.074
Years of education	12.2(4.3)		11.7(4.9)		262.500/.661
Sex (male/female)	13/14		15/6		2.634/.105
NPI	1.9(2.5)		6.3(5.8)		**418.000/ < .001**
BDI	5.1(4.7)		6.8(4.9)		298.500/.265
AS	8.9(5.3)		10.8(5.5)		312.000/.155
RBD-I	0.2(0.1)		0.6(0.2)		**466.000/ < .001**
RBD duration	–		4.62 (3.3)		–
MDS-UPDRS-III	–		2.5 (1.9)		–
Olfactory test	**adjusted Z**	**raw score**	**adjusted Z**	**raw score**	
Sniffin Discrimination	0.1(0.9)	12.3(2.0)	−1.6(1.6)	8.3(3.2)	**82.000/ < .001**
Sniffin Identification	0.1(0.8)	13.1(1.6)	−2.4(1.6)	8.0(2.8)	**48.000/ < .001**
Sniffin Threshold	−0.2(0.9)	5.7(2.0)	−0.9(1.5)	3.8(3.1)	134.000/.014
Sniffin Total	0.0(0.9)	31.1(4.5)	−2.1(1.6)	20.7(7.0)	**65.000/ < .001**
UPSIT-40	0.0(0.9)	30.6(4.6)	−2.1(1.4)	19.7(6.6)	**64.000/ < .001**

Abbreviations: AS, Starkstein's Apathy Scale; BDI, Beck Depression Inventory II; HC, healthy controls; IRBD, idiopathic form of REM-sleep behavior disorder; NPI, Neuropsychiatric Inventory; RBD-I, Innsbruck REM Sleep Behavior Disorder Inventory; Sniffin, Bughart Sniffin' Sticks extended test; MDS-UPDRS-III, Movement Disorders Society Unified Parkinson's Disease Rating Scale motor section; UPSIT-40, University of Pennsylvania Smell Identification Test. Measures for demographic and clinical data are presented as mean scores (SD). For the olfactory test, measures are presented as mean scores (SD) of the Z scores corrected for age, years of education, and sex; and mean (SD) of the raw scores. Group differences were tested using Mann-Whitney's *U* test or Chi-square test. For the olfactory data group differences in adjusted Z were tested using Mann-Whitney's *U* test. In bold those results that survive Bonferroni correction for multiple comparisons.

Table 2
Logistic regression analyses.

	B	SE	Wald/P value	Exp (B)	Nagelkerke R^2	PAC (HC/IRBD)	X^2/p value
UPSIT-40							
UPSIT-40	-.306	.080	14.630/ < .001	.736	.616	85.4 (88.9/81.0)	29.563/ < .001
Constant	7.636	2.114	13.048/ < .001	2071.755			
Sniffin Identification							
Sniffin-I	-.857	.232	13.688/ < .001	.425	.703	89.1 (92.0/85.7)	34.326/ < .001
Constant	9.202	2.628	12.260/ < .001	9920.754			
Sniffin Threshold							
Sniffin-Thr	-.289	.136	4.544/.033	.749	.153	77.3 (84.0/68.4)	5.312/.021
Constant	1.081	.690	2.453/.117	2.948			
Sniffin Discrimination							
Sniffin-D	-.533	.157	11.526/.001	.587	.468	82.6 (88.0/76.2)	19.842 < .001
Constant	5.479	1.746	9.849/.002	239.535			
Sniffin Total							
Sniffin-Total	-.263	.073	13.120/ < .001	.769	.560	81.8 (88.0/73.7)	23.755/ < .001
Constant	6.708	2.007	11.170/.001	818.587			

Abbreviations: HC, healthy controls, IRBD, idiopathic form of REM-sleep behavior disorder; PAC, percentage accuracy in classification for the whole sample, for HC and for IRBD patients; SE, standard error; Sniffin, Bughart Sniffin' Sticks extended test; Sniffin-D, Sniffin Discrimination; Sniffin-I, Sniffin Identification; Sniffin-Total, Sniffin Total score; Sniffin-Thr, Sniffin Threshold; UPSIT-40, University of Pennsylvania Smell Identification Test. Independent binary logistic regression with stepwise method was computed introducing group membership (HC vs. IRBD) as a dependent variable and the olfactory measures as predictive variables.

