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ORIGINAL ARTICLE

Correlation and agreement of olfactory perception assessed by the Connecticut Chemosensory Clinical Research Center olfactory test and the Brief-Smell Identification Test†

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KEYWORDS
B-SIT;
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Abstract
Introduction: Assessing olfactory perception in olfactory disorders is of utmost importance in therapy management. However, the University of Pennsylvania Smell Identification Test and the Sniffin' Sticks are the only tests validated in Brazil.
Objectives: To evaluate the correlation and agreement between the Chemosensory Clinical Research Center olfactory test and the Brief-Smell Identification Test – University of Pennsylvania Smell Identification Test – in healthy participants and in participants with olfactory disorders based on the results and technical aspects of both tests.
Methods: Fifty participants without olfactory complaints and 50 participants with olfactory disorders who underwent the Chemosensory Clinical Research Center olfactory test and the Brief-Smell Identification Test were included. The following tests were used for statistical analysis: Mann-Whitney *U* test, Spearman's correlation, intraclass correlation coefficient and Bland-Altman plot. An alpha error (significance level) of 0.05 was considered in the statistical analysis.
Results: Both tests were effective in distinguishing the groups without the presence of overlapping values for the measured markers. Additionally, there was a strong correlation between Spearman's correlation and intraclass correlation coefficient between the tests and for both nostrils. However, the correlations were lower when the groups were individually evaluated. The Bland-Altman plot showed no bias when all participants were simultaneously evaluated.

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Conclusions: The tests to assess olfactory perception presented a high level of agreement. In our sample, we could infer that the Connecticut Chemosensory Clinical Research Center olfactory test is similar to the Brief-Smell Identification Test and can be used in the routine diagnosis of patients with complaints of olfactory disorders, considering the advantage of its low cost.

Introduction

Olfaction is one of the senses that when altered or abolished can have an impact on quality of life.[1] Olfactory perception depends on the anatomical and physiological integrity of the elements that make up the olfactory pathway. Thus, preserved nasal airflow, intact olfactory neuroepithelium and transmission of stimulus of the peripheral nerves to the olfactory cortex are fundamental for olfaction.[2] However, these components can be affected by numerous factors, namely diseases with symptoms that may vary from reduced intensity and quality of perceived odors to anosmia.[3] There are a few tests available to assess olfactory perception, including that developed by the Connecticut Chemosensory Clinical Research Center (CCCRC) (Connecticut, USA) olfactory test,[4] the Sniffin' Sticks (SS16)[5] and that developed by the University of Pennsylvania Smell Identification Test (UPSIT).[6,7] The UPSIT test is validated in Brazil, already translated into Portuguese,[8] along with The Sniffin' Sticks test.[9] Moreover, there is also a reduced version of the UPSIT called the ''Brief-Smell Identification Test'', previously called the ''Cross-Cultural Smell Identification Test''. In countries where both tests are validated, the CCCRC may be of most value due to its low cost.

The CCCRC test consists of two components in each separate nostril: (i) the butanol threshold test and (ii) the odor identification test. The butanol threshold test is performed by successive dilutions of 1-butyl alcohol (low toxicity, high water solubility, specific and neutral odor) as odorant. The identification test is performed by using typical items of our daily lives. In contrast, the UPSIT is a multiple-choice test that comprises four ''scratch-and-sniff'' booklets with 10 microencapsulated fragrance labels each in its complete version. The test can be self-administered or administered with the help of an examiner in the event of difficulties understanding the procedures. The test has been used in various studies and has been proved effective in diagnosing changes in olfactory function in patients with otorhinolaryngological or neurological disorders, such as Parkinson's and Alzheimer's disease.[10] Additionally, a shorter version with 12 questions, called the Brief-Smell Identification Test, can be used to detect changes in olfactory perception. However, both olfactory tests were developed based on studies with populations in North America. Therefore, adapting and validating these tests for different populations such as in Brazil is of utmost importance. Moreover, the CCCRC test is less expensive with low administration costs when compared with the UPSIT or Brief-Smell Identification Test giving the opportunity to be widely used in the Brazilian population.

