Neurobiology of Disease 217 (2025) 107172

Contents lists available at ScienceDirect

Neurobiology of Disease

journal homepage: www.elsevier.com/locate/ynbdi

A multi-dimensional study on taste deficits, α-synuclein genetic profiling, and supervised learning for diagnosis and disease severity stratification in Parkinson's disease (PD)

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ARTICLE INFO

Keywords:
Taste perception in PD
α-Synuclein genetic variants
Supervised learning

ABSTRACT

Parkinson's disease (PD) is a complex neurological condition. Alfa-synuclein, and specifically the salivary oligomeric form, have been described as biomarkers of PD, and their genetic mutations have been associated with PD susceptibility. Taste impairments are less studied and have produced inconsistent results, and their diagnostic and prognostic significance remains underexplored. We evaluated taste perceptions for five taste stimuli and their association with four *α-synuclein* gene (*SNCA*) polymorphisms in PD patients and healthy controls (HCs). Demographic and clinical features of the PD patients were also determined. A Supervised Learning (SL) model classified PD versus HC and moderate versus high severity PD (MSPD versus HSPD), determining the impact of each feature. We found that taste impairments in PD are modality-specific, with saltiness and astringency most affected, and are modulated by the *SNCA* gene variations. NaCl under threshold, age, and incorrect identification of tannic acid were the most influential features for PD prediction. Specific genotypes of *SNCA* SNPs (e.g., *rs356219* GG, *rs181489* TT, *rs2583988* CC, *rs356186* GG) were enriched in PD patients with impaired astringency and saltiness. Tremor-dominant PD and shorter PD were associated with MSPD, while longer disease duration and akinetic-rigid type predicted HSPD. The *rs2583988* CC genotype was associated with moderate PD, while the *rs2583988* TT genotype and lower taste acuity predicted high severity. Our findings showed that, when combined with SL and genetic profiling, these sensory markers offer a powerful, non-invasive approach for early diagnosis and disease stratification, supporting the integration of sensory and genetic screening into clinical practice.

1. Introduction

Parkinson's disease (PD) is a common neurodegenerative disease characterized by the occurrence of motor and non-motor disturbances (Cersosimo and Benarroch, 2012; Cersosimo et al., 2011; Melis et al., 2021; Proulx et al., 2005). PD incidence has rapidly increased and is now one of the primary causes of disability worldwide, impacting over 10 million individuals (Olcay et al., 2024; Ou et al., 2021). Pathologically, PD is characterized by the loss of dopaminergic neurons within the *Substantia nigra pars compacta*, and is associated with intracellular inclusions in the neurons, known as Lewy bodies. The Lewy bodies are intracytoplasmic eosinophilic deposits of α-synuclein, a misfolded protein that spreads like a prion to various parts of the brain, causing a series of non-motor and motor symptoms (Kalia and Lang, 2015). Several studies have focused on identifying disease biomarkers that can help to better understand the underlying mechanisms of the disease, in addition to early diagnosis, and adequate tracking of the onset and progression of PD (Figura and Friedman, 2020). However, most of the

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https://doi.org/10.1016/j.nbd.2025.107172
Received 7 August 2025; Received in revised form 30 October 2025; Accepted 31 October 2025
Available online 3 November 2025

existing studies have focused on a single and specific compartment involved in PD, and this limits the overview of the possible interactions of different factors in the determination of the PD phenotype. In addition to age, which remains the most important risk factor for the disease (Lee and Gilbert, 2016), and the male sex (Gillies et al., 2014), other factors have been associated with risk of PD, such as taste and smell impairments or salivary biomarkers or individual motor, neurocognitive, social and affective profiles, etc. (Balestrino and Schapira, 2020; Melis et al., 2021; Nijakowski et al., 2024). Among them, changes in levels of α-synuclein forms (i.e. total, oligomeric, and phosphorylated) within the cerebrospinal fluid and peripheral fluids, such as blood and saliva, have been described as PD biomarkers, possibly reflecting the neuropathological consequence (Atik et al., 2016; Ganguly et al., 2021). However, other authors have described the salivary levels of oligomeric α-synuclein as one of the most promising biomarkers of PD (Angius et al., 2023). This role is supported by evidence that PD patients have higher salivary levels of the oligomeric α-synuclein than healthy controls (HC), but there are conflicting data regarding total amounts (Kharel et al., 2022). In addition, mutations in the *α-synuclein* gene (*SNCA*) have been associated with PD susceptibility (Campêlo et al., 2017; Han et al., 2015; Hou et al., 2019; Mohammadi et al., 2025; Winkler et al., 2007; Zhang et al., 2018). Interestingly, accumulation of α-synuclein in the olfactory bulb, amygdala, and other limbic structures is associated with loss of smell and olfactory disorders (Uemura et al., 2021). Besides, olfactory, as well as taste disorders, reflect the damage to dopaminergic and cholinergic pathways, providing a model for studying neurodegenerative evolution (Haehner et al., 2011).

Although the olfactory impairments are one of the most studied clinical markers of early PD (Melis et al., 2021), those relative to taste are less studied and have produced inconsistent results (Cecchini et al., 2015; Nigam et al., 2021; Roos et al., 2018; Shah et al., 2009). In addition, few studies have elucidated the mechanism behind taste changes and their clinical, diagnostic, and therapeutic significance (Ricatti et al., 2017; Tarakad and Jankovic, 2017). Besides, no association between hypogeusia and hyposmia has been observed, suggesting that these sensory deficits may have different underlying causes (Tarakad and Jankovic, 2017). Taste disorders can range from complete loss of taste (ageusia), reduced sensitivity (hypogeusia), distorted taste (dysgeusia) or phantogeusia that can result from various causes, including neurodegenerative diseases, such as PD (Alia et al., 2025; Braud and Boucher, 2020; Doty and Hawkes, 2019; Pugnaloni et al., 2020; Su et al., 2013). Hypogeusia and dysgeusia for all basic tastes have been found in PD patients and are correlated with disease severity (Alia et al., 2025; Zhu et al., 2025). Reduced taste sensitivity may occur in REM-BD, which can often be a prodromal form of PD (Nigam et al., 2021). Patients with PD have a preference for sweet, salty, and umami tastes which can influence their appetite and food choices (Alia et al., 2025; Jagota et al., 2022). Furthermore, the assumption of dopaminergic drugs has been linked to taste disorders (Rademacher et al., 2020). Commonly, late-stage PDs present an excessive salivation, which has been shown to affect taste perception (Lagalla et al., 2006; Miller et al., 2019).

Taste is mediated by the taste receptors that can distinguish five basic qualities (sweet, sour, salt, umami, and bitter) in the oral cavity (Chaudhari and Roper, 2010) and also detect chemical molecules in extra-oral tissues where they take part in numerous physiological functions (Behrens and Meyerhof, 2011; Clark et al., 2012; Depoortere, 2014; Laffitte et al., 2014; Lu et al., 2017; Singh et al., 2011; Yamamoto and Ishimaru, 2013). Genetic variants of these receptors are associated with a different affinity for the stimulus (Roudnitzky et al., 2015) and also with different human disorders, including PD (Cossu et al., 2018; Lu et al., 2017; Melis et al., 2019). Interestingly, an interaction between bitter taste receptors (T2R) signaling and toll-like receptors (TLRs), involved in innate immunity, has been suggested, and a TLR dysregulated function has been implicated in the abnormal accumulation of the α-synuclein aggregates in PD (Alia et al., 2025; Kim et al., 2018; Kwon et al., 2019). These considerations could link, via TLR/T2R signaling, altered taste receptors and/or taste impairments with inflammatory mechanisms associated with the α-synucleinopathy (Cecati et al., 2022; Oppo et al., 2020).

