Performance of a cost-effective olfactory test to evaluate hyposmia in Parkinson's disease patients

Desempenho de um teste de olfato de bom custo-benefício na avaliação de hiposmia em pacientes com doença de Parkinson

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Abstract

Background Parkinson's disease (PD) causes motor and non-motor symptoms such as hyposmia, which is evaluated through olfactory tests in the clinical practice.

Objective To assess the feasibility of using the modified Connecticut Chemosensory Clinical Research Center (mCCCRC) olfactory test and to compare its performance with the Sniffin' Sticks-12 (SS-12, Burghart Messtechnik GmbH, Wedel, Germany) test.

Methods A transversal case-control study in which the patients were divided into the PD group (PDG) and the control group (CG). The cost and difficulty in handling substances to produce the mCCCRC test kits were evaluated. Sociodemographic characteristics, smoking habits, past coronavirus disease 2019 (COVID-19) infections, self-perception of odor sense, and cognition through the Montreal Cognitive Assessment (MoCA) were also evaluated. The PDG was scored by part III of the Unified Parkinson's Disease Rating Scale (UPDRS-III) and the Hoehn and Yahr Scale (H&Y) scale. Correlations were assessed through the Spearman rank correlation coefficient test (ρ, or rho).

Results The mCCCRC test was easily manufactured and handled at a cost ten times lower compared with the SS-12. The groups (PDG: $n = 34$; CG: $n = 38$) were similar in terms of age, sex, level of schooling, smoking habits, and history of COVID-19. The tests results showed moderate correlation (rho = 0.65; $p < 0.0001$). The CG presented better cognitive performance and scored better in both tests ($p < 0.0001$). There was a tendency for a negative correlation with age, but good correlation with the MoCA ($p = 0.0029$). The results of the PDG group showed no correlation with olfactory results and motor performance or disease duration. The self-perception of hyposmia was low in both groups.

Keywords
- Olfaction Disorders
- Anosmia
- Parkinson Disease

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Conclusion The mCCCRC is an easy-to-apply and inexpensive method that demonstrated a similar performance to that of the SS-12 in evaluating olfaction in PD patients and healthy controls.

Resumo

Antecedentes A doença de Parkinson (DP) cursa com sintomas motores e não motores como a hiposmia, que é avaliada por diferentes testes olfativos na prática clínica.

Objetivo Avaliar a viabilidade do teste olfatório Connecticut Chemosensory Clinical Research Center modificado (mCCCRC) e compará-la à do teste Sniffin' Sticks-12 (SS-12, Burghart Messtechnik GmbH, Wedel, Alemanha).

Métodos Estudo transversal de caso-controle em que os pacientes foram divididos no grupo DP (GDP) e no grupo controle (GC). O custo e as dificuldades no manuseio das substâncias necessárias para a produção dos kits do teste mCCCRC foram avaliados. Características sociodemográficas, tabagismo, histórico de infecção por doença do coronavírus 2019 (*coronavírus disease 2019*, COVID-19, em inglês), autopercepção do olfato e cognição pelo Montreal Cognitive Assessment (MoCA) também foram avaliados. O GDP foi avaliado pela parte III da Unified Parkinson's Disease Rating Scale (UPDRS-III) e pela escala de Hoehn and Yahr (H&Y). As correlações utilizaram o teste do coeficiente de correlação de postos de Spearman (ρ, ou rho).

Resultados O mCCCRC foi facilmente poroduzido e manipulado com custo dez vezes inferior ao do SS-12. Os grupos (GDP: $n = 34$; GC: $n = 38$) eram similares em termos de idade, sexo, escolaridade, tabagismo e histórico de COVID-19. Os resultados obtidos em ambos os testes mostraram excelente correlação (rho = 0.65; $p < 0.0001$). O GC teve um desempenho cognitivo melhor e pontuou melhor nos dois testes ($p < 0.0001$). Houve uma tendência a uma correlação negativa com a idade, mas boa correlação com a pontuação no MoCA ($p = 0.0029$). Os resultados olfativos do GDP não mostraram correlação com desempenho motor ou duração da doença. A autopercepção de hiposmia foi baixa em ambos os grupos.

Conclusão O mCCCRC é um teste de fácil aplicação, baixo custo, e apresentou um desempenho semelhante ao do SS-12 na avaliação olfativa de pacientes com DP e controles saudáveis.

