Influence of age, schooling and cognition on olfactory test performance in Parkinson's Disease patients: a case-control study

Influência da idade, escolaridade e cognição no desempenho em testes olfativos de pacientes com doença de Parkinson: um estudo caso-controle

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ABSTRACT

Background: olfactory dysfunction is an early and prevalent non-motor symptom of Parkinson's disease (PD). However, factors such as age, schooling, and cognition also influence olfactory test performance and are essential for the proper interpretation of results, especially in populations with low educational levels.
Objectives: to evaluate the influence of age, schooling, and cognition on olfactory test performance in Parkinson's disease patients (PDG) and the control group (CG).
Materials and Methods: this cross-sectional case-control study included 106 participants (53 PDG and 53 CG), aged 60 to 85. All underwent olfactory testing with *Sniffin´Sticks-12* (SS-12) and the modified *Connecticut Chemosensory Clinical Research Center* (mCCCRC) and cognitive screening with the *Montreal Cognitive Assessment* (MoCA). The PDG was scored by part III of the UPDRS-III and the H&Y scale. Statistical analyses were performed to assess associations between variables.
Results: PDG scored lower on both olfactory tests and on the MoCA. Cognitive performance positively influenced olfactory scores, especially for SS-12 in both groups. Education significantly affected SS-12 and MoCA scores but had no important effect on mCCCRC performance. Age negatively impacted mCCCRC scores in the CG.
Conclusion: although education significantly influenced SS-12 scores, our findings showed that mCCCRC performance was less affected by lower educational levels. This highlights the mCCCRC as a more education-independent olfactory test, suitable for use in populations with limited schooling. Integrating cognitive and olfactory testing may enhance clinical evaluation and monitoring in PD.

Keywords: Parkinson's disease. Hyposmia. Olfaction disorders. Cognition. Neurocognitive Tests. Educational status. Case-control studies.

RESUMO

Fundamento: a disfunção olfatória é um sintoma não motor precoce e prevalente na doença de Parkinson (DP). Todavia, fatores como idade, escolaridade e cognição também influenciam o desempenho em testes olfatórios e são essenciais para a interpretação adequada dos resultados, especialmente em populações com baixa escolaridade.
Objetivos: avaliar a influência da idade, escolaridade e cognição no desempenho de testes olfatórios em pacientes com DP (GDP) e grupo de controles (GC).
Materiais e Métodos: estudo caso-controle transversal com 106 participantes (53 GDP; 53 GC), entre 60 e 85 anos. Todos foram submetidos aos testes olfatórios *Sniffin´Sticks-12* (SS-12), *Connecticut Chemosensory Clinical Research Center* modificado (mCCCRC) e avaliação cognitiva com o *Montreal Cognitive Assessment* (MoCA). O GDP foi avaliado pela parte III da UPDRS-III e escala H&Y. Foram aplicadas análises estatísticas para investigar associações entre as variáveis.
Resultados: o GDP teve pior desempenho nos testes olfatórios e no MoCA. A cognição influenciou positivamente os resultados olfatórios, especialmente no SS-12 em ambos os grupos. A escolaridade afetou significativamente os escores do SS-12 e MoCA, mas não do mCCCRC. A idade impactou negativamente os escores do mCCCRC no GC.
Conclusão: embora a escolaridade tenha influenciado significativamente os escores do SS-12, nossos resultados mostraram que o desempenho no mCCCRC foi pouco afetado por baixos níveis educacionais. Isso destaca o mCCCRC como um teste olfatório mais resistente à influência da escolaridade, sendo uma ferramenta útil para uso clínico em populações com baixa escolaridade. Integração entre testes cognitivos e olfatórios pode aprimorar a avaliação e monitoramento da DP.

Palavras-chave: Doença de Parkinson. Hiposmia. Transtornos do olfato. Cognição. Teste cognitivo. Escolaridade. Estudos de casos e controles.