Thus, in our study we have assessed the results and technical aspects of administering the CCCRC test and the Brief-Smell Identification Test in healthy participants and participants with olfactory disorders with the analysis of correlation and agreement between both tests.

Methods

Fifty participants aged between 20 and 80 years without olfactory complaints were allocated into the control group. The control group underwent otorhinolaryngological evaluation to exclude participants with altered rhinoscopy results caused by infectious or inflammatory agents, such as signs of allergic rhinitis, septal deviation, rhinosinusitis and nasosinusal polyps. In the group of 50 participants with olfactory disorders, with similar age range, the presence of olfactory complaints was the major inclusion criterion, regardless of the intensity of their symptoms. Those patients presented different causes for their impairment, such as allergic rhinitis, nasosinusal polyps, post-infectious of the upper airways[11] and absence of an identifiable cause (idiopathic). There were no patients with history of traumatic bone injury or neurodegenerative disorders in our study group.

In this study, the CCCRC test started with the preliminary test: two 250 mL bottles were presented to the participant, one with distilled water and another with a predetermined dilution of 1-butyl alcohol in distilled water. The test was performed in ascending concentration of the stimulus. Four consecutive correct identifications of the odorant in the bottle determined the minimum concentration defined as the olfactory threshold for the evaluated nostril. The identification test was performed unilaterally with the presentation of seven substances to be identified by the olfactory nerve, namely, coffee, chocolate, mothballs, cinnamon, peanut butter, classic Johnson & Johnson® baby powder and Palmolive® soap. A template (not shown) with a visual aid to identify the substances presented in the identification test was presented to the participants and contained 20 images representing: ammonia, peanuts, talc, black pepper, burnt paper, rubber, chocolate, sardines, cinnamon, soap, coffee, cigarettes, garlic, mites, ketchup, Vick VapoRub® (menthol, camphor, eucalyptus oil), mothballs, methyl salicylate, onions and sawdust. Fig. 1 and Table 1 represent the procedures to perform the CCCRC test. Trigeminal nerve nasal sensitivity was tested with ammonia at the end of the test. The final result of the test included the mean score of the two parts, ranging from zero to seven points, considering a result above six as normal.[12]