The aim of this work was to confirm the involvement of taste deficits in PD, elucidate the mechanisms underlying them, and clarify their diagnostic significance using Supervised Learning (SL) algorithms to search for data that correlate with specific features and automatically distinguish between PD patients and HCs. To this end, we evaluated, in PD patients and HCs, the identification of taste stimuli: sweet, salty, sour, bitter, including astringency, a sensation of dryness which is experienced when the stimulus interacts with salivary proteins (Charlton et al., 2002; Jöbstl et al., 2004; Siebert et al., 1996). We hypothesized that the perception of astringent stimulus in the PD patients could be influenced by the high levels of the α-synuclein protein in saliva and thus by *SNCA* SNPs, which affect its levels (Hou et al., 2019; Mohammadi et al., 2025). The possible interactions between taste impairments and *SNCA* mutations associated with PD susceptibility (Campêlo et al., 2017; Han et al., 2015; Hou et al., 2019; Mohammadi et al., 2025; Winkler et al., 2007; Zhang et al., 2018) were also analyzed. SL was also used to automatically classify PD patients based on disease severity.

2. Materials and methods

2.1. Subjects

Ninety-nine PD patients and sixty HCs, closely matched for age (range: 50–90 years), sex, and ethnicity, were recruited in the area of Cagliari, Italy. PD patients were enrolled at the Parkinson Center of the Department of Neurology, Brotzu Hospital, Cagliari, Italy, while HCs at the University of Cagliari, Italy. The exclusion criteria consisted of major diseases (e.g., kidney disease and diabetes), food allergies, chronic rhinosinusitis and medications that interfere with sensory functions. All PD patients were diagnosed according to Postuma criteria (Gibb and Lees, 1988). The age of onset, duration of illness (calculated as the difference between age and age of initial diagnosis), Hoehn and Yahr stage (moderate severity of PD, MSPD and high severity of PD, HSPD), Type of PD (Tremor-dominant, Akinetic-rigid, Mixed) and PD duration category (from 0 to 2 years, from 3 to 5 years, more the 5 years) were established. Unfortunately, for 2 PD patients, we could not have the Hoehn and Yahr stage and Type of PD, and for 1, the age of initial diagnosis. HCs were neurologically normal, and none had first-degree relatives with neurodegenerative diseases. After signing an informed consent, participants underwent a baseline medical screening to investigate their health status and anthropometric, demographic, and lifestyle factors, including

Table 1
Demographic and clinical features of the patient' cohort.

Features	
Males/ Females *(n)*	60/39
Smokers/Non-smokers *(n)*	9/90
Age (y)	69.91 ± 0.95
Age of onset (y)	61.74 ± 1.15
Duration of illness (y)	8.14 ± 0.55
Hoehn and Yahr stage	2.64 ± 0.13
Moderate severity PD (n)	48
High severity PD (n)	49
Type of PD:	
Tremor-dominant (n)	28
Akinetic-rigid (n)	14
Mixed (n)	55
PD duration category	
from 0 to 2 years (n)	13
from 3 to 5 years (n)	27
more the 5 years (n)	58

Data are shown as mean values ± S.E.

smoking habits and oral hygiene habits. The demographic and clinical features of the PD patients are shown in Table 1. Buccal swabs were collected and stored at −80°. Participants were asked not to drink, eat, or smoke for 1 h before the taste measurements. Each participant received a verbal explanation of the study's purpose and methodology. The ethics committee of the University Hospital of Cagliari approved (prot. PG/2017/17817, verbal number 06, December 20, 2017) all procedures used in this investigation, which was carried out in compliance with the 1975 Declaration of Helsinki (updated in 1983).

2.2. Taste measurements

The quality identification of stimulations with taste stimuli representative of four basic taste qualities (sweet, sour, salty, bitter) and of the astringency sensation was determined in PD patients and HCs. The measurements were performed by placing a taste strip of filter paper impregnated with taste solutions on the tongues of subjects. The "taste strips" used were the same as the validated "Taste Strip Test" (TST, Burghart Company, Wedel, Germany) (Landis et al., 2009; Mueller et al., 2003). Since PD patients are subjects who have difficulty maintaining concentration for long periods, to reduce the duration of taste measurements, only one stimulus was used for each quality in each subject. The choice of stimuli was based on the results of our previous work where an SL regression approach allowed us to automatically and accurately identify with high precision the different stimuli, which accurately predict the overall taste status of HCs and patients with chemosensory loss (Naciri et al., 2023). Taste stimuli were presented in a semi-random order, with astringent stimuli presented last due to their persistence. Participants were instructed to rinse their mouths with spring water before each new test. Since gustatory perception is shaped by the context, the measurements did not include umami, for which, unlike the stimuli used, is relatively unfamiliar to Europeans (Cecchini et al., 2019).

The following concentrations were used: 0.4 g/mL sucrose, 0.3 g/mL citric acid, 0.016 g/mL sodium chloride, 0.006 g/mL quinine hydrochloride, and 0.2 g/mL tannin. All subjects had to identify the taste quality of each stimulus by choosing from a list of five possible answers (sweet, sour, salty, bitter, astringent) in a forced choice procedure (Landis et al., 2009). The complete procedure required 10 min for each subject.

2.3. Molecular analysis

Participants were genotyped for the following single-nucleotide polymorphisms (SNPs) of *α-synuclein* gene (*SNCA*): the *rs356219* (A/G), whose allele G is associated with an increase of α-synuclein (Hou et al., 2019; Mohammadi et al., 2025), the *rs181489* (C/T), whose allele T is associated with a higher risk of developing PD (Zhang et al., 2018), the *rs2583988* (C/T), whose allele T is associated with higher risk of developing PD and cognitive deficits (Campêlo et al., 2017; Winkler et al., 2007), and the *rs356186* (A/G), whose allele A is associated with a lower risk of developing PD (Zhang et al., 2018).

A buccal swab was taken from each participant by using a sterile cytobrush, and DNA was extracted using the salting-out method. The buccal swab samples were suspended in 500 μL lysis buffer (MLS Medisen Lysis Solution: 1 M NaCl, 0.1 M Tris-HCl pH 8.0, 40 mM Disodium EDTA, and 0.2 % SDS), and 5 μL 50 mg/ml proteinase K was added. The samples were incubated overnight at 56 °C until the tissue was dissolved. Following lysis, a saturated Sodium Acetate solution (3 M, pH 8.0) was used to precipitate the proteins. Centrifugation at 8000 rpm for 10′ removed the pellet. DNA was then precipitated by adding 100 % isopropanol and isolated by centrifugation. After decanting the supernatant, 300 μL 70 % ethanol was added, and the pellet was dissolved; the mixture was centrifuged at 10000 rpm for 10 min, and the supernatant was decanted gently. The pellet was air-dried under laminar air flow, and the dried pellet was resuspended in 50 μL nuclease-free water. The concentration and purity of the extracted DNA were assessed by measuring absorbance at 260 nm with a NanoDrop One/One Spectrophotometer (Thermo Fisher Scientific).

Molecular analyses were carried out using the TaqMan® SNP Genotyping Assay, following the manufacturer's guidelines (Applied Biosystems, Life Technologies, Milan, Italy). Reactions were performed in 96-well plates under fast thermal cycling conditions. Ten ng of DNA, nuclease-free water, 1× TaqMan® Genotyping Master Mix (code: 4371355), 1× TaqMan® Genotyping Assays (C_1020193_10, C_3208976_10, C_1658278_10, C_3208925_10) were included in each reaction.