domain that better discriminated IRBD patients; specifically, Sniffin' Identification had the greatest accuracy classification for IRBD (89.1%), followed by the UPSIT-40 (85.4%). Although, Sniffin' Identification (AUROC = .922) had slightly higher AUC values than UPSIT-40 (AUCROC = .902), these differences did not reach statistical significance. In the same line, Sniffin' Identification was the only olfactory subtest that correlated with the RBD-I scale. A previous longitudinal study found Sniffin' Identification subtest had a diagnostic accuracy of 82.4% in predicting IRBD conversion to a Lewy body disease. Interestingly, in this same study, those subjects who converted had a baseline olfactory performance similar to that described in PD, whereas non-converters had significantly better smell function [3]. Similarly, a 5-year longitudinal study found that, compared with disease-free patients, IRBD subjects who eventually developed PD or DLB had lower scores at baseline in the UPSIT-40 [8]. In the same line, a recent work with a large multicenter cohort of IRBD patients found that the rate of neurodegenerative phenoconversion was significantly increased with olfactory deficit (hazard ratio = 2.62) [29]. Taken together, these results suggested that olfactory tests may be useful tools for discriminating HC from IRBD. In addition, previous longitudinal studies also showed the relevance of olfactory measures for predicting which IRBD patients are more likely to convert earlier to PD and DLB. Identifying these patients during the prodromal phase will conceivably help to select subjects in the design of future disease-modifying trials.

As far as we know, this is the first study providing diagnostic accuracy data and optimal cut-off scores for both UPSIT-40 and Sniffin' Sticks tests for discriminating IRBD patients from healthy subjects. As suggested by the logistic regression, taking an IRBD optimal cut-off revealed that smell identification tests had the greatest sensitivity and specificity (respectively, 85.7% and 85.2% for the UPSIT-40; and 90.5% and 88.0% for the Sniffin' Identification). In line with our results, data from a previous work with Japanese IRBD patients reflected Sniffin'

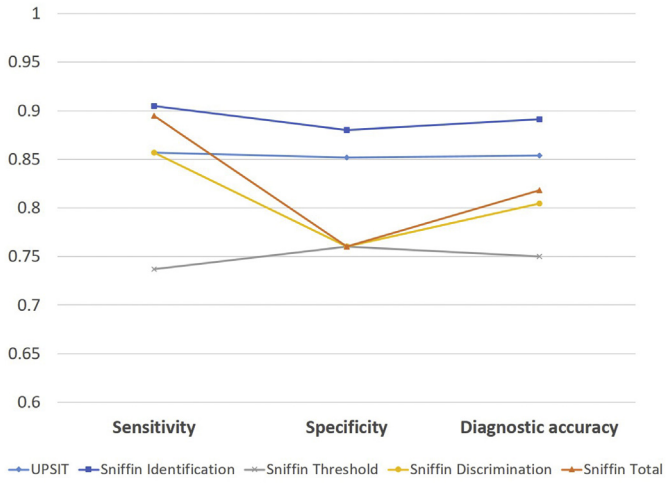

Fig. 1. Diagnostic accuracy measures for UPSIT-40 and Sniffin' Sticks tests.

Identification was the Sniffin' subtest with greatest sensitivity [23]. From a clinical point of view, both UPSIT-40 and Sniffin identification are useful, but Sniffin' identification is less time consuming.