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INTRODUCTION

Parkinson's disease (PD), initially described by James Parkinson in 1817, is a neurodegenerative condition characterized primarily by motor symptoms. Diagnosis is still based on the clinical picture, where bradykinesia must be present associated with resting tremor or rigidity[1]. Olfactory dysfunction is a significant non-motor symptom in PD, present in up to 90% of patients, often preceding motor symptoms and serving as an early marker for the disease, as well[2-4]. Previous works highlight the prevalence of olfactory dysfunction in PD and its potential use as a diagnostic tool[5-8]. However, some studies have linked aging per se and cognitive decline with reduced olfactory function[9-14]. Additionally, education is a key factor in cognitive reserve, potentially influencing olfactory test outcomes[15,16]. Therefore, it is of particular importance to consider the interaction between age, education level, and cognition to evaluate olfaction in Parkinsonians to enhance clinical assessment and management of the disease.

Among the olfactory tests commonly used in PD research are the Sniffin' Sticks screening test (SS-12, Burghart Messtechnik GmbH, Wedel, Germany)[17] and the University of Pennsylvania Smell Identification Test (UPSIT). A recent paper of our research group called attention to the modified version of the Connecticut Chemosensory Clinical Research Center (mCCCRC)[5,18] to evaluate olfactory function of Parkinsonians. Due to the high price of industrialized smell tests, the mCCCRC is a good option for developing countries as it is easily self-manufactured at low cost.

This study aimed to assess olfaction in PD patients and non-PD controls using two distinct olfactory tests: SS-12 and mCCCRC. Some partial results of this research have already been published[5]. For this paper we bring together the previous results and additional analysis, considering specifically the impact of age, schooling and cognitive function on test performance. Our main objective was to determine to what extent these variables influence olfactory test results in a Brazilian cohort of PD patients.

MATERIALS AND METHODS

This was a cross-sectional case-control study conducted between July 2021 and September 2022. PD patients were recruited from the outpatient Neurology Clinic at Hospital Universitário Clementino Fraga Filho, Universidade Federal do Rio de Janeiro (UFRJ).

The PD group (PDG) included individuals with a PD diagnosis assessed by a movement disorders specialist following the diagnostic criteria of the International Parkinson and Movement Disorders Society[1]. Inclusion criteria were disease duration of > 2 years and age 60 to 85 years. The exclusion criterion was a clinical dementia diagnosis.

The control group (CG) comprised volunteers aged 60 to 85 years without any known neurodegenerative conditions. These individuals were selected from the unrelated companions of neurologic patients or individuals attending other outpatient clinics at the same hospital.

Exclusion criteria for both research groups included a history of significant head trauma, current rhinosinusitis symptoms, previous nasal surgery or incomplete testing.

A semi-structured questionnaire was administered to obtain sociodemographic and clinical data, including COVID-19 infection history (SARS-CoV-2) and smoking habits. Self-evaluation of smell was also registered in both groups.

All participants underwent olfactory testing using the SS-12 and the mCCCRC, with a minimum interval of 30 minutes between tests. Scores were based on the number of correct identifications: maximum of 12 points for SS-12 and 7 points for mCCCRC.

Cognition was evaluated through the Montreal Cognitive Assessment (MoCA – Portuguese experimental version[19]) for all participants. The Unified Parkinson's Disease Rating Scale part III (UPDRS-III[20]) and the modified Hoehn and Yahr Scale[21] (H&Y) were utilized to assess PD patients.

All participants provided written informed consent before being included in the study, which received approval from the Ethics Committee of UFRJ (CAAE 58752422.6.0000.5257).

Statistical Analysis

Data were analyzed using Jamovi 2.6.26 (open-source). Results are presented by descriptive statistics. Statistical tests were conducted to assess the relationship between age, sex, education, smoking status, MoCA scores and olfactory test performance: Mann-Whitney test, Spearman's rank correlation, linear regression analyses, ANCOVA, rank-based MANOVA (Wilks' Lambda, Pillai's Trace, Hotelling-Lawley, and Roy's Largest Root), and post-hoc one-way ANOVA tests.