The StepOne™ Real-Time PCR System was used for amplification and detection, and the Sequence Detection Software (Genotyping - Applied Biosystems, version 2.3; Life Technologies Italia, Monza, Italy) was used to determine genotypes through allelic discrimination. Replicates and positive and negative controls were included in every reaction. The low concentration and/or purity of the extracted DNA did not allow us to determine the genotype of some PD patients (2 for *rs356219*, 3 for *rs181489*, 5 for *rs2583988*, and 3 for *rs356186*) and HCs (2 for *rs356219*, 3 for *rs181489*, 3 for *rs2583988*, and 3 for *rs356186*).

2.4. Statistical analysis

The distribution of PD patients and HCs who perceived no taste (under threshold), recognized the taste (correct identification), or described a different quality (incorrect identification) for each taste stimulus (sucrose, NaCl, citric acid, quinine, and tannic acid) was analyzed using Fisher's exact test.

The genotype distribution and allele frequency of the *rs356219*, *rs181489*, *rs2583988*, and *rs356186* SNPs of *SNCA* of the PD patients and HCs who correctly recognized the taste (PD-yes and HCs-yes) and those of PD patients and HCs who perceived no taste or described a different quality (PD-no and HCs-no) for each taste stimulus were compared using Fisher's exact test (Genepop software version 4.2; http://genepop.curtin.edu.au/genepop_op3.html). P values ≤ 0.05 were considered significant.

2.5. Supervised learning

Supervised Learning (SL) is a class of algorithms that uses labeled datasets of features previously recorded from subjects to train models to predict new samples. By identifying patterns that relate input features to their corresponding labels, SL can be applied to tasks such as classifying patients by diagnosis or evaluating disease severity. This approach allows for a systematic comparison of different algorithms to determine which one best captures relevant differences in the data. In this work, two automatic binary classification tasks were carried out by using SL algorithms: the first to clarify the diagnostic significance of taste stimuli distinguishing between PD patients and HCs, and the second to make a prediction of the disease severity of PD patients and classify them into those who had a moderate severity of PD (MSPD; 1, 1.5, 2, 2.5 in the Hoehn and Yahr scale) and those who had high severity of PD (HSPD; 3, 3.5, 4, 5 in the Hoehn and Yahr scale). In both tasks, we used the same algorithms: Random Forest, Logistic Regression, K-Nearest Neighbors (KNN), Decision Tree, Gradient Boosting, and CatBoost Classifier. These models learned the relationships between input features and target classes during training, allowing them to predict the correct class for new data. The features for the first task included: Sucrose under threshold, Sucrose correct identification, Sucrose incorrect identification, NaCl under threshold, NaCl correct identification, NaCl incorrect identification, Citric acid under threshold, Citric acid correct identification, Citric acid incorrect identification, Quinine under threshold, Quinine correct identification, Quinine incorrect identification, Tannic acid under threshold, Tannic acid correct identification, Tannic acid incorrect identification, Total strips identified, Age, Male, Female, Smoker and Non-smoker. For the second task the following features

were added: Type of PD (to which were assigned numerical categories: 0 = Tremor-dominant, 1 = Akinetic-rigid, 2 = Mixed), Years with PD (calculated as difference between age and age of initial diagnosis), PD duration category (to which were assigned numerical categories: 1 = from 0 to 2 years, 2 = from 3 to 5 years, 3 = more the 5 years), Age of initial diagnosis, and the genotypes of the four *rs356219*, *rs181489*, *rs2583988* and *rs356186* SNPs of *SNCA*.

For both classification tasks, the One-Hot Encoding was applied to convert categorical variables into a numerical format (Samuels, 2024) and the model performance was assessed using standard classification metrics, such as accuracy and macro-averaged F1-score (Opitz, 2024). The overall performance of the models was evaluated on both the training and testing sets using the mentioned metrics, providing insights into their ability. Since in the first task, the training dataset showed a class imbalance (more PD patients than HCs), the class balancing was addressed using the Synthetic Minority Oversampling Technique (SMOTE) to generate synthetic samples for the minority class (Barua et al., 2011). For training models, the datasets were randomly split into training and testing sets using an 80:20 ratio to avoid bias and ensure generalization. In the first task, the dataset consisted of 158 samples (98 patients and 60 HCs) and 19 features, resulting in 126 training samples and 32 testing samples. After SMOTE, the training set was balanced with 78 samples per class. In the second task, the dataset comprised 88 samples described by 34 features, randomly split into 70 samples for training and 18 for testing, with balanced class representation between the MSPD class and HSPD class.

The interpretation of the SL model predictions was performed by using the Shapley Additive exPlanations (SHAP), a game-theoretical method that links feature importance with feature effect (Lundberg and Lee, 2017). It returns a SHAP summary plot that connects the significance of the features to their impacts.

3. Results

3.1. Determination of the taste perception of PD patients and healthy controls (HCs)

The distribution of PD patients and HCs who perceived no taste (under threshold), recognized the taste (correct identification), or described a different quality (incorrect identification) for each taste stimulus: sucrose, NaCl, citric acid, quinine, and tannic acid is shown in Fig. 1. Fisher's exact test showed no differences between the two populations when subjects had to identify the sweet quality ($p > 0.05$) (Fig. 1a): most subjects (89 % of PD patients and 97 % of HCs) correctly recognized the stimulus. The two populations showed different sensitivities when tasting the salty stimulus ($\chi^2 = 30.113$, $p < 0.0001$) (Fig. 1b); 11 % of PD patients and 50 % of HCs correctly identified salty stimulus, 50 % of PD patients and 23 % of HCs perceived no taste, and