Palavras-chave
- Transtornos do Olfato
- Anosmia
- Doença de Parkinson

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disorder that primarily affects dopamine-producing neurons in the substantia nigra region of the brain. The loss of these neurons leads to reduced dopamine levels in the striatum, causing motor symptoms such as bradykinesia, resting tremor, rigidity, and postural instability. Non-motor symptoms, including hyposmia, rapid eye movement (REM) sleep behavior disorder, depression, and constipation, are frequently present and represent important features of a prodromal stage.[1] Hyposmia occurs in up to 90% of people with PD and is sometimes one of the earliest signs of the disease.[2–5]

As impaired olfaction may manifest in the very early stages of PD, it has been investigated as a potential biomarker for early diagnosis and to monitor disease progression.[4,5] Among the olfactory tests relevant to clinical use, we can mention The Sniffin' Sticks-12 (SS-12, Burghart Messtechnik GmbH, Wedel, Gemany) and the Connecticut Chemosensory Clinical Research Center (CCCRC), which was developed in the 1990s by Caim et al.[6] The CCCRC comprises two parts: the olfactory threshold test with butanol and the smell identification test. The smell identification part can be assembled using odorants that are available for purchase. It was recently adapted to the Brazilian population but it has not yet been studied in PD patients.[7]

Due to the high cost of industrialized tests, we conducted the present preliminary work to assess the feasibility of using the CCCRC to evaluate olfactory function in PD. We correlated it with motor status, disease duration, and factors known to impair the sense of smell, such as age, cognitive status, smoking habits, and a history of coronavirus disease 2019 (COVID-19) infection. Nonetheless, the main objectives of the present work were to verify the ease of manufacturing and handling a modified version of the CCCRC (mCCCRC) and to compare olfaction evaluation through the two olfactory tests: the SS-12 and the CCCRC.

METHODS

Study population

A cross-sectional case-control study was conducted between July 2021 and September 2022. All PD patients included were recruited from the outpatient Neurological Clinic of Hospital Universitário Clementino Fraga Filho (Universidade Federal do Rio de Janeiro, UFRJ). The PD patient group (PDG) was diagnosed by a movement disorders specialist based on the criteria of the International Parkinson and Movement Disorders Society; they were aged up to 85 years, with a disease duration of at least 2 years, and had no dementia diagnosis. The control group (CG) consisted of volunteers without diagnosis of any neurodegenerative condition, aged between 60 and 85 years, selected from partners of patients or patients with appointments in other clinics of the hospital. The Hoehn and Yahr Scale (H&Y) and the Unified Parkinson's Disease Rating Scale part III (UPDRS-III) were used to stage PD patients. Cognition was assessed through the Montreal Cognitive Assessment (MoCA) for all participants.

A semistructured questionnaire was administered to collect epidemiological and clinical data, including a history of infection by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, that is COVID-19) and smoking habits. Complaints of hyposmia were also assessed in both groups. The exclusion criteria were history of significant head trauma, current symptoms of rhinosinusitis or previous nasal surgery.

All participants provided written informed consent prior to inclusion in the study, which was approved by the Ethics Committee of UFRJ.

Olfactory tests

All participants underwent olfactory testing with the SS-12 and mCCCRC, with a minimum interval of 30 minutes between the tests.

The SS-12, an industrialized test, consists of 12 felt-tip pens filled with different dissolved odorants,[8] which include orange, leather, peppermint, banana, coffee, cinnamon, cloves, liquorice, lemon, pineapple, rose and fish. Each odorant is presented to the patient and four written options with only one correct answer are provided. The patient selects one of the options. The test was imported at a total cost of US$200 and has an expiration date of one year after the first use.

The other test is the mCCCRC, which involves administering only the smell identification part of the original test. The odorants were purchased at a nearby supermarket with a final cost of approximately US$ 5. They were weighed and stored in flasks, following the methodology described by Fenolio et al.[7] The odorants included *paçoca* (a Brazilian candy made of ground peanuts, sugar, and salt, of the brand Paçoquita [Santa Helena Indústria de Alimentos, Ribeirão Preto, SP, Brazil]), neutral soap (Colgate-Palmolive Comercial Ltda., São Paulo, SP, Brazil), powdered coffee (Três Corações Alimentos SA, Eusébio, CE, Brazil), talcum powder (Johnson & Johnson do Brasil Indústria e Comércio de Produtos para Saúde Ltda., São José dos Campos, SP, Brazil) powdered cinnamon, mothballs, and powdered chocolate (Nescau, Nestlé Brasil Ltda., São Paulo, SP, Brazil). Each substance was tested individually, and a list of 15 names (including 8 distractor names) was provided to guide the answers. The test can be reused within a period of 90 days.

