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ORIGINAL COMMUNICATION

Specific intranasal and central trigeminal electrophysiological responses in Parkinson's disease

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Abstract

Olfactory dysfunction is a frequent early non-motor symptom of Parkinson's disease (PD). There is evidence that with regard to trigeminal perception, PD-related olfactory dysfunction is different from other olfactory disorders. More specifically, trigeminal sensitivity, when measured behaviorally, was unimpaired in PD patients as opposed to patients with non-Parkinsonian olfactory dysfunction (NPOD). We sought to investigate the trigeminal pathway by measuring electrophysiological recordings from the nasal epithelium and EEG-derived event-related potentials in response to a specific trigeminal stimulus in 21 PD patients and compare them to 23 patients with NPOD and 25 controls (C). The peripheral trigeminal response, as measured by the negative-mucosa potential, showed no difference between patients with PD and controls whereas PD patients showed faster responses than patients with NPOD, the latter having shown slower and larger responses than controls (18 PD, 14 NPOD, 20 C). The central trigeminal response, as measured by event-related potentials, revealed larger early component response in PD patients compared to patients with NPOD (15 PD, 21 NPOD, 23 C). As expected, psychophysical olfactory testing showed impaired olfactory function in both groups of patients as opposed to controls. Discriminant analysis revealed a model that could predict group membership for 80% of participants based on the negative-mucosa potential latency, olfactory threshold and discrimination tests. These results provide novel insights into the pattern of trigeminal activation in PD which will help to differentiate PD-related olfactory loss from NPOD, a crucial step towards establishing early screening batteries for PD including smell tests.

Keywords Parkinson's disease · Olfactory dysfunction · Trigeminal system · Negative-mucosa potential · Event-related potential

Introduction

Olfactory dysfunction (OD) is an early non-motor symptom of Parkinson's disease (PD) present in 90–96% of patients [1, 2]. Olfactory loss related to PD seems to be distinct from other forms of OD (e.g., due to viral infection, sinonasal disease, or traumatic brain injuries), especially with regard to its influence on the trigeminal system. This third chemosensory system, next to smell and taste, is stimulated by most volatiles and allows for the perception of sensations such as freshness, warmth, stinging, or tickling from odorous stimuli [3]. The trigeminal system is intimately connected to the olfactory system as both systems are stimulated simultaneously by most of odorants [4]. Both systems interact by mutually enhancing or suppressing each other [5] and the stimulation with respective stimuli leads to central activation of overlapping brain areas [6]. As a consequence of

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this connection, the trigeminal system is typically impaired in patients with OD when compared to healthy controls [7–10]. This appears to be different in PD: when measured by the behavioral trigeminal localization task, the trigeminal sensitivity is not impaired in patients with PD compared to patients with non-Parkinsonian olfactory dysfunction (NPOD) [11]. This task is based on the fact that localization of an odorous stimulus presented to one nostril is only possible if the stimulus also activates the trigeminal system. This result suggests that the assessment of trigeminal sensitivity may help to discriminate between PD-related OD and NPOD. This finding may contribute to an early diagnosis of the disease, which is needed to evaluate the potential of early therapeutic interventions [12]. However, the underlying mechanisms behind this disparity still need to be elucidated.

To understand the reason why the trigeminal system is not affected—or affected differently—in PD-related OD, one has to look at how OD typically impairs trigeminal processing. Electrophysiological methods allow for the investigation of trigeminal processing at different levels with high temporal precision. When applied to patients with NPOD, a typical pattern emerges in response to trigeminal stimuli: central measures, such as the EEG-derived trigeminal event-related potentials (tERP) are significantly smaller in patients with OD compared to controls [10, 13, 14], in line with behavioral results [7]. However, on the receptor level at the nasal respiratory mucosa, the negative-mucosa potential (NMP [15]) shows increased peripheral responses with larger amplitudes in patients with NPOD. This is likely to be a consequence of compensation [16] and underlines the intimate connection between both sensory systems.

It is still unknown whether the different levels of trigeminal processing are affected in the same way in patients with PD as in patients with NPOD. There is some indirect evidence that this is not the case. First, patients with PD have significantly superior abilities than patients with NPOD to localize odorous stimuli [11] and they perceive the trigeminal dimensions of odors as well as controls [17]. Second, tERP are not different between patients with PD and controls with a normal sense of smell [18–20]. A differentiation between groups would allow to characterize a specific pattern of OD in PD. However, no study has yet compared patients with PD and patients with NPOD using these electrophysiological measurements. Further, no investigations on the peripheral trigeminal system in PD have been conducted so far. Measuring electrophysiological responses to trigeminal stimulation may help to comprehend how PD affects olfactory and trigeminal processing. Two possible alternative hypotheses may be put forward: (1) the entire trigeminal pathway, including its periphery, may be unimpaired in patients with PD and show similar responses as in controls. In other words, one would expect significantly smaller peripheral and significantly larger central responses in patients with PD compared to patients with NPOD. Alternatively, (2) the peripheral compensation observed in NPOD may be even more pronounced in patients with PD. In other words, one would find significantly larger peripheral and significantly larger central responses in patients with PD compared to patients with NPOD.