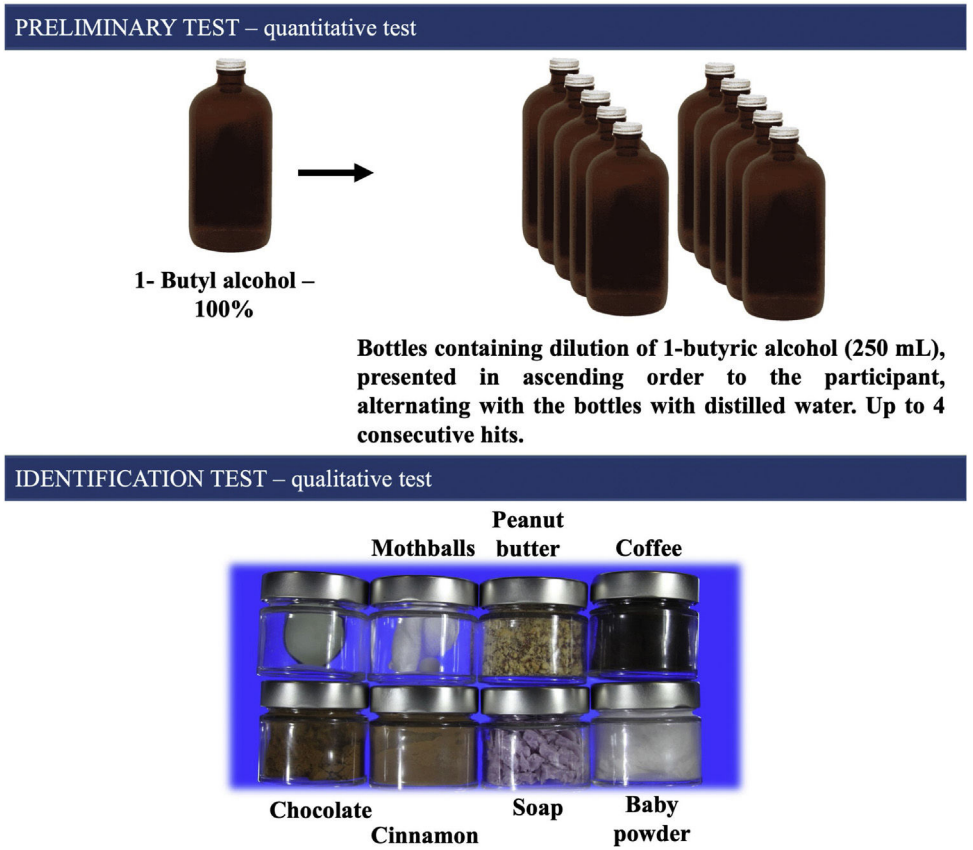

Figure 1 Preliminary test and identification test analysis for the Connecticut Chemosensory Clinical Research Center olfactory test. In the identification test, the first bottle is the Ammonia test (positive control).

Table 1 Detailed description of the Connecticut Chemosensory Clinical Research Center olfactory test.

Preliminary test								
	Right nostril				Left nostril			
Concentration	10	10	10	10	10	10	10	10
	9	9	9	9	9	9	9	9
	8	8	8	8	8	8	8	8
	7	7	7	7	7	7	7	7
	6	6	6	6	6	6	6	6
	5	5	5	5	5	5	5	5
	4	4	4	4	4	4	4	4
	3	3	3	3	3	3	3	3
	2	2	2	2	2	2	2	2
	1	1	1	1	1	1	1	1
	Bottle:				Bottle:			
Identification test								
Smell	Right nostril 1			Right nostril 1		Left nostril 1		Left nostril 1
Chocolate								
Cinnamon								
Talc								
Coffee								
Peanut butter								
Mothballs								
Soap								
Total								
Ammonia test (positive)								
Points	Right nostril					Left nostril		
Identification test								
Preliminary test								
Compound points								
Normal (6–7)								
Mild hyposmia (5–5.75)								
Moderate hyposmia (4–4.75)								
Severe hyposmia (2–3.75)								
Anosmia (0–1.75)								

The Brief-Smell Identification Test was administered by a physician if the participant had difficulties performing the test, aiming to ensure the reliability of the results. This was the test of choice because the Complete UPSIT test is significantly more expensive, which would reduce the number of patients that would be assessed. The test consisted of a kit with four booklets with specific microencapsulated fragrance labels to be scrapped. The participant identified the perceived substance/odor from four alternatives. The final result summed the correct responses, and the test was considered normal if the participant responded with nine or more correct items.[13]

In this study, the results of both olfactory tests were presented according to the group with healthy control and the group with olfactory disorders. In addition, the olfactory tests were classified as normal test or hyposmia because the Brief-Smell Identification Test is limited to this classification. The analysis comparing both groups was performed by the Mann-Whitney *U* test for independent samples of the olfactory tests; also, to compare the sex and age distribution for both groups (healthy participants and participants with olfactory disorders) the Chi-Square and *t*-test were used, respectively. Correlation and agreement between both tests were performed, respectively, by Spearman's correlation and intraclass correlation coefficient. The Bland-Altman plot was performed considering the laterality of the nostril and the group evaluated. For the Bland-Altman plot, the data are presented by the z-score of each marker using as markers the line of equality (difference = 0); 95% Confidence Interval (CI) of mean difference; 95% CI of limits of agreement. The significance level was set to 5%.

In addition, a first statistical analysis was carried out using a population with a sample size of 25 participants in each group that gave the estimation of 50 participants in each group to achieve a sample power of 0.80.

The study was approved by the institution ethics committee under the approval #981/2011 (CAAE: 0888.146.000-11).

Table 2 Association between groups of healthy participants and participants with olfactory disorders for the Brief-Smell Identification Test and the Connecticut Chemosensory Clinical Research Center olfactory test.