The voxel-based-morphometry analysis showed that, in anosmic IRBD patients, worse performance in the UPSIT-40 was associated with gray matter reduction in orbitofrontal regions with a right hemisphere predominance. Our results are in line with a previous work in healthy subjects that found a positive correlation between gray matter volume in right orbitofrontal and olfactory performance [30], highlighting the important role of this region in olfactory function. Using cortical thickness analysis, previous studies with IRBD reported lower performance on the UPSIT-40 to be correlated with bilateral orbitofrontal, left precentral [31] and occipital thinning [32]. Another study, assessing brain perfusion in IRBD, showed that performance in the UPSIT 12-item version was related to regional cerebral blood low reduction in the anterior parahippocampal gyri [33]. Regarding results in PD samples, and in line with our results, a study conducted with early PD patients showed that atrophy in the orbitofrontal cortex was associated with olfactory dysfunction [34]. On the whole, evidence suggest a potential role of orbitofrontal cortex not only in healthy subjects, but also in IRBD and PD patients. We can speculate that orbitofrontal involvement in anosmic IRBD could be reflecting that patients with worse odor identification may be those that eventually evolve to PD.

The strengths of this work are the inclusion of two smell assessment tools commonly used worldwide, the study of olfactory test structural correlates in IRBD patients, and the exclusion of potential causes of secondary smell loss in our sample. Main limitation is a relatively small sample, especially to detect MRI correlates for the Sniffin' subtests.

In summary, we found that both, UPSIT-40 and Sniffin' Identification, had high accuracy to detect olfactory dysfunction in IRBD patients. Moreover, we found that gray matter reduction in orbitofrontal regions in anosmic IRBD may contribute to the degree of impairment in UPSIT-40 performance.

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Disclosures

The authors declare no conflict of interest.

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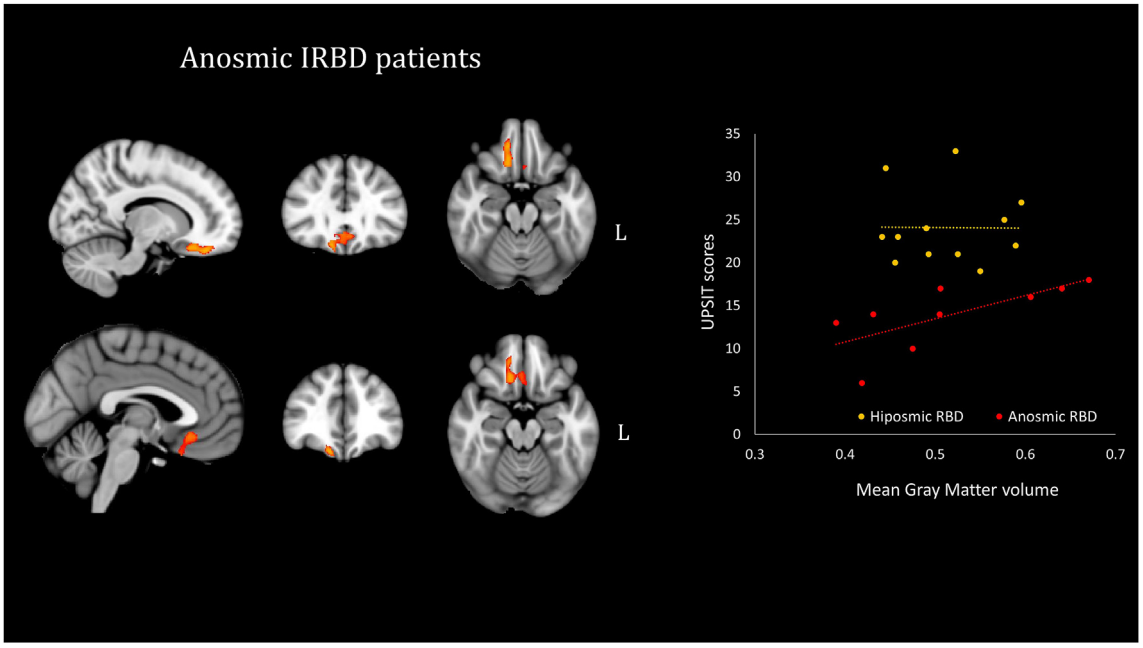

Fig. 2. Correlation between gray matter volume and UPSIT-40 scores in IRBD anosmics. VBM correlation between UPSIT-40 total score and gray matter volume. Significant voxelwise correlation is marked in warm colors. Results are displayed over the sagittal, coronal, and axial sections of the MNI standard brain at $p \leq .05$ FDR-corrected. . (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.06.013.

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