Statistical analysis

Data analysis was performed using the StataBE 17 (StataCorp, College Station, TX, United States) software. The quantitative data were presented as mean ± standard deviation (SD) values, and the categorical data were expressed as percentages. The non-parametric Mann-Whitney test was used to compare the scores obtained by the groups in the two olfactory tests. The correlation between the scores on the two olfactory tests, and regarding the clinical and epidemiological data and the scores were assessed using the Spearman rank correlation coefficient (ρ, or rho). Statistical significance was set at 5.0%.

RESULTS

►**Table 1** displays the characteristics of the 72 individuals evaluated (34 in the PDG and 38 in the CG). The groups were similar in terms of age, gender, and level of schooling. However, performance on the MoCA test was better in the CG (21.3 ± 4.0 versus 17.1 ± 6.2 points; $p = 0.003$). Among all participants, only 2 controls were active smokers, but 60.5% of CG subjects and 35% of PDG patients reported previous smoking. Past COVID-19 was reported by 3 PD patients (8.8%) and 10 controls (26.3%). The PDG showed a mean UPDRS-III score of 28.1 ± 13.6 points, with the majority (85.2%) in H&Y scale stages I to III.

The CG scored higher in both smell tests: 7.76 ± 2 hits in the SS-12 and 4.63 ± 2.1 hits in the mCCCRC versus 4.70 ± 2.3 hits and 1.17 ± 1.6 hits in the PDG respectively ($p < 0.0001$) (►**Table 1** and ►**Figure 1**). The results of both tests showed a moderate correlation (rho = 0.65; $p < 0.0001$) (►**Figure 2**).

The tests results showed a non-significant tendency toward a negative correlation with age for both groups together (SS-12: rho =-0.05; mCCCRC: rho =-0.13). However, there was a positive correlation between MoCA scores and odor results on both tests, which was stronger with the SS-12 (rho = 0.55; $p < 0.0001$) than with the mCCCRC (rho = 0.39; $p = 0.0007$). The scores obtained in the cognitive test differed between the groups. The CG exhibited better cognitive performance (21.3 ± 4 points versus 17.1 ± 6.2 points in the PDG; $p = 0.0029$).

No correlation was found between motor performance and olfactory test scores in the PDG. Patients with a moderate severity score (> 33 points on the UPDRS-III) scored slightly above the overall mean of the group on the mCCCRC (1.4 hits) and slightly below on the SS-12 test (4.53 hits). The scores on the olfactory tests were inversely proportional to disease duration, but without significance (for the mCCCRC: rho = -0.03; $p = 0.8518$; for the SS-12: rho = -0.23; $p = 0.1947$).

Considering literature-determined normalcy values for both tests (> 10 hits on the SS-12 and ≥ 6 hits on the mCCCRC),[7–9] we found low frequencies of normal

Table 1 Demographics, clinical characteristics, and scores on the olfactory tests of the two research groups

		CG	PDG	*p*
N		38	34	
Age (years): mean(± SD)		65.5(± 6.2)	68.5(± 8.2)	0.5631
Male gender: %		71.0	67.6	0.7541
> 8 years of schooling: %		39.5	38.3	0.2788
Disease duration (years): mean(± SD)		–	7.6(± 5.8)	
Smoking: %	Current smoker	5.3	0	< **0.001**
	Ex-smoker	60.5	35.3	< **0.001**
Past COVID-19: %		3 (8.8)	10 (26.3)	< **0.001**
Hoehn&Yahr scale (in stages I-III): %		–	85.2	
UPDRS-III points: mean(± SD)		–	28.1(± 13.6)	
MoCA points: mean(± SD)		21.3(± 4.0)	17.1(± 6.2)	**0.003**
SS-12 hits: mean(± SD)		7.76(± 2.0)	4.70(± 2.3)	< **0.0001**
mCCCRC hits: mean(± SD)		4.63(± 2.1)	1.17(± 1.6)	< **0.0001**