Marker	Healthy participants	Participants with olfactory disorders	*p*-value
Brief-Smell Identification Test	9.72 ± 1.47; 10 (9–11)	4.76 ± 2.50; 4 (3–7)	<0.001
Connecticut Chemosensory Clinical Research Center olfactory test			<0.001
Right nostril (total test value)	6.59 ± 0.89; 7 (6–9)	2.65 ± 1.88; 2.50 (1–4)	<0.001
Left nostril (total test value)	6.65 ± 0.83; 7 (6.5–7.5)	2.48 ± 1.97; 2.50 (0.5–3.25)	<0.001
Butanol threshold test in the right nostril	6.76 ± 1.27; 7 (6–8)	3 ± 1.95; 3 (1.75–4.25)	<0.001
Butanol threshold test in the left nostril	6.86 ± 1.09; 7 (6–8)	2.96 ± 2.11; 3 (1–5)	<0.001
Odor identification test in the right nostril	6.42 ± 0.73; 7 (6–9)	2.46 ± 2.17; 2 (1–3.5)	<0.001
Odor identification test in the left nostril	6.40 ± 0.78;7 (6–7)	2.16 ± 2.28 (0–2)	<0.001

The data are presented as mean ± standard deviation; median (minimum to maximum value). Statistical analyses were performed by the Mann-Whitney *U* test for independent samples. Alpha = 0.05.

Table 3 Correlation between the Brief-Smell Identification Test and the Connecticut Chemosensory Clinical Research Center olfactory test considering the groups of healthy participants and participants with olfactory disorders and the laterality of the nostrils.

Spearman's correlation coefficient (CC)		
Brief-Smell Identification Test	Connecticut Chemosensory Clinical Research Center olfactory test	
	Right nostril – CC (*p*-value)	Left nostril – CC (*p*-value)
Complete sample	0.904 (<0.001)	0.902 (<0.001)
Healthy participants	0.778 (<0.001)	0.720 (<0.001)
Participants with olfactory disorders	0.647 (<0.001)	0.660 (<0.001)
Intraclass correlation coefficient (CC)		
Brief-Smell Identification Test	Connecticut Chemosensory Clinical Research Center olfactory test	
	Right nostril – CC (*p*-value)	Left nostril – CC (*p*-value)
Complete sample	0.924 (<0.001)	0.932 (<0.001)
95% Confidence Interval	0.887 to 0.949	0.899 to 0.954
Healthy participants	0.824 (<0.001)	0.783 (<0.001)
95% Confidence Interval	0.690 to 0.900	0.618 to 0.877
Participants with olfactory disorders	0.798 (<0.001)	0.823 (<0.001)
95% Confidence Interval	0.644 to 0.885	0.689 to 0.900

Alpha = 0.05.

Results

The healthy participants and participants with olfactory disorders showed an equal proportion of male individuals 23/50 (46%) vs. 15/50 (30%), *p*-value = 0.149. However, healthy participants were younger than participants with olfactory disorders (34.3 ± 9.66 vs. 49.04 ± 14.13; *p*-value < 0.01). In addition, the results of the descriptive analysis are summarized in Table 2, according to the groups evaluated and the tests administered, showing that both tests were effective in distinguishing the groups without the presence of overlapping values for the measured markers. As shown in Table 2, healthy participants showed higher values for the Brief-Smell Identification Test (9.72 ± 1.47 vs. 4.76 ± 2.50; *p*-value < 0.001) and for CCCRC test right nostril: total test value (6.59 ± 0.89 vs. 2.65 ± 1.88), butanol threshold test (6.76 ± 1.27 vs. 3 ± 1.95) and odor identification test (6.42 ± 0.73 vs. 2.46 ± 2.17); left nostril: total