To investigate these hypotheses, this study was designed to assess the trigeminal pathway by measuring peripheral NMP and central ERP electrophysiological responses to trigeminal stimuli in (1) patients with PD and compare them to (2) patients with NPOD and to (3) healthy controls.

Methods

This study was conducted at the Smell and Taste Clinic of the Department of Otolaryngology of the Technical University of Dresden (TU Dresden). All aspects of the study were performed in accordance with the Declaration of Helsinki on biomedical research involving human subjects. The study protocol was approved by the TU Dresden Ethics Committee (EK 268072017). After a detailed explanation of the study, all participants provided written informed consent prior to their inclusion in the study. The total testing last 3 h including breaks.

Participants

A total of 69 participants were tested. Twenty-one were PD patients and were recruited from the Department of Neurology at the TU Dresden and the local PD association. All participants went through a complete neurological exam and had received the diagnosis of PD according to United Kingdom PD Society Brain Bank diagnostic criteria [21]. All Parkinson patients were on stable anti-Parkinsonian medication. We recorded disease duration, age of onset, Unified PD Rating Scale (UPDRS) motor score, Hoehn and Yahr stage, medication, and we calculated the levodopa equivalent daily dose (LEDD) [22]. Patients with unclear diagnosis or symptoms compatible with an atypical Parkinsonian syndrome were excluded. Patients with nasal pathology that might have caused concurrent OD non-related to the disease (such as sinonasal pathologies, head trauma, or viral infections) were excluded. Furthermore, 23 patients with NPOD were recruited from the Smell and Taste Clinic. They were examined and diagnosed for post-infectious olfactory loss by an ENT specialist and they had an olfactory score indicative of hyposmia or anosmia. The mean duration of OD was 9.9 months. Patients with idiopathic olfactory loss were specifically excluded considering their possibly elevated risk of developing PD [23]. Twenty-five healthy control participants, in good general health with a normal sense of smell,

were enrolled from the community. They were matched in terms of sex and age to patients with PD (Table 1).

To avoid any effect of cognition or depression, cognitive function was assessed using the Montreal Cognitive Assessment (MoCA) [24] and possible depression was addressed with the Beck Depression Inventory (BDI) questionnaire [25].

Electrophysiological measurements

NMP recordings, as previously described [15, 16, 26], were obtained using a tubular electrode, polytetrafluoroethylene tubing filled with 1% Ringer agar containing a silver chloride wire [27]. A new electrode was prepared for each participant. The electrode was placed onto the nasal septum, site of high trigeminal sensitivity [28], under endoscopic control in the most easily accessible nostril. The electrode was fixed to an adjustable clip mounted on a frame similar to lensless glasses. To validate the position of the electrode, one test stimulus of CO_2 was delivered. If no NMP was recorded, the electrode was replaced in another position, up to five times. In case of no signal, the participant was excluded [15].

Simultaneously to the NMP recordings, tERPs were obtained from position Fz, Cz and Pz (according to the International 10/20 System). For reference, electrodes were placed on both earlobes. An electrode at position Fp2 was used to track eye blinks. Recordings were made with an EEG amplifier (SIR, Röttenbach, Germany). The sampling frequency was 125 Hz, and the measurement period of 8.2 s including a 0.5-s pre-trigger period; time constant was 5 s with a low pass of 15 Hz.

During recording, participants were comfortably seated in an air-conditioned room. White noise was used to mask the noise from the switching clicks of the stimulator. Participants were instructed to perform a tracking task on a video monitor to keep them in a wake and vigilant state during the recording [29]. Participants were taught to use a specific breathing technique (velopharyngeal closure [30]) to avoid respiratory flow inside the nasal cavity.

Stimuli were presented using a computer-controlled olfactometer (OM6b, Burghart, Wedel, Germany) that allows for the presentation of odorants in a constant odorless air flow of 7 L/min, humidified air of controlled temperature (36 °C, relative humidity 80%) [15]. The stimuli were presented by means of a Teflon tube (8 cm length, 4/2 mm outer/inner diameter) inserted into the same nostril of the NMP recording electrode. CO_2 was selected as a selective trigeminal stimulus which does not produce olfactory co-activation [31]. Each participant received 25 stimulations of CO_2 (concentration 50% v/v; Air Liquide, Düsseldorf, Germany), embedded in the air flow. The number of stimulations was chosen to avoid the effect of fatigue as well as to obtain enough epochs to analyze [32]. The duration of each stimulus was 500 ms with an inter-stimulus interval (ISI) of 30 (±3) s to avoid habituation.