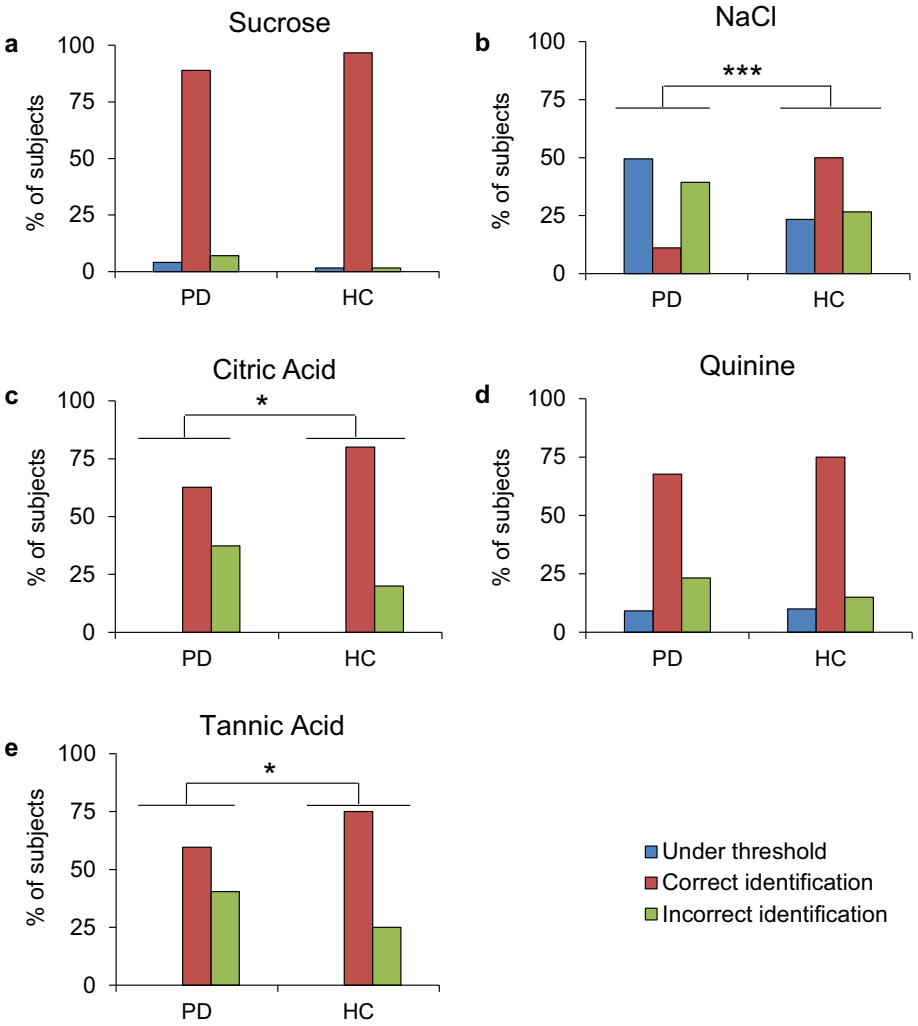

Fig. 1. Distribution of PD patients and healthy controls (HCs) who perceived no taste (under threshold), recognized the taste (correct identification), or described a different quality (incorrect identification) for each taste stimulus: sucrose, NaCl, citric acid, quinine, and tannic acid. The significant difference between PD patients and HCs is indicated by *** ($\chi 2 = 30.113$, $p < 0.0001$) or * ($\chi^2 > 3.917$, $p < 0.047$; Fisher's exact test). PD patients ($n = 99$), HCs ($n = 60$).

39 % of PD patients and 27 % of HCs described a different taste quality. The two populations showed different sensitivities also when tasting the sour stimulus ($\chi^2 = 5.289$, $p = 0.021$) (Fig. 1c); 63 % of PD patients and 80 % of HCs correctly recognized the sour stimulus, no subjects in either group perceived any taste, and 37 % of PD patients and 20 % of HCs perceived a different quality. Fisher's exact test showed no differences between the two populations tasting the bitter taste stimulus ($p > 0.005$) (Fig. 1d). Most subjects (68 % of PD patients and 75 % of HCs) correctly recognized the bitter stimulus. Finally, the two populations showed different sensitivities when tasting the astringent stimulus ($\chi^2 = 3.917$, $p = 0.047$) (Fig. 1e); 60 % of PD patients and 75 % of HCs correctly identified the astringent stimulus, no subjects of either group reported any taste, and 40 % of PD patients and 25 % of HCs perceived a different quality.

3.2. Taste stimuli diagnostic significance, by supervised learning

In the first automatic binary classification task carried out to clarify the diagnostic significance of taste stimuli distinguishing between PD patients and HCs, the metrics that evaluated the training and testing performance of the SL algorithms showed that the CatBoost algorithm achieved the best results (Table S1). Specifically, the CatBoost algorithm showed 91 % training accuracy, 91 % training macro-averaged F1-score, 84 % testing accuracy, and 82 % testing macro-averaged F1-score.

The SHAP algorithm allowed us to obtain an overview of the most important features and their impact in distinguishing between PD patients and HCs (Fig. 2). In the SHAP summary plot, the order of importance of the features is shown on the left-hand side of each Y-axis, going from the most significant at the top to the least significant at the bottom. Each point on the SHAP summary plot is a SHAP value that allows to understand the contribution of an input feature to that single prediction. In addition, SHAP values also indicate whether a feature has a favorable (red color) or unfavorable (blue color) influence on predictions. Specifically, the SHAP summary plot for the PD class highlights that the NaCl under threshold and age were the first and second important features, with high values (red color) strongly associated with PD prediction (Fig. 2a). Importantly, the Tannic acid incorrect identification resulted in the third position of importance, and high values (red color) pushed the model towards PD predictions. The male sex was the fourth important feature positively correlated with PD prediction. NaCl incorrect identification was the fifth important feature and strongly and positively correlated with PD prediction. The Total strips identified was the sixth feature, and low values (blue color) pushed the model towards PD predictions. The NaCl correct identification was the seventh important feature and correlated negatively with PD class. Notably, the smoking-related features showed an important impact on PD prediction: smoker and non-smoker status were positively and negatively correlated to PD class, respectively. Interestingly, Quinine under the threshold strongly and positively correlated with this class.

The SHAP summary plot for the HC class revealed a different pattern of feature importance (Fig. 2b). For this class, the NaCl under threshold was the most important for the model, and low estimated values (blue color) were strongly and positively correlated with the prediction of the HC class. Age was the second important feature, and the low and medium values (blue and violet colors) pushed the model to predict a subject as an HC, despite some outliers being present. The NaCl correct identification was the third important feature, and high values (red color) were positively correlated with HC class. The male sex was the fourth important feature and was strongly and negatively correlated with HC prediction. The Tannic acid incorrect identification and the NaCl incorrect identification were the fifth and the sixth in order of importance, and low values (blue color) pushed the model prediction towards the HC class. The Total strips identified followed in order of importance, with high values (red color) positively correlated with an HC prediction, while female sex showed a negative correlation with HC class.

3.3. Relationships between the PD patients and HCs' taste perception and SNCA mutations

Genotype distribution and allele frequencies of *SNCA* polymorphisms in PD patients and HCs are shown in Table S2. A significant difference was found between PD patients and HCs based on the genotype distribution and allele frequency of the *rs356186* SNP ($\chi^2 > 7.389$; $p < 0.015$). On the other hand, no differences were found between PD patients and HCs according to the genotype distribution and allele

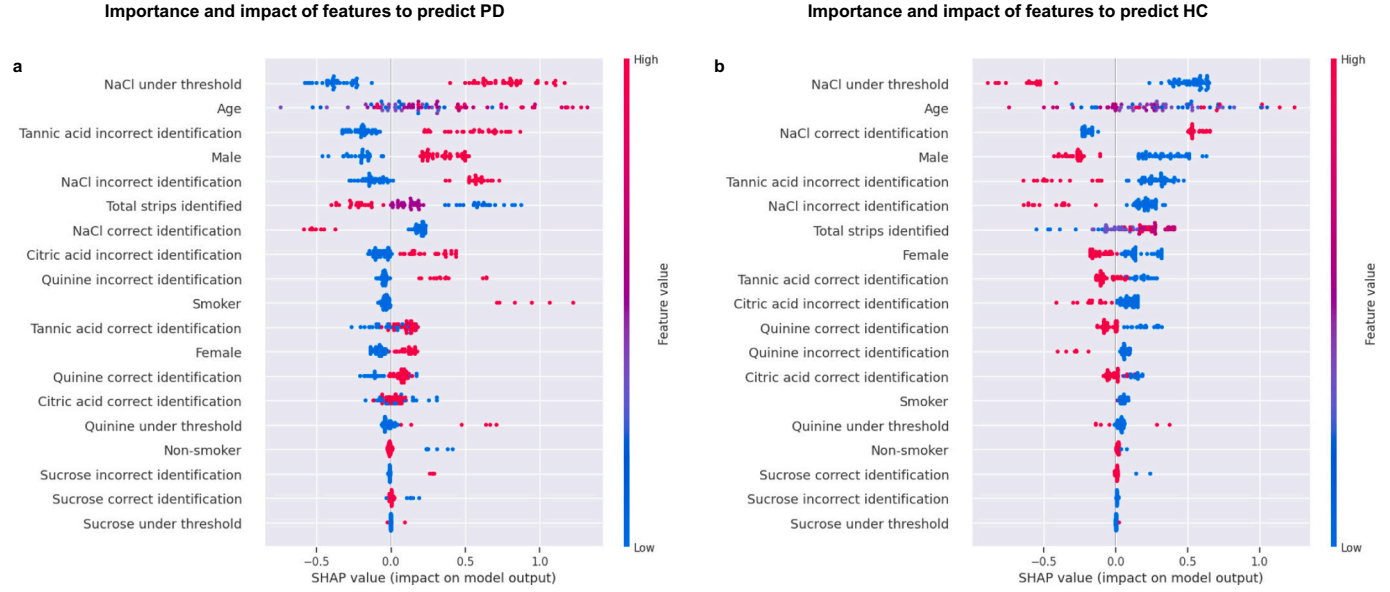

Fig. 2. SHAP summary plots showing feature importance and their impact on the CatBoost classifier to make predictions of PD patients (a) or HCs (b). The descending order of importance of the features (from top to bottom) is shown on the left of each Y-axis; the impact on the model output (SHAP value) is shown on the X-axis. The position of the SHAP value on the X-axis shows whether the feature is associated with a higher or lower prediction score for the class. Each point in the plot is a SHAP value of a feature. The color of the line to the right of each graph represents the feature value: high value (red color), medium value (violet color), and low value (blue color). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

frequency of *rs356219, rs181489*, and *rs2583988* SNPs of *SNCA* ($\chi^2 > 1.557$; $p < 0.459$, Fisher's method).

