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Running head: vocal emotion in asymmetric PD

Differential effects of disease duration and dopaminergic replacement therapy on vocal emotion recognition in asymmetric Parkinson's disease

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ABSTRACT

Introduction. Recently, studies have suggested a role of motor symptom asymmetry on impaired emotional recognition abilities in Parkinson's disease with a greater vulnerability in patients with a predominance of left-sided symptoms. However, none of them explored the interaction between motor symptom asymmetry and dopamine replacement therapy in different stages of the disease.

Methodology. We explored the recognition of vocal emotion (i.e., emotional prosody) in 15 newly diagnosed Parkinson's disease patients in the early stages of the disease, 15 patients in the advanced stages of the disease and 15 healthy controls. The early patients were studied in two conditions: ON and OFF dopaminergic replacement therapy and both Parkinson's disease groups (early and advanced) were divided into two subgroups according to the asymmetry of motor symptoms.

Results. The analyses revealed two patterns of results. First, as predicted, we observed a reduction in performance for the recognition of vocal emotions in patients with a predominance of left-sided symptoms as compared to both healthy controls and predominantly right-sided symptom patients. Secondly, in the early stages of the disease, we observed a deleterious effect of dopatherapy on the recognition of vocal emotions for the patients with left-predominant symptoms, and the inverse pattern (i.e., a positive effect of dopatherapy) for the patients with right-predominant symptoms.

Conclusions. Our results bring to knowledge the differential effects of disease duration, dopaminergic replacement therapy and motor symptom asymmetry on vocal emotion recognition in Parkinson's disease.

Key words: Parkinson’s disease; Asymmetry; Dopamine Therapy; Emotion recognition; Phenotypes

Word count: 4017 (all sections); 2751 without methodology

Abbreviations: DRT: dopaminergic replacement therapy; FDR: False Discovery Rate; fMRI, functional magnetic resonance imaging; HC, healthy control; H&Y, Hoehn and Yahr scale; LEDD, levodopa-equivalent daily dose; LPD, patients with Parkinson’s disease exhibiting predominantly left-sided motor symptoms; MADRS, Montgomery-Åsberg Depression Rating Scale; MCST, Modified Wisconsin Card Sorting Test; MDRS, Mattis Dementia Rating Scale; PD, Parkinson’s disease; RPD, patients with Parkinson’s disease exhibiting predominantly right-sided motor symptoms; S&E, Schwab and England scale; STAI, State-Trait Anxiety Inventory; UPDRS, Unified Parkinson’s Disease Rating Scale.

1. Introduction

Parkinson's disease (PD) impacts emotional processing, likely due to the involvement of the cortico-subcortical-cerebellar limbic network [1-3]. Increasing evidence suggest that motor symptom asymmetry may influence the recognition of vocal emotions (i.e., emotional prosody) [4-6]. However, how this asymmetry, combined with dopaminergic treatment, impacts emotion recognition over time remains unclear. This raises important questions about the underlying mechanisms and the differential effects on patients.

Recent research on PD has emphasized the role of motor symptom asymmetry, particularly at different stages of the disease, on emotion prosody recognition [4-11]. The majority of behavioral studies revealed overall reduced performance in emotion recognition abilities in PD patients exhibiting predominantly left-sided motor symptoms (LPD) [4-11] as compared to PD patients exhibiting predominantly right-sided motor symptoms (RPD), whether in the context of emotional facial and/or emotional prosody evaluation. Moreover, These effects have been corroborated by observations at the psycho-physiological level in PD (e.g., electro-encephalography studies) [8, 12], but also by results from neuroimaging studies on healthy participants. These results have been interpreted in the context of a right hemispheric specialization for some essential emotion processing mechanisms, and notably the involvement of the right part of the limbic cortico-subcortico-cerebellar loop [1, 13, 14]. However, findings in this area remain inconsistent. While the majority of studies report deficits in emotional recognition among LPD patients, some studies find no differences between LPD and RPD groups [15, 16], and one study even found poorer performance in RPD patients [17]. This inconsistency underscores the need for further research into the role of motor asymmetry in emotional processing, particularly because these studies employed cross-sectional designs, lacked longitudinal evaluation, and involved patients with varying stages of PD progression.