Psychophysical tests

Olfactory function was assessed using the "Sniffin Sticks" test (Burghart, Wedel, Germany), details are described elsewhere [33]. It includes three individual subtests: phenyl ethyl alcohol odor threshold, odor discrimination, and odor identification. As it is standard procedure, we obtained a

Table 1 Characteristics of study population and main results

Variable	Controls ($n=25$)	PD patients ($n=21$)	NPOD patients ($n=23$)
Sex (F/M)	16;9	11;10	18;5
Age	63.0 ± 7.3	66.33 ± 5.5	62.0 ± 7.8
Female	62.5 ± 6.9	65.4 ± 4.8	62.6 ± 7.8
Male	63.7 ± 8.4	67.4 ± 4.8	59.6 ± 7.9
Age at onset (years)	NA	59.9 ± 6.7	NA
Disease duration (years)	NA	6.39 ± 4.6	NA
UPDRS motor score	NA	24.7 ± 12.8	NA
Hoehn and Yahr stage	NA	2.4 ± 0.7 (1–3)	NA
LEDD (mg)	NA	709.7 ± 326.3 (0–1500)	NA
MoCA test	27.1 ± 5.4	26.4 ± 2.7	26.5 ± 2.3
BDI	1.42 ± 1.6	2.67 ± 3.0	1.8 ± 2.2
TDI score	34.5 ± 3.1	17.8 ± 6.7	20.4 ± 4.3

Data are shown as means and standard deviation

LEDD levodopa equivalent daily dose, *MoCA* Montreal Cognitive Assessment, *UPDRS* Unified Parkinson Disease Rating Scale, *BDI* Beck Depression Inventory, *TDI* summation of the three olfactory subtests; threshold, discrimination and identification

global olfactory score by adding the results of the three subtests (TDI score) for which normative values are available to allow for the diagnosis of anosmia (below 16), hyposmia (between 16 and 30.3) and normosmia (above 30.3) [33].

To further assess any possible correlation between trigeminal sensitivity and pain threshold, electrical pain threshold was measured (model DS7a; Digitimer Ltd., Welwyn Garden City, UK). Electrical stimuli were presented through a stimulating bar electrode placed on the forearm of the participant. The stimulation started at 0.5 mA with a stimulus duration of 500 ms. Every 20 s, the intensity was gradually increased up to a maximum of 10 mA. Participants were asked to rate the intensity of the stimulus after each stimulation from 0 (no irritation) to 10 (very irritating) and to stop when the stimulus would be irritating for them. The mean mA value of two trials was used as pain threshold.

Participants were asked to rate the intensity and the pain perceived of the CO_2 presented during the electrophysiological recordings twice, after the first test stimulation and after 25 stimulations. They rated the stimulus on Likert scales graded from 0 to 10, 0 being "not perceived" to 10 "very intense" and 0 being "not painful" to 10 "very painful", respectively.

Statistical analysis

Pre-processing of electrophysiological data was carried out using Letswave 5 software in Matlab (R2017). First, recordings that might have been contaminated by movements, blinks or other artifacts were excluded from further analysis. After artifact rejection on the data, some participants had to be excluded from further analysis because of insufficient number of epochs; therefore, NMP analysis included 18 PD patients, 14 NPOD patients and 20 control participants, and ERP analysis included 15 PD patients, 21 NPOD patients and 23 controls. Then all remaining epochs were baseline corrected and filtered (low-pass filter, 15 Hz). For the NMP signal, epochs were averaged, peak amplitudes, latency (P1, N1) and peak-to-peak amplitudes (P1N1) were measured. For the ERP signal from electrodes Fz, Cz and Pz, peak amplitudes, latencies (P1, N1, P2) and peak-to-peak amplitudes (P1N1 and N1P2) were measured.

There were no dropouts; therefore, all participants were included in the analysis and no measured variable was discarded. Statistical analyses were carried out using SPSS 23.0 (SPSS Inc., IL, USA). For NMP measurements, separate univariate ANOVA analyses were computed to compare the amplitude of the negativity, the latency of the negativity and peak-to-peak amplitude (positivity/baseline to the negativity) between groups, with post hoc group comparisons (Bonferroni corrected unless otherwise stated).

For ERP analysis, separate multivariate ANOVAs were computed to compare effects between groups. Specifically, the dependent variables were (1) ERP peak-to-peak amplitude P1N1 and N1P2 with group (three levels: PD, NPOD, control) as between-subject factor and position (three levels: Fz, Cz, Pz), and measure (two levels: P1N1, N1P2) as within-subject variable; (2) ERP latency and amplitude using group (three levels) as between-subject factors and position (three levels: Fz, Cz Pz) and latencies or amplitude (three levels: P1, N1, P2) as within-subject variable. Separate univariate ANOVAs were computed for amplitudes and latencies for each ERP peak (P1, N1, P2).

For behavioral data, separate univariate ANOVAs were computed to compare the TDI, pain threshold, CO_2 intensity ratings, CO_2 pain ratings, BDI and MoCA, with post hoc group comparisons. We computed Pearson correlation between trigeminal measurements (NMP negativity, ERP amplitudes), and cognitive function (MoCA), and motor severity scores (UPDRS, Hoehn and Yahr stage, disease duration, LEED), amongst the PD group.