Fig. 3 shows the percentage of PD patients and HCs who correctly recognized the taste (PD-yes and HC-yes) and those of PD patients and HCs who perceived no taste or described a different quality (PD-no and HC-no) for each taste stimulus (sucrose, NaCl, citric acid, quinine and tannic acid) according to the *rs356219*, *rs181489*, *rs2583988,* and *rs356186* SNPs of *SNCA*. When subjects tasted tannic acid, the molecular analysis at the *rs356219*, *rs181489*, *rs2583988* and *rs356186* SNPs of *SNCA* showed that the four groups differed statistically based on the genotype distributions (*rs356219*: $\chi^2 = 10.794$, $p = 0.0045$; *rs181489*: $\chi^2 = 10.428$, $p = 0.0054$; *rs2583988*: $\chi^2 = 8.386$, $p = 0.015$; *rs356186:* $\chi^2 = 7.280$, $p = 0.026$, Fisher's method) and allelic frequencies (*rs356219*: $\chi^2 = 10.331$, $p = 0.0057$; *rs181489*: $\chi^2 = 10.0627$, $p = 0.0065$; *rs2583988*: $\chi^2 = 8.855$, $p = 0.0119$; *rs356186* $\chi^2 = 7.681$, $p = 0.021$, Fisher's method) (Fig. 3e). Pairwise comparisons discriminated PD-no and HC-no in the four SNPs ($\chi^2 > 7.080$, $p < 0.028$ and $\chi^2 > 6.017$, $p < 0.049$, Fisher's method), PD-yes and PD-no in the *rs356219*, *rs181489*, and *rs2583988* SNPs ($\chi^2 > 11.068$, $p < 0.0039$; $\chi^2 > 11.182$, $p < 0.0037$, Fisher's method), HC-yes and PD-no in the *rs356219* and *rs2583988* SNPs ($\chi^2 > 6.159$, $p < 0.045$; $\chi^2 > 6.044$, $p < 0.048$, Fisher's method), and PD-yes and HC-no in the *rs356186* SNP ($\chi^2 = 10.023$, $p < 0.0066$; $\chi^2 = 10.290$, $p < 0.0058$, Fisher's method).

Specifically, in the *rs356219* locus, PD-yes had a high frequency of subjects with a least one allele A (91 %), and a low frequency of genotypes GG (9 %), whereas PD-no had a high frequency of subjects with a least one allele G (79 %) and a low frequency of genotypes AA (21 %). It is interesting to note that HC-yes and HC-no had a high frequency of subjects with at least one allele A (HC-yes: 88 % and HC-no: 97 %) and a low frequency of genotypes GG (HC-yes: 12 % and HC-no: 13 %).

In the *rs181489* locus, PD-yes had a high frequency of subjects with at least one allele C (93 %), and a low frequency of genotypes TT (7 %),

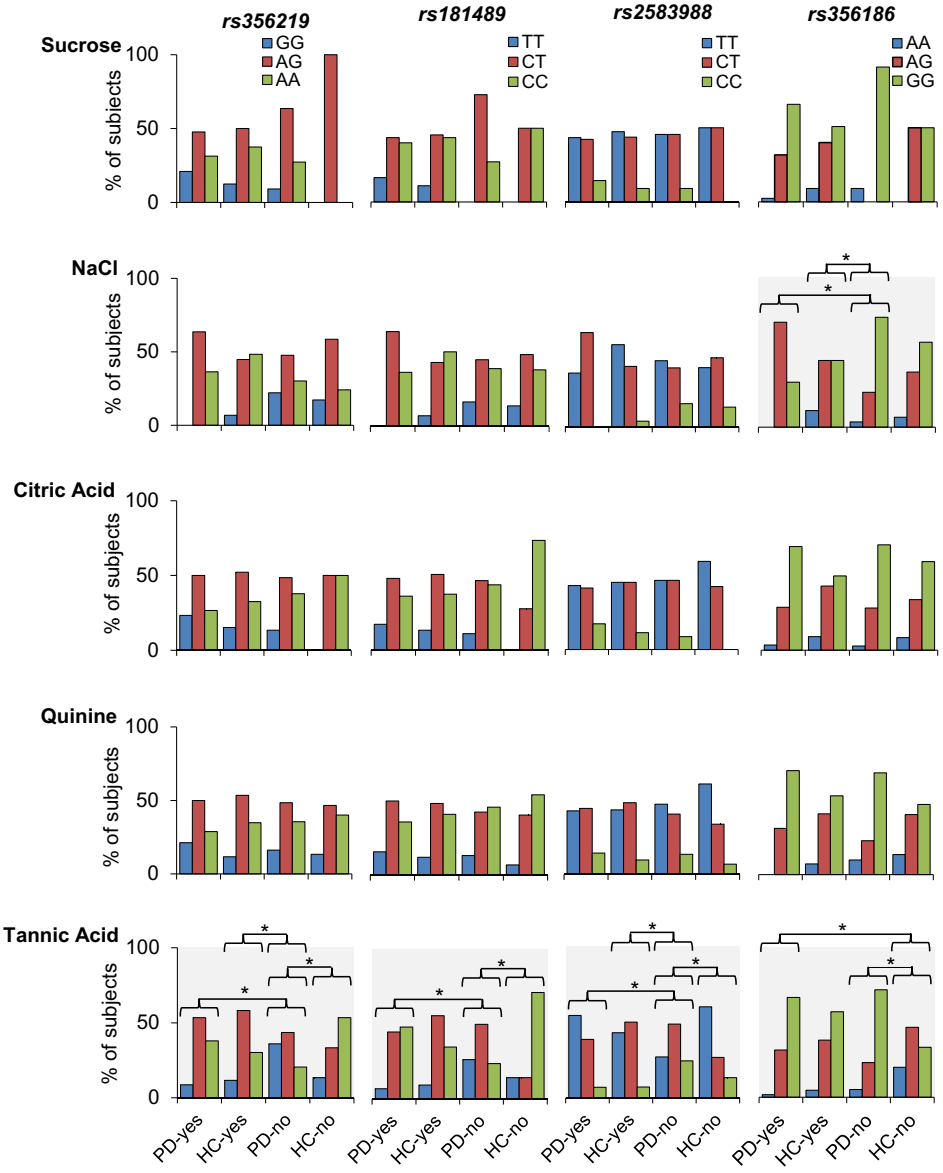

Fig. 3. The percentage of PD patients and HCs who correctly recognized the taste (PD-yes and HC-yes) and those of PD patients and HCs who perceived no taste or described a different quality (PD-no and HC-no) for each taste stimulus (sucrose, NaCl, citric acid, quinine, and tannic acid) according to the *rs356219*, *rs181489*, *rs2583988*, and *rs356186* SNPs of *SNCA*. The graphic area highlighted in grey indicates significant difference across the four group (PD-yes, HC-yes, PD-no and HC-no) based on their genotype distributions (*rs356219*: $\chi^2 = 10.704$, $p = 0.0045$; *rs181489*: $\chi^2 = 10.428$, $p = 0.0054$; *rs2583988*: $\chi^2 = 8.386$, $p = 0.015$; *rs356186* $\chi^2 = 7.280$, $p = 0.026$, Fisher's method) and allelic frequencies (*rs356219*: $\chi^2 = 10.333$, $p = 0.0057$; *rs181489*: $\chi^2 = 10.0627$ $p = 0.0065$; *rs2583988*: $\chi^2 = 8.855$, $p = 0.012$; *rs356186:* $\chi^2 = 7.681$, $p = 0.021$, Fisher's method). * Indicates significant difference for population pair.