RESULTS

A total of 106 individuals were evaluated – 53 in PDG and 53 in CG (Table 1). The groups had similar age, gender, and level of schooling. Most participants had less than 8 years of formal schooling.

The PDG showed a mean UPDRS-III score of 26.8 ± 13.8 points, with the majority (84.9%) in H&Y scale stages II and III.

The CG scored higher in both smell tests: 7.53 ± 1.9 points (maximum 12 points) for the SS-12 and 4.37 ± 2.1 points (maximum 7 points) for the mCCCRC vs PDG scores of 4.6 ± 2.4 points and 1.33 ± 1.6 points respectively ($p<0.0001$) (Figure 1). Results from both tests were strongly correlated ($rho=0.65$; $p<0.0001$)[5].

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

	CG	PDG	p
N	53	53	
Age (years): mean (±SD)	65.5 (±6.2)	68.5 (±8.2)	0.5631
Male gender: %	71	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 points: mean (±SD)	7.76 (±2.0)	4.7 (±2.3)	<0.0001
mCCCRC points: 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.

The scores obtained in the MoCA test differed between the groups. The CG exhibited better cognitive performance, scoring 21.5 ± 3.7 points, compared to 17.9 ± 5.6 points in the PDG (p=0.001) (Figure 1).

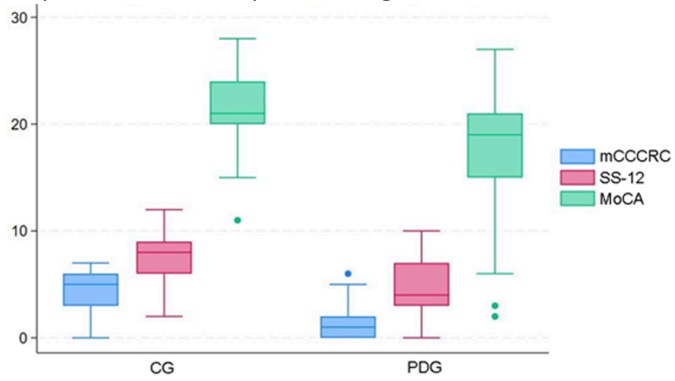

Figure 1 Boxplot of the scores on the olfactory tests (p<0.0001) and cognitive test (MoCA) (p=0.001) obtained in the study groups.

mCCCRC and SS-12 in CG and PDG: p<0.0001
MoCA in CG and PDG: p=0.001
mCCCRC, modified Connecticut Chemosensory Clinical Research Center olfactory test; SS-12, Sniffin' Sticks-12 test; MoCA, Montreal Cognitive Assessment; CG, control group; PDG, Parkinson's disease group.

MoCA scores had a significant positive effect on SS-12 performance in both groups, indicating that higher MoCA scores corresponded to better olfactory performance in the test (PDG p<0.001; CG p=0.012). After controlling for age, smoking, and education, MoCA scores still maintained a significant effect in the CG (p=0.04). For the mCCCRC olfactory test, however, the positive association between MoCA scores and olfactory scores could only be observed for the PDG (p=0.021) (Figure 2 and Figure 3).

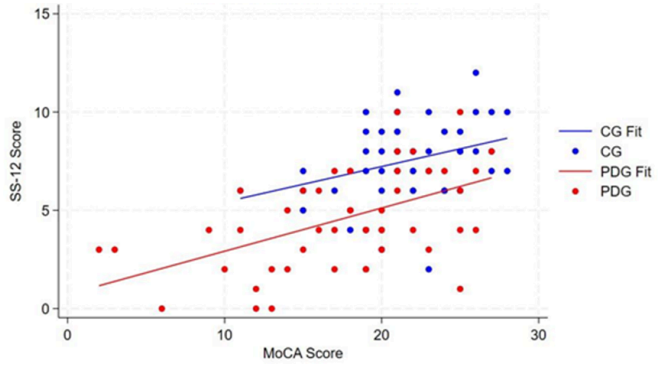

Figure 2 Correlation between Sniffin' Sticks-12 test scores and Montreal Cognitive Assessment in the Parkinson's disease group and control group.