Further, a predictive discriminant analysis was computed to determine the probability of group membership based on predictor variable. This analysis looks for a linear combination of variables which best describe the major differences between groups and classify the subjects into different groups. Therefore, this analysis points to which variables amongst those we measured would help the best to differentiate the three groups of participants and how accurately the discriminant function can predict group membership. To do so, group was used as the dependent variable and all the measured variables (NMP amplitude and latency, EEG amplitudes and latencies, olfactory threshold, identification and discrimination, pain threshold, CO_2 intensity ratings and CO_2 pain ratings) were included in the analysis as potential predictors.

For all analyses, the level of significance was set at $p < 0.05$.

Results

Negative mucosa potential

With regard to peak latency, a significant effect of group was observed [$F(2,49) = 7.08$; $p = 0.002$, $\eta_p^2 = 0.224$]; post hoc comparisons revealed a significantly prolonged latency in patients with NPOD compared to controls ($p = 0.005$) and to patients with PD ($p = 0.005$) but no differences between patients with PD and controls. With regard to peak amplitudes, again an effect of group was found [$F(2,49) = 4.87$; $p = 0.012$, $\eta_p^2 = 0.224$]; post hoc comparisons revealed a significantly larger amplitude in patients with NPOD compared to controls ($p = 0.01$). There were no differences between patients with PD and patients with NPOD patients and between patients with PD and controls (Fig. 1).

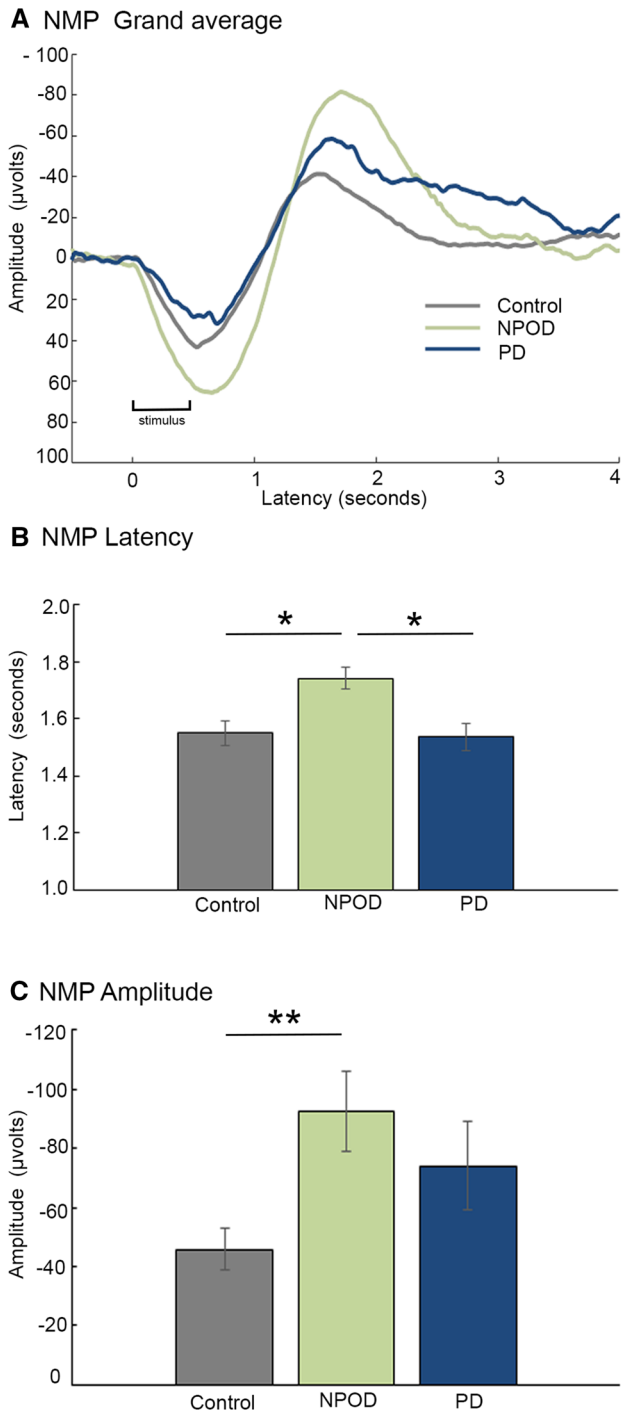

Fig. 1 Peripheral negative mucosa potential response. **a** Grand means of the peripheral negative mucosa potential (NMP) in response to trigeminal stimulus in patients with PD (PD), patients with non-parkinsonian olfactory dysfunction (NPOD) and healthy controls. **b** Latency of the response for the three groups. **c** Amplitude of the response for the three groups. Data are presented as means and standard deviation of the mean

Event-related potentials

With regard to peak-to-peak amplitudes, multivariate ANOVA revealed a significant effect of *measure* [$F(1, 47) = 122.63$; $p < 0.001$, $\eta_p^2 = 0.584$], position [$F(2, 47) = 61.10$; $p < 0.001$, $\eta_p^2 = 0.722$] and an interaction between measure and position [$F(2, 47) = 25.38$; $p < 0.001$, $\eta_p^2 = 0.519$]. To disentangle these effects, separate multivariate ANOVA was carried out for peak-to-peak amplitudes P1N1 and N1P2.