Abbreviations: CG, control group; COVID-19, coronavirus disease 2019; mCCCRC, modified Connecticut Chemosensory Clinical Research Center olfactory test; MoCA, Montreal Cognitive Assessment; PDG, Parkinson's disease group; SD, standard deviation; SS-12, Sniffin' Sticks-12 test; UPDRS-III, Unified Parkinson's Disease Rating Scale part III.

performance in both groups. In the CG, 21.05% of participants scored normally on the SS-12 and 44.7%, on mCCCRC, while in the PDG, only 2.9% had normal scores on the SS-12 and 0%, on the mCCCRC. Regarding the self-perception of olfactory function, we found that among participants classified as having hyposmia, 96.6% in the CG and 30.3% in the PDG denied it.

No correlation was found between past COVID-19 diagnosis and performance on the olfactory tests in the CG ($n = 10$). However, in the PDG, a history of COVID-19 infection ($n = 3$) yielded inferior results in both olfactory tests. Among current or former smokers, there was no clear correlation with smell test scores.

DISCUSSION

To the best of our knowledge, the present is the first study to investigate the use of the CCCRC[6] olfactory test in PD, which is a low-cost, easily-manufactured test. The present preliminary work found it very easy to produce the mCCCRC test kit with a cost ten times lower than that of purchasing the SS-12. Additionally, handling the mCCCRC test kit was simple, and there were no major concerns about durability, as it can be easily re-manufactured as necessary.

The first study on olfactory dysfunction in PD was published in 1975.[10] Since then, the issue has been extensively investigated, and a large proportion of Parkinsonians, up to 90%, are reported to have an impaired sense of smell, sometimes beginning years before the onset of motor symptoms.[5] Accordingly, the PD patients in our cohort scored significantly lower on both olfactory tests, which is consistent with many other studies.[8,11–19]

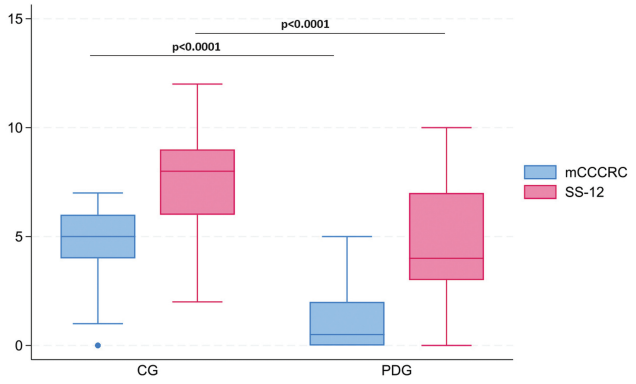
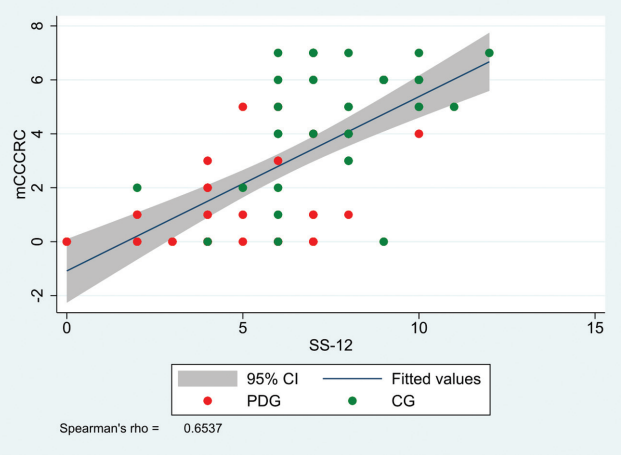


Figure 1 Boxplot of the scores on the olfactory tests obtained in the control group (CG; $n = 38$) and Parkinson's disease group (PDG; $n = 34$) depicting significantly lower scores by PDG on both tests ($p < 0.0001$).



Abbreviations: CG, control group; PDG, Parkinson's disease group; CI, confidence interval; mCCCRC, modified Connecticut Chemosensory Clinical Research Center olfactory test; SS-12, Sniffin' Sticks-12 test.

Figure 2 Graphic showing good correlation between the scores on the two olfactory tests (mCCCRC and SS-12) in the CG and PDG, as demonstrated by the Spearman correlation coefficient (rho = 0.65; $p < 0.0001$).