whereas PD-no had a high frequency of subjects with a least one allele T (76 %) and low frequency of genotypes CC (23 %). It is noteworthy that HC-yes and HC-no had a high frequency of subjects with at least one allele C (HC-yes: 91 % and HC-no: 86 %) and a low frequency of genotypes TT (HC-yes: 9 % and HC-no: 14 %).

In the *rs2583988* locus, PD-yes had a high frequency of subjects with at least one allele T (87 %), and a low frequency of genotypes CC (7 %), PD-no had a high frequency of subjects with a least one allele T (76 %) and low frequency of genotypes CC (24 %). In this locus, HC-yes and HC-no had a high frequency of subjects with at least one allele T (HC-yes: 91 % and HC-no: 87 %) and a low frequency of genotypes CC (HC-yes: 7 % and HC-no: 13 %).

In the *rs356186* locus, PD-yes and PD-no had a low frequency of subjects with at least one allele A (33 % and 28 %), and a high frequency of genotypes GG (67 % and 72 %), HC-no had a high frequency of subjects with a least one allele A (67 %) and a low frequency of genotypes GG (33 %) and HC-yes had a similar frequency of subjects with least one allele A and subjects with genotype GG (43 % and 57 %).

The genotype distributions and allelic frequencies of the *rs356186* SNP also differed when subjects tasted NaCl ($\chi^2 = 8.193$, $p = 0.0166$; $\chi^2 = 9.659$, $p = 0.008$, Fisher's method). Pairwise comparison discriminated PD-no from PD-yes and HC-yes ($\chi^2 > 9.559$, $p < 0.008$; $\chi^2 > 10.248$, $p < 0.0059$, Fisher's method). PD-yes had a high frequency of heterozygous subjects (70 %), a low frequency of genotypes GG (30 %) and none had genotype AA, while PD-no had a high frequency of GG subjects (73 %) and a low frequency of subjects with at least one allele A (27 %). On the other hand, 56 % of HC-yes and 43 % of HC-no had at least one allele A, and 44 % and 57 % had genotypes GG.

3.4. Classification of PD patients based on disease severity by supervised learning

In the second automatic binary classification task carried out to classify PD patients into those who had a moderate severity of PD (MSPD) and those who had high severity of PD (HSPD), the standard metrics to evaluate the training and testing performance of the SL algorithms showed that the CatBoost algorithm had the best performance, showing very high values of training accuracy (98 %), training macro-averaged F1-score (98 %), testing accuracy (94 %), and testing macro-averaged F1-score (94) (Table S3).

The SHAP algorithm also provided comprehensive insights on the importance of features and their impact on the CatBoost model to classify PD patients into those who had moderate severity of PD (MSPD) and those who had high severity of PD (HSPD) (Fig. 4). The analysis revealed distinct feature contribution patterns that differentiate the severity classes. The SHAP summary plot for the MSPD class highlights that the type of PD was the most important feature for the model, and low estimated values (blue), which represent the Tremor- dominant type, were strongly and positively correlated with the prediction of MSPD (Fig. 4a). The Years with PD and the PD duration category were the second and third features in order of importance, and low and medium estimated values, which represent a shorter duration of PD (blue and violet, respectively) had a high impact on making the MSPD prediction. Age of initial diagnosis was the fourth significant feature, and low and medium estimated values (blue and violet, respectively) positively correlated with the MSPD class. The feature total strips identified was the fifth significant one; however, in the plot, its impact on the model predictions was unclear. Among the genetic features, *SNCA rs2583988* CC and *rs356186* AA genotypes were the most important genetic features and positively correlated with the MSPD prediction. The Citric acid incorrect identification was the seventh important feature, and high values positively correlated with the target prediction. Interestingly, the female sex had a negative impact to make a prediction of the MSPD prediction, contrary to the male, which had a positive impact on the target and were the ninth and tenth in order of importance, respectively.

The SHAP summary plot highlights the link between the importance of features and their impact on predicting the HSPD class, is shown in Fig. 4b. Specifically, the plot shows that the Years with PD was the most important feature for the model, and high and medium estimated values (red and violet, respectively) were strongly and positively correlated with the prediction of the HSPD class. The type of PD was the second in order of importance, and high and medium estimated values (which represent the Akinetic-rigid and Mixed type) had a high impact on

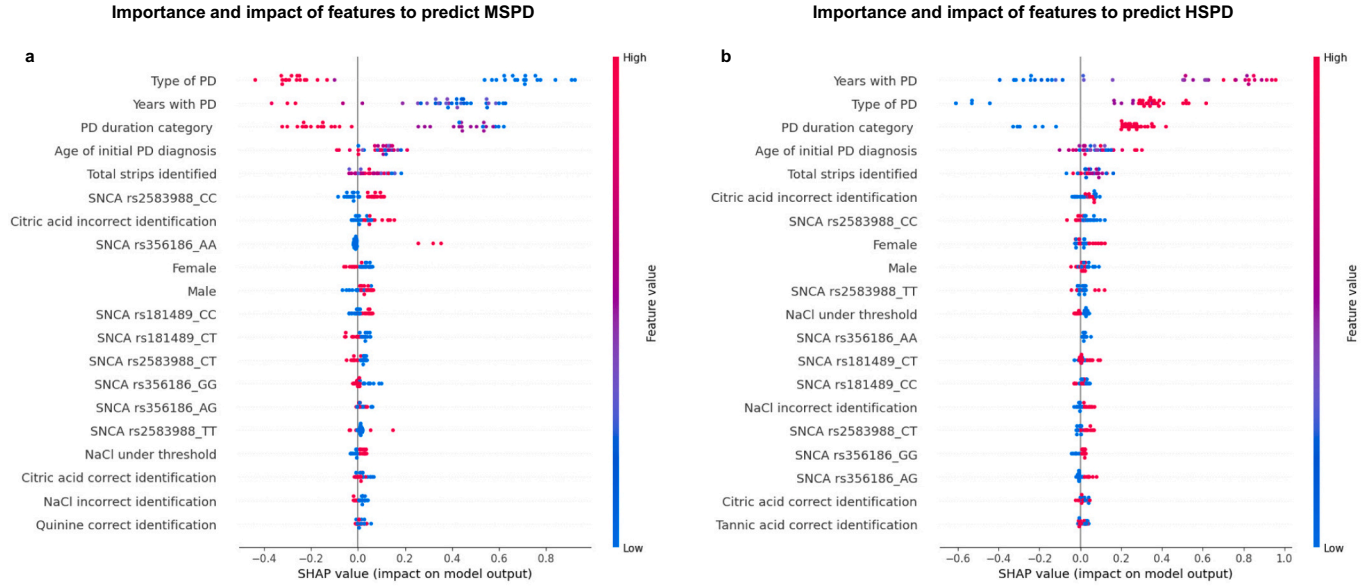

Fig. 4. SHAP summary plots showing feature importance and their impact on the CatBoost classifier to make predictions of the disease severity of PD patients and classify them into those who had a moderate severity of PD (MSPD) (a) and those who had high severity of PD (HSPD) (b). The descending order of importance of the features (from top to bottom) is shown on the left of each Y-axis; the impact (SHAP value on the model output) is shown on the X-axis. The position of the SHAPE value on the X-axis shows whether the feature is associated with a higher or lower prediction score for the class. Each point in the plot is a SHAP value of a feature. The color of the line to the right of each graph represents the feature value: high value (red color), medium value (violet color), and low value (blue color). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