SS-12 vs MoCA in CG: ρ (rho) = 0.315, p = 0.022.
SS-12 vs MoCA in PDG:ρ (rho) = 0.515, p < 0.001.
MoCA, Montreal Cognitive Assessment; SS-12, Sniffin' Sticks-12 test; CG, control group; PDG, Parkinson's disease group

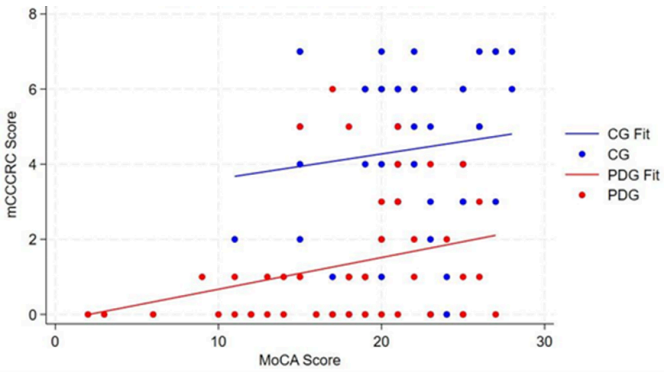

Figure 3 Correlation between the modified Connecticut Chemosensory Clinical Research Center olfactory test scores and Montreal Cognitive Assessment in the Parkinson's disease group and control group.

mCCCRC vs MoCA in CG: ρ (rho) = 0.077, p = 0.583.
SS-12 vs MoCA in PDG: ρ (rho) = 0.317, p = 0.021.

mCCCRC, modified Connecticut Chemosensory Clinical Research Center olfactory test; MoCA, Montreal Cognitive Assessment.

Age negatively impacted mCCCRC scores in the CG (p=0.010). ANCOVA test for mCCCRC in the CG revealed that age remained an important predictor (p=0.009) even after adjusting for MoCA scores, smoking, and education. ANCOVA test for mCCCRC in the PDG also indicated a similar trend (p = 0.076) after adjusting for those factors and disease duration. For SS-12 in the CG, age had a significant negative effect (p=0.01). However, for SS-12 in the PDG, age did not show a significant effect (p=0.116), along with education (p=0.107) and MoCA scores (p=0.1) that exhibited only a marginal effect.

Sex did not impact test performance for both groups.

As expected, schooling showed a positive correlation with MoCA results for both groups. In the CG, education level was moderately correlated with MoCA scores (rho=0.369, p=0.008), while in PDG, the relationship was even stronger (rho = 0.659, p<0.001).

Further analysis through the rank-based MANOVA test showed a significant positive effect of schooling on overall performance across the combined dependent variables, including MoCA, SS-12, and mCCCRC (Wilks' Lambda=0.7627, F[3,90]=9.33, p<0.001).

Additional tests (Pillai's Trace p<0.001, Hotelling-Lawley p<0.001 and Roy's Root p<0.001) supported the statistically significant association between education and the combined scores of SS-12, mCCCRC and MoCA.

Post-hoc one-way ANOVA analyses indicated that the significant effect observed in MANOVA was primarily driven by SS-12 (F[1, 91]=5.69, p=0.019) and MoCA (F[1,91]=22.65, p < 0.001). In contrast, education did not show a significant association with mCCCRC performance (F[1, 91]=0.0048, p = 0.945).

The mCCCRC score was inversely proportional to disease duration in PDG. Participants with >10 years of PD had an average score of 1.05 points on the mCCCRC and 4.2 points on the SS-12, both under the overall group mean. Among patients with >20 years of disease, the average scores were even lower (0.25 points on the mCCCRC and 3.5 points on the SS-12). Correlation analysis revealed a significant negative relationship between disease duration in the PD group and MoCA performance (rho=−0.285, p=0.039).