Despite the high prevalence of hyposmia, a considerable proportion of our hyposmic PD patients (1/3) reported no perception of their decreased olfactory function. Other researchers have found similar low prevalence of self-awareness of hyposmia. One study[13] found that 52% of hyposmic PD patients had no perception of their deficits either. These data suggest the unreliability of self-reports of olfactory perception, emphasizing the need for the use of olfactory tests in the clinical practice to evaluate this symptom in PD patients and individuals at a higher risk of developing PD.

In the present study, PD duration showed a poor correlation with the scores on both olfactory tests. Although it may seem plausible to expect a direct correlation between poorer smelling and disease duration, our finding is consistent with those of previous studies.[11,16–19] As already pointed out, a hypothesis to explain this finding is that the perceptual disorder may be non-progressive and fully present from the beginning of the disease process.[11,20]

In a validation study of a Portuguese version of the CCCRC for Brazilians,[7] the authors classified scores > 6 hits of normal odor identification on the test as normosmia. They found an average of more than 80% of normosmia in their sample, which consisted of 334 healthy individuals aged between 18 and 76 (mean: 39.9 ± 14.5) years. The authors[7] observed poorer scores with aging. Indeed, olfactory dysfunction is a relatively common feature in older individuals, probably related to multiple factors, such as nasal engorgement, cumulative damage to the olfactory epithelium, and sensory loss of receptor cells to odorants, among others.[21–24]

Although we could only observe a slight tendency of lower scores for older individuals, it is important to note that our sample was significantly older compared with that of the reference study.[7] This factor explains the low proportion of normosmia found in the present study, even in the healthy CG, highlighting the need for larger studies to establish cut-off scores on the mCCCRC to classify normosmia or hyposmia based on age in Brazil. Notably, we found no participants with normosmia in the PDG using the reference criterion.

Cognitive ability needs to be considered in the evaluation of olfactory function in adults using olfactory tests.[24,25] Impairment in olfaction has been associated with cognitive decline in the elderly,[24–27] and it is considered a marker of cognitive decline with aging.[28] Our results showed a score on the olfactory tests proportional to the MoCA, which is in agreement with previous findings.[24,25] The lower level of schooling in the population of the present study may have interfered with the olfactory test scores due to difficulties in reading the options and interpreting what was requested.

The COVID-19 pandemic has generated significant interest among the scientific community regarding olfactory dysfunction. In the present study, a worse performance on olfactory tests was observed in the PDG patients who had contracted COVID-19. This finding had not been reported in previous studies. All patients in the PDG with a history of COVID-19 (8.8%) scored 0 on the mCCCRC test and had an average of 4 correct answers on the SS-12 test. Although there is evidence that the metabolic findings of prolonged hyposmia after COVID-19 involve cortical areas that do not overlap with the pathological alteration found in PD,[29] our preliminary results showed a more pronounced loss of olfactory identification ability among PD patients with a history of COVID-19.

The limitations of the present study should be taken into consideration. The small number of participants in both groups did not enable the conduction of an accuracy study. Further studies to establish cut-off scores on the test adjusted for age and cognitive status are necessary. Additionally, the low proportion of smokers and participants with a history of COVID-19 infection prevents a conclusive association with hyposmia in Parkinsonian patients. Nevertheless, our results encourage future studies on this important subject in the field of movement disorders in Neurology.

In conclusion, the mCCCRC exhibited a good performance, similar to that of the SS-12, in evaluating olfaction. As a high proportion of Parkinsonians present with hyposmia, the assessment of olfaction is important not only for diagnostic purposes, but also to anticipate safety issues caused by the impaired sense of smell. The ease of manufacturing and the low cost may increase the use of the mCCCRC olfactory test in the neurological practice in the future, especially in medium-to-low-income countries.

Authors' Contributions

JFLA: conceptualization or design of the work, data acquisition, analysis and interpretation, and writing of the manuscript; LDS, RTB, and MASDL: writing of the manuscript;; GCM: analysis and interpretation; ALZR: conceptualization or design of the work and writing of the manuscript; RCLF: conceptualization or design of the work, analysis and interpretation, and writing of the manuscript. All authors approved the final version of the manuscript and are responsible for all aspects of the work.

Conflict of Interest

The authors have conflict of interest to declare.

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