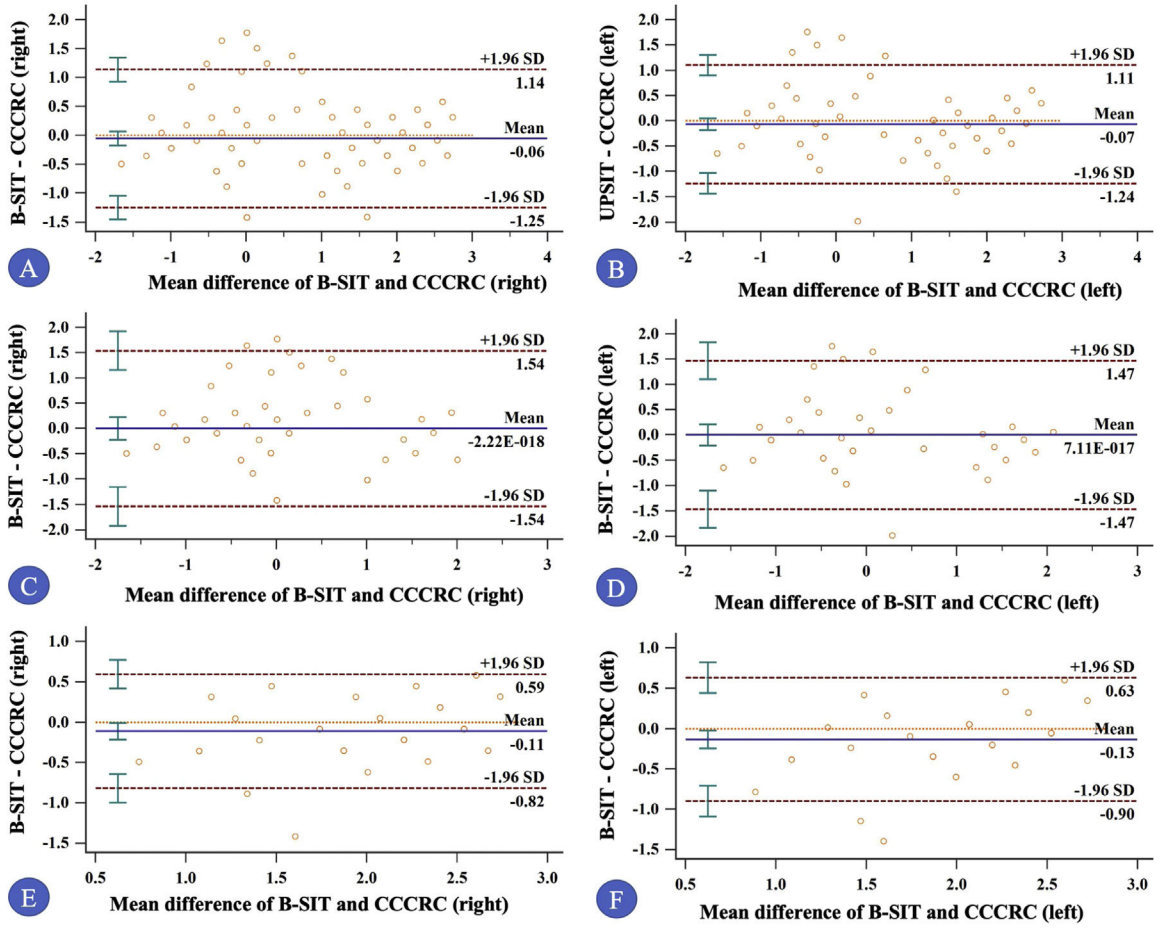

Figure 2 Bland Altman plot for the z-score results of the Brief-Smell Identification Test and Connecticut Chemosensory Clinical Research Center olfactory test. (A) Analysis of all participants comparing the result bias of the Connecticut Chemosensory Clinical Research Center olfactory test (right nostril) with the result of the Brief-Smell Identification Test. (B) Analysis of all participants comparing the result bias of the Connecticut Chemosensory Clinical Research Center olfactory test (left nostril) with the result of the Brief-Smell Identification Test. (C) Analysis of participants with olfactory disorders comparing the result bias of the Connecticut Chemosensory Clinical Research Center olfactory test (right nostril) with the result of the Brief-Smell Identification Test. (D) Analysis of participants with olfactory disorders comparing the result bias of the Connecticut Chemosensory Clinical Research Center olfactory test (left nostril) with the result of the Brief-Smell Identification Test. (E) Analysis of healthy participants comparing the result bias of the Connecticut Chemosensory Clinical Research Center olfactory test (right nostril) with the result of the Brief-Smell Identification Test. (F) Analysis of healthy participants comparing the result bias of the Connecticut Chemosensory Clinical Research Center olfactory test (left nostril) with the result of the Brief-Smell Identification Test. The data are presented by the z-score of each marker. The figures show: line of equality (difference = 0); 95% Confidence Interval (CI) of mean difference; 95% CI of limits of agreement.