A significant effect of group was found for P1N1 [$F(2, 48) = 4.23$; $p = 0.02$, $\eta_p^2 = 0.150$], but no effect of position [$F(2, 48) = 1.27$; $p = 0.28$, $\eta_p^2 = 0.052$] and no interaction between position and group [$F(2, 48) = 0.73$; $p = 0.57$, $\eta_p^2 = 0.030$] were found. Post hoc group comparisons detected significantly larger amplitudes in patients with PD compared to patients with NPOD ($p = 0.026$), no significant difference but a trend was found between patients with PD and controls ($p = 0.059$) with the former having larger amplitudes. There were no differences between patients with NPOD and controls either.

No effect of group [$F(2, 48) = 0.63$; $p = 0.94$, $\eta_p^2 = 0.003$], position nor any interaction was found for N1P2.

Moreover, there was no effect on amplitudes or latencies of the peaks P1, N1, and P2 (all $p > 0.05$) (Fig. 2).

Psychophysical tests

One patient with PD exhibited olfactory score indicating normosmia, 13 patients exhibited hyposmia and 7 functional anosmia. In patients with NPOD, the corresponding numbers were 0, 21 and 2. All controls had normal olfactory function. Comparison of olfactory function (TDI), revealed a significant effect of group [$F(2,64) = 75.8$; $p < 0.001$, $\eta_p^2 = 0.703$]. Post hoc comparison showed that the controls performed significantly better than both patients with PD and patients with NPOD (both $p < 0.001$).

There was no significant difference between groups for depression [BDI: $F(2, 63) = 1.671$; $p = 0.196$] or cognition [MoCA: $F(2, 64) = 0.191$; $p = 0.827$]. Similarly, no group difference was found for pain threshold [$F(2,61) = 0.46$; $p = 0.64$], CO_2 intensity [$F(2,64) = 0.17$; $p = 0.85$] and CO_2 pain ratings [$F(2,62) = 0.12$; $p = 0.89$] (Fig. 3).

There were no correlations between the trigeminal measurements and cognitive function; MoCA and NMP latency ($r = 0.058$, $p = 0.688$), NMP amplitude ($r = 0.081$, $p = 0.574$), ERP N1 amplitude in Cz ($r = -0.126$, $p = 0.362$) and P2 amplitudes in Cz ($r = 0.082$, $p = 0.553$).

No correlations were found between trigeminal measurements and motor symptom severity scores either.