While motor asymmetry appears to play a critical role in emotion recognition, another factor that could modulate these effects is dopaminergic replacement therapy (DRT), which is commonly used in PD management. Several studies have indicated that DRT can negatively impact emotional processing [18-21], suggesting that both motor symptom asymmetry and treatment may interact in shaping emotional recognition abilities. The majority of these studies focused on emotional facial recognition abilities, except for one, which demonstrated a deficit in emotion prosody processing, driven by difficulties in recognizing anger, fear and disgust for early PD patients under DRT, compared to both advanced PD patients in ON DRT and HC [19]. The authors speculated a probable dopaminergic overstimulation/overdoses effect on the cerebro-subcortico-cerebellar limbic loop. In other words, regions of the dopaminergic circuit less affected by the pathology would be overstimulated or would suffer from an overdose of dopamine administered exogenously [22]. Despite these findings, no studies have thoroughly examined how motor asymmetry and dopaminergic treatment interact over time to influence emotional recognition. Understanding this interaction is crucial for improving therapeutic strategies in PD and for shedding light on the neural mechanisms underpinning emotional processing in the disease. In the domain of cognitive functions, a study demonstrated a distinct effect of DRT based on motor symptom asymmetry. Patients with predominantly left-sided symptoms responded positively to DRT, showing improvements in both cognitive performances (specifically attention and verbal episodic memory) and sensorimotor functions. Conversely, patients with right-sided symptoms responded poorly to DRT, with a decline in verbal episodic memory and stagnation in attention, suggesting a dopaminergic overdose effect in the less affected hemisphere, which plays a key role in these cognitive processes [23]. Clarifying the interplay between motor symptom asymmetry and dopaminergic treatment on emotional functions could therefore have important implications for patient care. A more tailored approach to treatment, considering individual motor symptom profiles, may enhance not only motor but also cognitive and emotional well-being in PD patients.

In this context, the present study aimed to examine emotional prosody recognition in 15 early-stage PD patients under both OFF and ON DRT conditions, compared to 15 advanced PD patients, while accounting for motor symptom asymmetry in both groups. The performance of these patients was also compared to that of 15 healthy controls (HC).

Building on the findings of Péron, Grandjean [15]'s results, as well as previous research on the effects of motor asymmetry [1-7] and DRT [18] on emotion recognition, we hypothesize that LPD patients will exhibit poorer emotion recognition abilities than both RPD patients and HC, due to the right hemisphere's dominance in processing emotions. However, this hypothesis is tempered by the interaction between DRT and disease progression. Specifically, we suggest that early-stage RPD patients may experience a dopaminergic overdose effect, impacting the right hemisphere during ON-DRT, which could impair emotion recognition. From these considerations, we formulated several operational hypotheses. First, early-stage LPD patients are expected to show reduced performance in the OFF-DRT condition due to greater right-hemisphere deterioration. In contrast, early-stage RPD patients are predicted to exhibit deficits in emotional prosody recognition primarily in the ON-DRT condition, reflecting an overdose effect of DRT on the less affected hemisphere. Second, as the disease progresses, we hypothesize that advanced-stage LPD patients will display more severe impairments in emotional prosody recognition compared to both advanced-stage RPD patients and early-stage LPD patients in the ON-DRT condition. In contrast, advanced-stage RPD patients are expected to perform better than early-stage RPD patients in the ON-DRT condition, as the degradation of dopaminergic pathways at this stage may be sufficiently compensated by DRT, avoiding the overdose effect observed in earlier stages.

2. Methods

2.1 Participants

The experimental data and paradigm were extracted from a previous study [19]. One group of patients with PD at the early stage of the disease (< 5 years after diagnostic and a score < 2 on the revised Hoehn and Yahr (H&Y) disability scale [24]), one group of patients with an advanced PD being evaluated for eligibility for deep brain stimulation of the subthalamic nucleus and a HC group took part in the study (*n* = 15 in each group). All the patients met the clinical criteria of the United Kingdom PD Society brain bank for idiopathic PD [25]. Disease severity was rated using Unified Parkinson's Disease Rating Scale (UPDRS III; [26]), H&Y [24] and the Schwab and England (S&E) daily living activities scale [27]. The early PD group was examined in two separate conditions: ON and OFF daily DRT (> 12 hours off levodopa preparations and/or dopamine receptor agonists), while for ethical considerations, the advanced group was only seen in the ON daily DRT condition. The Levodopa equivalent dose was calculated on the basis of correspondences adapted from Tomlinson, Stowe [28]. For the OFF-DRT condition, patients were asked to abstain from taking their medication the night before the assessment.