test value (6.65 ± 0.83 vs. 2.48 ± 1.97), butanol threshold test (6.86 ± 1.09 vs. 2.96 ± 2.11) and odor identification test (6.40 ± 0.78 vs. 2.16 ± 2.28) (p-value < 0.001).

Spearman's correlation coefficient (SCC) and intraclass correlation coefficient (ICC) were strong between both tests and for both nostrils (right nostril: SCC = 0.904 and ICC = 0.924; left nostril: SCC = 0.902 and ICC = 0.932); however, the correlations were lower when considering the groups separately [(Healthy participants – right nostril: SCC = 0.778 and ICC = 0.824; left nostril: SCC = 0.720 and ICC = 0.783); (participants with olfactory disorders – right nostril: SCC = 0.647 and ICC = 0.924; left nostril: SCC = 0.798 and ICC = 0.823)] (Table 3); the lower correlation can be association with the low number of subjects in each group (n = 50), which reduces the sample power to perform the statistical analysis.

Finally, Fig. 2(A–F) displays the Bland-Altman plot for the z-score results for the Brief-Smell Identification Test and for CCCRC tests as follows: (a) CCCRC (right nostril) with the result of the Brief-Smell Identification Test; (b) CCCRC (left nostril) with the result of the Brief-Smell Identification Test; (c) CCCRC (right nostril) with the result of the Brief-Smell Identification Test; (d) CCCRC (left nostril) with the result of the Brief-Smell Identification Test; (e) CCCRC (right nostril) with the result of the Brief-Smell Identification Test; (f) CCCRC (left nostril) with the result of the Brief-Smell Identification Test. It seems relevant to mention that the data is

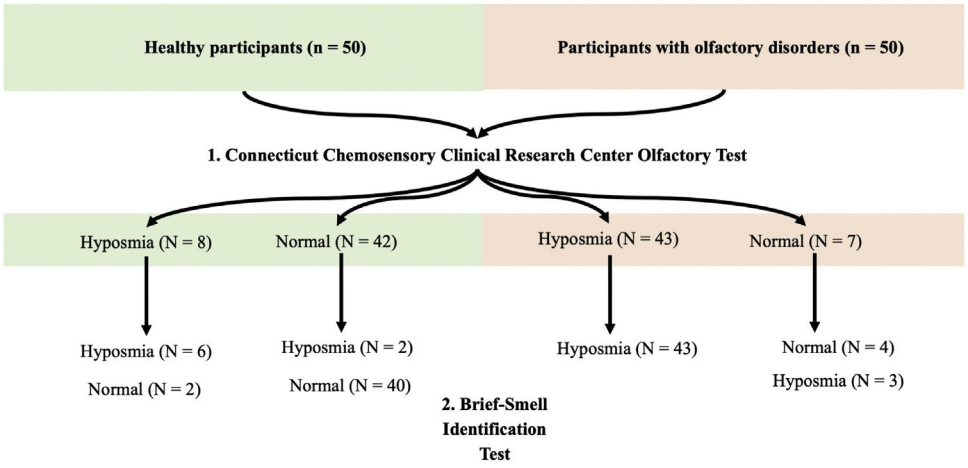

Figure 3 Representation of the participants with olfactory disorders and healthy participants considering the olfactory classification for Connecticut Chemosensory Clinical Research Center olfactory test and brief-smell identification test. The brief-smell identification test was administered by a physician if the participant had difficulties performing the test and the test consisted of a kit with four booklets with specific microencapsulated fragrance labels to be scrapped. The participant identified the perceived substance/odor from four alternatives. The final result summed the correct responses, and the test was considered normal if the participant responded nine or more correct items or as hyposmia in cases of correct smell identification for less than nine items.[11]

distributed near of the line equality, however, some markers were set out of 95% CI of limits of agreement.