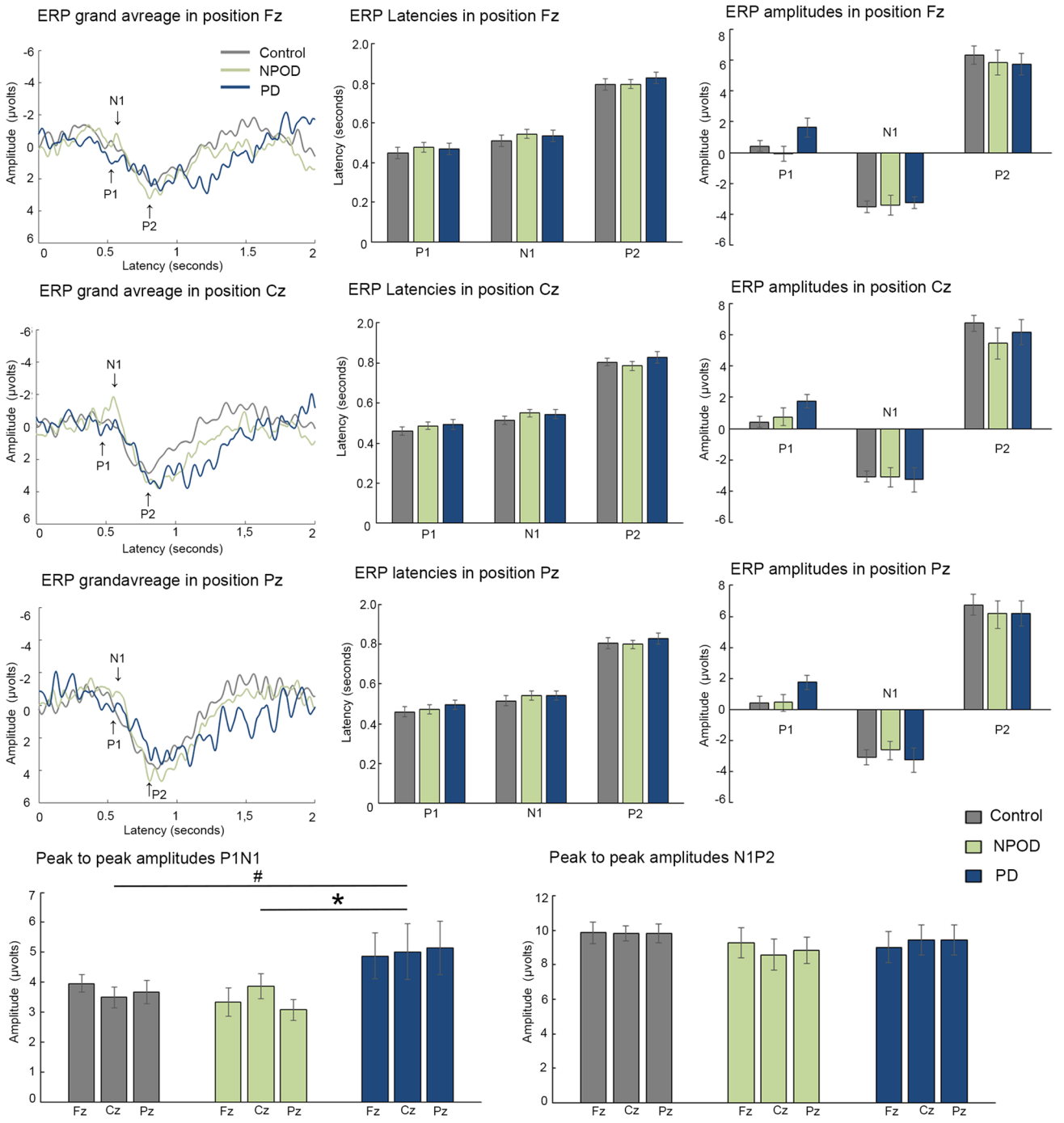

Fig. 2 Central event-related potential response. Grand means of trigeminal event-related potential (tERP) in position Fz, Cz and Pz for patients with PD (PD), patients with non-parkinsonian olfactory dysfunction (NPOD) and healthy controls (C). Amplitudes and latencies are represented for the main peaks P1, N1, and P2 and peak-to-peak amplitudes are represented for P1N1 and N1P2. Data are presented as means and standard deviation of the mean

Discriminant analysis

The discriminant model obtained identified three significant predictor variables, namely NMP latency, olfactory threshold, and olfactory discrimination score. Group predictions were statistically significant in their accuracy and could correctly identify group membership for 80.3% of the participants, with 76.6% patients with PD, 83.3% of patients with NPOD and 80.8% of the control group being correctly classified. The parameters of the two discriminant functions

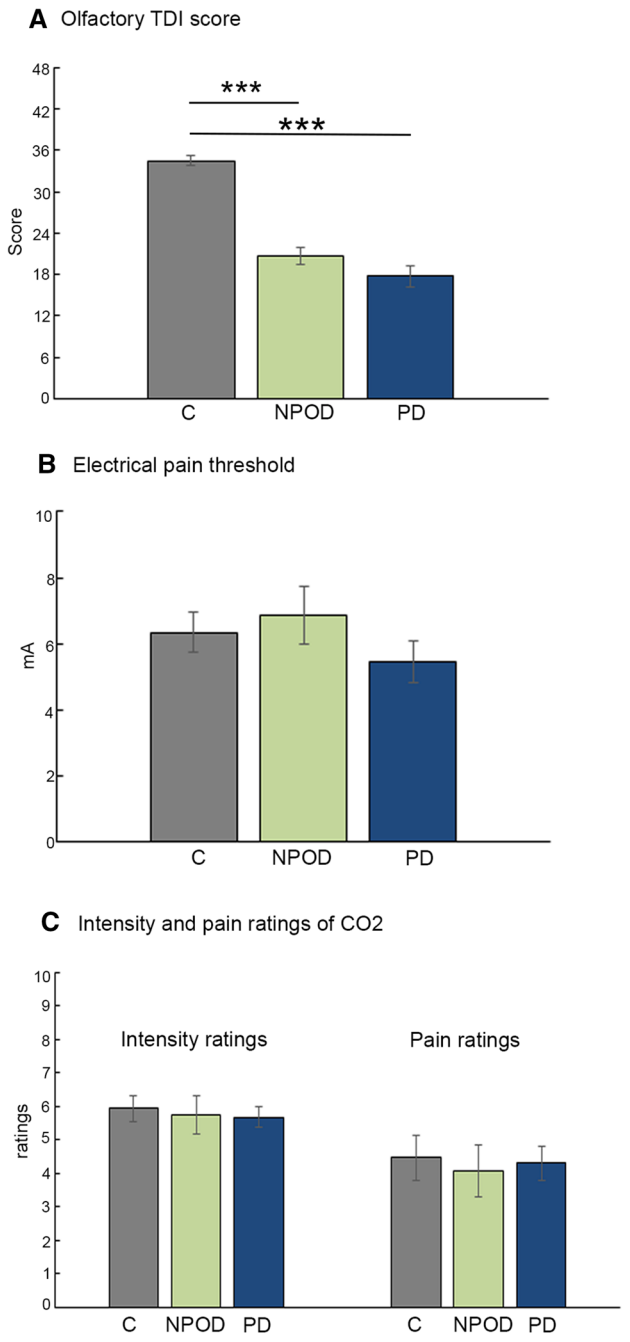

Fig. 3 Psychophysical assessments. **a** Mean of the olfactory score TDI (summation of threshold, discrimination, and dentification) for patients with PD (PD), patients with non-parkinsonian olfactory dysfunction (NPOD) and healthy controls (C). **b** Mean of the electrical pain threshold measure at the forearm for the three groups. **c** Ratings of the intensity and the pain perceived of the CO_2 stimulus presented during the EEG recordings session for the three groups