DISCUSSION

Our findings reinforce the relationship between education, age, and cognition in olfactory testing in PD. The significant association found in this cohort between the level of scholarity and MoCA scores aligns with previous studies that link higher education levels to better cognitive outcomes[15,16]. This effect was more pronounced in the PD group, a result that may suggest that formal education provides greater cognitive resilience against the neurodegeneration effects on mental functioning, even in face of the ongoing disease[22]. A recent meta-analysis supports this, demonstrating that education correlates with better cognitive function and a lower risk of progression to mild cognitive impairment in PD patients[23].

Although education significantly influenced SS-12 scores, our results evidenced that mCCCRC performance was less impacted by lower educational levels. This finding suggests that mCCCRC could be a more reliable olfactory test in populations with limited schooling, such as those in developing countries with low literacy rates or limited access to formal education. Its low cost and easy manufacturing make the mCCCRC a viable testing option for widespread clinical use in Brazil and other developing countries [5,18].

This distinction highlights the complexity of olfactory processing, where objective smell identification results yield different outcomes depending on which olfactory test is used in the evaluation.

The lack of association between schooling level and objective olfactory function was found only for mCCCRC, perhaps because this test uses substances which may be more culturally familiar to the patients, such as coffee, cinnamon, and mothballs, and suggests that the mechanisms that predominantly govern this ability are quite independent of cognition and appear resistant to educational background[8,4]. So, it seems that olfaction testing is more likely to depend on cognitive performance per se than on the absolute level of schooling in Brazil when the adapted CCCRC test is to be used in clinical practice.

Our results also evidenced that age plays a significant role in testing olfactory function. Once again, this was more pronounced for the mCCCRC. Aging itself is a well-documented factor influencing both cognition and olfaction. Structural and functional changes in the brain, including neurodegeneration of the olfactory bulb, decreased neurogenesis, and alterations in brain regions involved in olfactory processing, contribute to age-related declines in cognition and olfactory function[24,14]. Cognitive decline with aging affects memory, attention, and executive function - key processes involved in olfactory identification and discrimination[22,26]. This overlap underscores the challenge in distinguishing between normal senescence-related olfactory decline and the more severe deficits observed in PD. Also, olfactory impairment in PD may reach a functional floor in the early stages of the disease, making additional age-related decline less evident. Notably, olfaction relies not only on sensory perception but also on higher-order cognitive processes. The less consistent responses to the olfactory tests emphasize odor-semantic associations that involve linking smells to names or meanings, often based more on language and culture than on the smell itself[26,27]. This highlights the intricate connection between olfaction and cognition, reinforcing the potential of olfactory testing as a clinical tool for early detection of neurodegenerative conditions [28,29].

Our findings provide additional evidence of the important interplay between cognition and olfactory function in PD. MoCA scores correlated positively with olfactory function (mCCCRC: p=0.083; SS-12: p=0.0029), and participants with lower education levels had significantly poorer test performance. These findings suggest that while olfactory dysfunction is an early biomarker of PD, cognitive reserve may modulate its perception. Notably, age and disease duration did not significantly impact SS-12 scores, further emphasizing the role of cognitive function in subjective olfactory assessments.

These findings support the importance of cognitive reserve in PD and highlight the necessity of integrating cognitive assessments into olfactory testing. Future research should investigate the longitudinal impact of cognitive reserve on olfactory and cognitive decline, particularly in diverse educational and socioeconomic contexts.

CONCLUSION

The findings of this work emphasize the importance of integrating cognitive evaluations and olfactory assessments to improve diagnostic accuracy and disease monitoring in PD. Given the potential clinical relevance of mCCCRC in populations with lower literacy levels, future research should explore its application in diverse healthcare settings to investigate its predictive role in cognitive decline and intervention strategies in PD.

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