A representation of the participants with olfactory disorders and healthy participants considering the olfactory classification for CCCRC Test and for Brief-Smell Identification Test was performed. In our data, only 4 healthy participants and 3 participants olfactory disorders presented controversial results with disagreement between both olfactory tests (Fig. 3).

Discussion

The assessment of patients with complaints of olfactory disorders is often a diagnostic challenge for otolaryngologists, given that it is a subjective complaint and associated with high variability of environmental factors and diseases.[14] Decreased olfactory function is very common in the older population, being present in over half of those between the ages of 65 and 80 years and in over three quarters of those over the age of 80 years.[15] Hyposmia is also related to initial onset of various neurodegenerative diseases such as Alzheimer and Parkinson disease.[16,17] In the context of the current COVID-19 pandemic, the olfactory assessment is gaining more importance, since it is one of the symptoms that is associated with infection by SARS-CoV-2,[18,19] potentially increasing diagnostic suspicion.

Olfactory tests seek to objectively limit the discomfort reported by the patient, to help physicians grade the changes in olfactory perception and to evaluate clinical evolution during the treatment.[20,21] In this study, both the Brief-Smell Identification Test and CCCRC olfactory tests were applied to assess olfactory disorders.[22] Although they were developed in North America, these tests are used in some research centers in Brazil and the UPSIT test has a validated Portuguese version. It has some advantages, allowing the patient to take the test at home, for example, not depending on the physician being present. However, it is important to highlight the costs involved in using these kits. Both versions of the UPSIT test and the Brief-Smell Identification Test are imported, which incurs high costs and limits its large-scale administration in patients treated by the Brazilian public health care system (SUS). Furthermore, a kit with four booklets per patient should be used, which greatly increases the administration costs. In this scenario, in countries where both tests are validated, the CCCRC may be of best interest for its affordability.

In this context, the CCCRC test has some advantages: (i) 1-butyl alcohol and the substances used for the identification test are inexpensive and easy to access; (ii) the test setup is simple; and (iii) the test items may be used with multiple patients prior to replacement.[23]

Furthermore, the analysis of both tests indicates that most individuals had no difficulties identifying the substances in the test and no technical difficulties were observed regarding test administration. However, due to the individual assessment of nasal passages and the division into identification and preliminary testing, the CCCRC test requires a longer administration period than the Brief-Smell Identification Test.

We assessed the olfactory function with the two tests on the same day, starting with the Brief-Smell Identification Test and after at least fifteen minutes the CCCRC. In order minimize the chance of an allergic response from the patient the identification part was the last part of the test, since it included mothballs, Johnson & Johnson® baby powder and Palmolive® soap. Although the test was satisfactorily performed during our study, the peanut butter was noted as the most difficult substance to be identified, perhaps because it is not common in the routine diet in Brazil when compared to North America or other countries.[24] The medical team responsible for the test replaced every substance each two or three months, in order to prevent a decrease in the odorant sample because of low humidity or regular use.

With more evidence associating olfactory disorders and early signs of neurodegenerative disorders and infectious disease such as COVID-19, besides the complementary evaluation of patients complaining of this impairment, the olfactory tests appear as important tools in the day-to-day medical practice.

Conclusion

The results provided further evidence that both tests to assess olfactory perception have a high level of agreement. In our sample, we could infer that the CCCRC test is similar to the Brief-Smell Identification Test and can be administered in the routine diagnosis of patients with complaints of olfactory disorders with the advantage of its low costs. The application of CCCRC is quite simple with visual help (a leaflet with figures of substances), and feasible in the ambulatory routine.

Consent to participate

The participants signed a free informed consent form before to be included in the study.

Consent to publication

The participants and authors approved the submission and publication of the results achieved during the study.

Ethics approval

The study was approved by the institution ethics committee (Approval: #981/2011 and CAAE: 0888.146.000-11).

Conflicts of interest

The authors declare no conflicts of interest.

Availability of data

The data will be available on request.

Code availability

Not applicable.

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