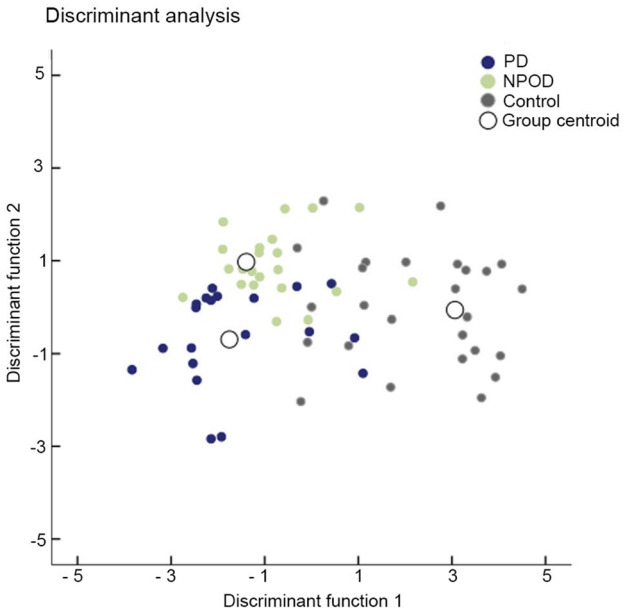

Fig. 4 Discriminant analysis. Distribution of the three groups of participants (PD, NPOD, C) based on the functions of the predictive discriminant analysis. Three significant predictors variables, peripheral negative-mucosa potential latency, olfactory threshold and olfactory discrimination tasks, were identified and included in the discriminant functions. Discriminant function 1: −6.207 + 0.528 (NMP latency) + 0.472 (threshold) + 0.342 (discrimination) and discriminant function 2: −9.896 + 4.698 (NMP latency) − 0.239 (threshold) + 0.342 (discrimination). The discriminant model obtained based on these variables could discriminate and predict group membership correctly for 80.3% of the participants, with 76.6% patients with PD, 83.3% of patients with NPOD and 80.8% of the control group

are canonical discriminant function 1: $D_1 = -6.207 + 0.528$ (NMP latency) + 0.472 (threshold) + 0.342 (discrimination), eigenvalue = 5.38; canonical correlation = 0.92; Wilks' $\lambda = 0.105$; $p < 0.001$. Canonical discriminant function 2; $D_2 = -9.896 + 4.698$ (NMP latency) − 0.239 (threshold) + 0.342 (discrimination), eigenvalue = 0.493; canonical correlation = 0.575; Wilks' $\lambda = 0.670$; $p < 0.002$) (Fig. 4).

Discussion

In this study, we described the result of the evaluation of the trigeminal pathway by recording electrophysiological responsiveness to a trigeminal stimulus in patients with PD compared to patients with NPOD and controls. We showed a specific pattern of trigeminal activity in patients with PD which is distinct from one of patients with NPOD. As olfactory loss is an early feature of PD, these results are promising to help to differentiate PD-related olfactory loss in early stages of the disease and, therefore, may contribute in the future to an early diagnosis of the disease.

On peripheral levels, we observed prolonged NMP latencies in patients with NPOD as opposed to both patients with PD and controls. Additionally, larger NMP amplitudes were detected in patients with NPOD when compared to controls. No differences were found between patients with PD and

controls. The findings on patients with NPOD correspond to a previous study on patients with acquired post-infectious and post-traumatic OD which reported larger NMP amplitudes in patients compared to controls [16]. Our result demonstrates a specific pattern of trigeminal response in PD-related OD and suggests that the peripheral trigeminal system is unimpaired in PD, in contrast to patients with NPOD and in line with our hypothesis 1. As previously proposed, larger NMP amplitudes in patients with NPOD may be due to missing olfactory inhibition of the peripheral trigeminal system [16]. However, this mechanism appears to be different in patients with PD-related OD. Hence, different etiologies of OD seem to affect the peripheral trigeminal system differently. In the present study, patients with NPOD suffered from post-infectious OD consequent to upper respiratory tract infection mainly caused by viruses [34]. These viruses also lead to significant peripheral damage of the olfactory epithelium [35, 36] and the consequent inflammatory reaction leads to epithelial changes and as a consequence to olfactory loss [37]. Conversely, in patients with PD, OD is rather related to central nervous impairment and no peripheral differences were reported yet. In fact, no histochemical differences of the olfactory epithelium were observable [38]. In summary, functional differences between NPOD and PD-related OD are observable at the level of the respiratory mucosa. Future studies should investigate to what extent this difference has a histological underpinning.