making an HSPD prediction. The PD duration category was the third significant feature, and high estimated values (red) positively correlated with the target. The age of initial diagnosis was the fourth significant feature, and high estimated values (red) positively correlated with the prediction of the HSPD class. The total strips identified was the fifth significant feature, and low and medium estimated values (blue and violet, respectively) positively correlated with the HSPD prediction. The Citric acid incorrect identification was the sixth most important feature, and low values estimated were positively correlated with the target or had a low impact. The *SNCA rs2583988* CC genotype was the seventh important genetic feature and pushed the model forward to the other class. The sex features were the eighth and ninth in order of importance and impacted the model in making predictions contrary to that for the MSPD.

4. Discussion

By integrating behavioral, demographic, computational, and genetic data, this study provides a multi-dimensional analysis of how taste perception is altered in PD, explores the underlying mechanisms, and offers a comprehensive view of how these alterations can be exploited for both diagnostic and disease severity purposes, by highlighting key sensory markers. Our study also provides new insights into the interactions between the taste deficits in PD and specific SNPs of the *SNCA* gene, already associated with PD predisposition (Campêlo et al., 2017; Han et al., 2015; Hou et al., 2019; Mohammadi et al., 2025; Winkler et al., 2007; Zhang et al., 2018). Our findings provide compelling evidence that taste impairments in PD are modality-specific, with saltiness and astringency most affected, and that genetic variations in the *SNCA* gene, which encodes alpha-synuclein, a key protein in PD pathology, modulate taste perception, contributing to the sensory phenotype of PD. These results support the hypothesis that modality-specific taste deficits in PD are not only functional but also genetically influenced, potentially offering a biomarker for early or prodromal PD. Specifically, the most significant taste deficit in PD was observed for salty taste (NaCl). Behavioral assessments revealed that PD patients showed different sensitivity to the salty stimulus compared to HCs. Only 11 % of them correctly identified the stimulus with respect to 50 % of HCs, and for half of PD patients, the NaCl stimulation was below threshold, while only 14 % of HCs did not perceive any taste of NaCl. Astringency and sourness were also less accurately identified by PD patients, while sweet and bitter tastes showed no significant group differences. These findings suggest that PD-related taste deficits are selective, likely reflecting differential involvement of taste receptor pathways or central gustatory processing circuits. An altered perception of astringency, a complex oral-sensory experience, may also indicate broader deficits in sensory integration.

In addition to behavioral measurements, we used SL models to confirm the involvement of taste impairments in PD and verify their possible diagnostic significance and distinguish between PD patients and HCs. The models learned the relationships between input features and target classes during training, allowing them to predict the correct class for new data. The training and testing performance of the SL models was evaluated using standard classification metrics, which provided insights into their ability to predict the two classes. The CatBoost algorithm achieved the best performance in classifying PD vs. HC, based on taste and demographic features, with 91 % training accuracy, 91 % training macro-averaged F1-score, 84 % testing accuracy, and 82 % testing macro-averaged F1-score.

Interpreting the results of the CatBoost classifier, performed using the SHAP algorithm, allowed us to establish a link between the importance of each feature and its impact on prediction. The SHAP analysis revealed that, among the sensory features, the perception of any taste (under threshold) when subjects taste salty, or the description of a different quality (incorrect identification), when they taste astringent stimulus (tannic acid), were the most influential features for PD classification. The NaCl under threshold feature was also important for the HC classification, but negatively correlated with HC target, whereas the NaCl correct identification was the third important feature with a positive correlation for the HC classification. These results indicate that our SL model classifies a subject as a PD patient if he/she perceived no taste for salty or described a different quality for the astringent stimulus, while it classifies as HC if he/she correctly identified the salty stimulus. The incorrect identification of sour stimulus was also positively correlated with the PD class, while sucrose-related features or bitter taste had little or no impact on the model prediction, consistent with behavioral findings. The total number of taste strips identified was inversely correlated to the PD classification, although it ranked sixth in importance, suggesting a general reduction in taste acuity in PD. These findings highlight the potential of taste testing as a non-invasive, biologically grounded tool for the diagnosis of PD and open new pathways for understanding the sensory dimensions of neurodegeneration. Age, sex, and smoking status also contributed significantly to PD prediction and were considered as variables that enhance the predictive power of the SL model. Age was a strong predictor of the PD classification, consistent with age-related PD risk (Lee and Gilbert, 2016). Sex showed the already known pattern (Gillies et al., 2014), with male sex associated with PD prediction. According to previous data (Mappin-Kasirer et al., 2020), smoking status was positively associated with PD. Overall, these results demonstrate the diagnostic potential of modality-specific taste disorders, especially when behavioral assessments are combined with interpretable SL-based analyses.

Genetic analysis of the *SNCA* SNPs, *rs356219*, *rs181489*, *rs2583988*, and *rs356186*, showed significant associations between genetic variations and the ability to perceive certain taste stimuli, particularly tannic acid and NaCl, in both PD patients and HCs. Specifically, when participants were exposed to tannic acid, the perception of astringency varied significantly across genotypes. Both genotype distributions and allele frequencies at all four *SNCA* loci differed significantly among the four groups (PD-yes, PD-no, HC-yes, HC-no). PD patients who failed to recognize astringency (PD-no) had distinct genotype and allele distributions compared to PD-yes and HCs, particularly at *rs356219*, *rs181489*, and *rs2583988*. PD-no also differed from HCs-no, suggesting that the inability to perceive astringency in PD may be genetically driven and not simply a result of general sensory decline. Specifically, at *rs356219*, PD-yes individuals had a high frequency of the A allele, while PD-no had a high frequency of the G allele, which has been associated with increased α-synuclein levels (Hou et al., 2019; Mohammadi et al., 2025). This suggests that the A allele may be protective or associated with preserved astringency perception. At *rs181489*, a similar pattern emerged, with PD-yes enriched for the C allele and PD-no for the T allele, which has been associated with a higher risk of evolving PD (Zhang et al., 2018). At *rs2583988*, the T allele, which has been associated with a higher risk of developing PD (Campêlo et al., 2017; Winkler et al., 2007), was more common in PD-yes, while the CC genotype was more frequent in PD-no. Finally, at *rs356186*, both PD-yes and PD-no had high frequencies of the GG genotype, but HCs-no had a significantly higher frequency of the A allele, suggesting a potential protective role in non-PD individuals, in agreement with data showing a reduced risk of developing PD in A allele carriers (Zhang et al., 2018). These findings suggest that specific *SNCA* variants may influence the integrity of astringency perception pathways, potentially through effects on alpha-synuclein expression or aggregation in gustatory-related brain regions (Fathy et al., 2019; Hou et al., 2019; Mohammadi et al., 2025). However, since other α-synucleinopathies, such as Dementia with Lewy Bodies (DLB) and Multiple System Atrophy (MSA) (Miglis et al., 2021) are characterized by the abnormal accumulation of aggregates of alpha-synuclein protein, it cannot be ruled out that the taste deficits may not only be limited to PD alone. The *rs356186* SNP also showed a significant association with salt taste perception. PD-no individuals had a high frequency of the GG genotype and a low frequency of the A allele, while PD-yes individuals were predominantly heterozygous (AG) and lacked

AA genotypes. In contrast, HCs-yes had a more balanced distribution, with more than 50 % carrying at least one A allele and 44.44 % having the GG genotype. These results suggest that the A allele at *rs356186* may be associated with preserved salt taste perception, while the GG genotype may predispose individuals to salt taste deficits, particularly in the context of PD. This study, which used a medium-sized cohort of PD patients, highlights the need for future studies with larger samples to further investigate the taste deficits in PD and their associations with SNPs of the SNCA gene.