On a central level, patients with NPOD exhibited a smaller P1N1 peak amplitude than patients with PD. The P1N1 peak is an early-ERP component thought to reflect the exogenous cortical activity related to sensory detection and linked, amongst other, to stimulus concentration and utilization time at the receptor level rather than the cognitive processing [39, 40]. No group difference was observed for late-ERP components. These findings could, therefore, again be explained by a difference in peripheral trigeminal sensitivity in patients with PD compared to patients with NPOD.

Previous studies on trigeminal ERPs in patients with PD did not report any differences when compared to controls [18–20]. In contrast to this, we observed a trend to larger N1P1 peaks in patients with PD compared to controls. Although this difference was not significant, one may question the conclusion that that the whole trigeminal pathway is unchanged in patients with PD. This is particularly interesting in the context of patients with PD being hypersensitive to painful stimuli [41]. Actually, stimulation of the trigeminal system activates chemosensory somatosensory fibers (Aδ and C fibers), leading to the activation of central trigeminal processing areas as well as pain-related pathways. The CO_2 stimulus we used was mildly painful, and patients with PD might be hypersensitive to it as well. In fact, pain is a common early feature of PD, and patients experience more pain than age-matched controls [42]. However, we did not observe any group differences in pain thresholds, possibly due to the fact that patients were all on anti-Parkinsonian medication known to affect pain sensitivity [41]. Future studies with larger samples may have a closer look at the relation between pain threshold and trigeminal sensitivity, preferably in non-medicated patients. One potential way could be to look at correlation between somatosensory electrical and mechanical pain threshold of the trigeminal nerve and chemosensory stimulation of intranasal branches of the trigeminal nerve [43].

Typically, patients with OD are known to show reduced central trigeminal ERP responses when compared to controls [10, 13, 14, 16]. However, we were unable to detect this difference; small sample size may have played a role, but it is also possible that patients with NPOD did not suffer from a pronounced olfactory loss, as most patients exhibited hyposmia and only few exhibited functional anosmia [10].

Trigeminal responsiveness in PD exhibits a specific pattern. This suggests that interactions between the olfactory and the trigeminal systems are affected differently between different etiologies of OD. In patients with PD, OD is thought to be related to central nervous impairment, with the accumulation of Lewy bodies typically starting in olfactory bulb [44], and central cholinergic denervation [45]. There is evidence of functional microstructural changes in olfactory structures in the early stages of PD as opposed to controls [46]. Moreover, central ERP responses to olfactory and trigeminal stimuli display a continuous chaotic brain pattern in PD, as opposed to the ordered state observed in healthy participants [20]. Further, the localization of brain sources provided evidence for differences in mainly late-EEG components suggesting a decline of central brain networks as a causal factor for olfactory loss in PD and indicating a different pattern of olfactory processing in PD compared to patients with NPOD [47]. Interestingly, primary olfactory cortex was shown to be hyperactive in PD despite an impaired olfactory function [48]. These possible compensatory mechanisms that take place in PD were not reported in NPOD. In fact, patients with post-viral olfactory loss show an intact central functional olfactory network despite a reduced connectivity [49]. It is, therefore, conceivable that a deficient olfactory system in PD affects the trigeminal system differently in these patients. Actually, the trigeminal system can be affected by the olfactory system by neuroanatomical connections between both systems at the level of the olfactory epithelium and bulb [50, 51] and on central regions responsible for processing of both trigeminal and olfactory stimulus [6, 52]. Our understanding of the underlying mechanisms would benefit from futures studies investigating central trigeminal connectivity in patients with PD compared to patients with NPOD.

Although our conclusions were drawn using a limited number of participants, we used specific tools to assess the

trigeminal function and differentiate intranasal and central effects that were never used in patients with PD. Even though these experimental methods are not yet applicable to large populations in a clinical context clinical, due to technical and time constraints, we report a specific trigeminal central activation in PD patients. To elucidate the underlying mechanism, techniques such as functional MRI should be used. Our model could correctly predict group membership in 80% of participants based on olfactory testing and on the peripheral trigeminal latency response, as evidence that both olfactory and trigeminal testing could lead to the development of crucial tools to discriminate PD-related olfactory loss. Therefore, the development of more efficient tools to assess precisely and rapidly the trigeminal sensitivity, for instance, the reaction time to respond to trigeminal stimuli is a promising avenue to help the diagnostic of PD.

To conclude, we found a specific pattern of trigeminal activation in patients with PD that allowed to differentiate PD-related olfactory loss from other forms of OD. Futures studies should now characterize the trigeminal profile in the prodromal phase to better define this early stage of the disease and help to establish a biomarker profile including other early symptoms of PD, in a common goal to select suitable candidate for potential neuroprotective essay.

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

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