The CatBoost classifier was also used to classify PD patients based on disease severity with very high accuracy values. In this second SL task, the SHAP software showed distinct patterns of feature importance and directionality for each severity class, reflecting the complex interplay between clinical, sensory, and genetic factors in PD progression. The SHAP analysis for the MSPD class highlighted features that were protective or indicative of less severe disease. PD Type was the most important, and low SHAP values, corresponding to the Tremor-dominant subtype, were strongly associated with the MSPD classification. This is consistent with the clinical literature suggesting that Tremor-dominant PD often progresses more slowly and is associated with a more favorable prognosis (Hoehn and Yahr, 1967; Rajput et al., 2017; Reinoso et al., 2015). Years with PD and PD Duration Category were the next most important features. Shorter disease duration (low and medium SHAP values) was positively associated with MSPD, indicating that earlier stages of the disease are more likely to be classified as moderate. Age of initial diagnosis also played a significant role. A younger age at diagnosis (blue and violet SHAP values) was associated with MSPD, suggesting that earlier onset may initially present with milder symptoms or slower progression. Among sensory features, the Total strips identified, an indicator for global taste acuity, was the fifth most important feature. Although its impact was less clear, higher taste acuity may reflect preserved sensory function and thus milder disease. The Citric acid incorrect identification was positively associated with MSPD, which may seem counterintuitive. However, this may indicate that mild sensory deficits are present even in moderate stages. Among genetic features, the *SNCA rs2583988* CC genotype was positively associated with MSPD class, confirming its potential protective role (Campêlo et al., 2017; Winkler et al., 2007). The *rs356186* AA and *rs181489* CC genotypes, already associated with a high risk of PD (Zhang et al., 2018), were also positively correlated with MSPD class, while heterozygous or alternative genotypes were negatively associated. Interestingly, the *rs2583988* TT genotype, typically associated with high risk, also showed a positive correlation with MSPD class, indicating a complex, likely context-dependent genetic influence. Interestingly, male sex was positively associated with MSPD class, while female sex had a negative impact, suggesting potential sex-based differences in disease progression.

The SHAP summary plot for the HSPD class revealed a mirror image of the MSPD class profile, with features indicative of more advanced disease. Years with PD was the most important predictor. High SHAP values were strongly associated with HSPD class, reflecting the natural progression of PD over time. PD Type again played a major role. High and medium SHAP values, corresponding to Akinetic-Rigid and Mixed subtypes, were associated with HSPD class. These subtypes are known to be more disabling and progress more rapidly (Rajput et al., 2009). PD Duration Category and Age at Diagnosis followed in terms of importance. Longer disease duration and older age at onset were both positively associated with HSPD class, consistent with clinical expectations (Pagano et al., 2016). Among sensory features, Total strips identified was inversely related to the HSPD class: lower taste acuity was associated with more severe disease, strengthening the link between sensory decline and PD progression. Citric acid incorrect identification had a lower impact, but still contributed positively to the HSPD classification, likely reflecting more widespread sensory dysfunction in advanced stages. NaCl incorrect identification was among the lower-ranked features, but still contributed positively to HSPD classification, suggesting that salt taste impairment may worsen with disease progression. Finally, among genetic features, the *rs2583988* CC genotype displaced the model from the HSPD class, while the *rs2583988* TT genotype was positively associated with HSPD class, confirming the non-protective role of the T allele. Other genotypes, such as *rs181489* CT, *rs2583988* CT, *rs356186* GG, and *rs356186* AG, although with low impact, were positively associated with HSPD class, while *rs356186* AA and *rs181489* CC were negatively associated, reinforcing the idea that specific *SNCA* variants modulate disease severity. In contrast to the MSPD class, female sex was positively associated with HSPD class, while male sex had a negative impact. This reversal may reflect sex-specific differences in disease progression or symptom burden. These SHAP-based insights underscore the multifactorial nature of PD severity, in which clinical history, sensory function, and genetic background interact to shape disease expression. The model's ability to distinguish the MSPD class from the HSPD class suggests that SL could be a powerful tool for personalized disease monitoring, leveraging the integration of clinical, sensory, and genetic data into predictive models for PD staging and management.

It is not surprising that the CatBoost algorithm was the most suitable algorithm for both binary SL classification tasks. Indeed, CatBoost is a gradient boosting algorithm for decision trees that uses an approach that prevents information overlap with the target variable and reduces overfitting, while maintaining high predictive accuracy, characteristics that are particularly advantageous when analyzing small datasets containing a relatively large number of categorical features (Hancock and Khoshgoftaar, 2020; Prokhorenkova et al., 2018).

In conclusion, this study provides compelling evidence that deficits in taste perception, particularly saltiness and astringency, are not only early and selective markers of PD, but are also influenced by genetic and demographic factors. We analyzed the possible interactions between taste impairments and four SNCA gene mutations associated with PD susceptibility. However, the literature points to other SNCA SNPs (i.e., *rs3822086*, *rs11931074*, *rs356165, rs2737029, rs2736990, rs2619364, rs2619363*) as potential factors contributing to PD risk. Future studies will focus on these additional SNPs to provide a more comprehensive understanding of SNCA's genetic contributions to the disease. By integrating behavioral tests with machine learning and genetic profiling, we demonstrate a powerful, non-invasive approach for both early diagnosis and disease severity stratification. These findings pave the way for the development of personalized screening tools that could enable earlier intervention, thus preserving neuronal function and reducing symptomatic burden, ultimately improving the quality of life for individuals at risk of developing PD. Future researchers should focus on validating these biomarkers in larger, longitudinal cohorts and integrating them into clinical practice to support precision neurology.

CRediT authorship contribution statement

Lala Chaimae Naciri: Writing – review & editing, Formal analysis, Data curation. **Melania Melis:** Writing – review & editing, Investigation, Funding acquisition, Formal analysis, Data curation. **Giorgia Sollai:** Writing – review & editing, Investigation, Data curation. **Silvia Deligia:** Investigation. **Giuseppe Fenu:** Investigation. **Paolo Mellino:** Investigation. **Beatrice Pinna:** Investigation. **Roberto Crnjar:** Writing – review & editing, Data curation. **Giovanni Cossu:** Writing – review & editing, Supervision, Investigation. **Iole Tomassini Barbarossa:** Writing – original draft, Supervision, Formal analysis, Conceptualization.

Funding sources

This work was supported by UniCA - Progetti di Ricerca Start-Up D. M. 737/2021 (F25F21002720001 to MM. Annualità 2023) and by the COMETA project PIANO SVILUPPO E COESIONE SALUTE – Traiettoria 4 "Biotecnologie, bioinformatica e sviluppo farmaceutico": "Hybrid Hub (H2UB): Modelli cellulari e computazionali, micro e nanotecnologie per

la personalizzazione di terapie innovative". Funded by University of Cagliari under DR 344/2025 'Open Access Awards: call for applications for contributions to the open access publication'.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors thank the volunteers without whose contribution this study would not have been possible. We also thank Professor Micaela Morelli (University of Cagliari, Italy) for critically reviewing the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nbd.2025.107172.

Data availability

The data obtained in this research are available from the corresponding author upon reasonable request.

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