Motor asymmetry index. The patients with early and advanced PD were divided into two subgroups, based on which side of symptom onset: primarily left-affected (both groups of LPD; *n* = 7) versus primarily right-affected (both groups of RPD; *n* = 8). We then calculated an asymmetry index based on the lateralized items (Items 20–26) of Part III of the Unified Parkinson's Disease Rating Scale, by subtracting the item scores related to the left side of the body from the item scores related to the right side of the body, in order to use the patients' current asymmetry status to corroborate our distinction [4-6, 29-32]. The asymmetry score was congruent with the side of motor symptoms onset for all the patients. Non-parametric tests for independent groups revealed a significant difference between the two early patient subgroups on the asymmetry index in both the ON-DRT (*t* = -4.72, *p* < .001) and OFF-DRT (*t* = -3.25, *p* = .003) conditions.

The HC group consisted of healthy individuals who had no history of neurological disease, head injury or alcohol abuse, and no signs of dementia, as attested by their scores on the Mini-Mental State Examination (MMSE) [33].

Based on non-parametric Kruskall-Wallis analysis, Mann-Whitney U tests (for continuous variables) and Chi-squared tests [χ2 test] (for categorical variables), all groups were of comparable age (early-RPD: 63.13 ± 4.27, early-LPD: 56.86 ± 8.90, adv-RPD: 55.13 ± 6.01, adv-LPD: 64.43 ± 8.90, HC: 55.93 ± 7.80; [*H* = 9.23, *p* = .056]), handedness (all right-handed), gender (early RPD: 75.00% of men, early LPD: 57.14% of men, advanced RPD: 75.00% of men, advanced LPD: 57.14% of men, HC = 66.66% of men; [*p* = .899]) and education level in years (early RPD: 11.38 ± 4.75, early LPD: 14.00 ± 3.96, advanced RPD: 14.13 ± 3.23, advanced LPD: 13.57 ± 4.20, HC: 13.87 ± 2.33; [*H* = 2.96, *p* = .56]). Moreover, within both PD groups (early and advanced), no significant differences for disease duration were observed between the LPD and RPD (early RPD: 2.88 ± 0.99 compared to early LPD: 2.71 ± 1.55 [*Z* = -0.59, *p* = .557]; advanced RPD: 11.13 ± 3.98 compared to advanced LPD: 11.14 ± 2.91[*Z* = 0.00, *p* = 1]).

	Early				**Advanced**			
	RPD		**LPD**		**RPD**		**LPD**	
	ON **Mean ± SD**	**OFF** **Mean ± SD**	**ON** **Mean ± SD**	**OFF** **Mean ± SD**	**ON** **Mean ± SD**	**OFF** **Mean ± SD**	**ON** **Mean ± SD**	**OFF** **Mean ± SD**
UPDRS III	-	-	-	-	8.38 ± 4.65[#]	37.83 ± 12.84	8.14 ± 5.81[#]	36.00 ± 7.35

S&E (%)	94.29 ± 5.35	90.00 ± 5.77	92.86 ± 7.56	87.14 ± 9.51	91.67 ± 7.53#	60.00 ± 29.66	78.57 ± 6.90#	91.43 ± 9.00
H &Y	0.57 ± 0.79#	1.36 ± 0.75	0.71 ± 0.76#	1.36 ± 0.56	1.50 ± 0.9#	2.57 ± 1.27	1.21 ± 0.64#	2.29 ± 0.64
DRT (mg/ml)	431.25 ± 138.02	-	444.29 ± 316.54	-	1006.43 ± 571.47	-	943.00 ± 406.23	-

Table 1. Motor scores and DRT for PD subgroups (early RPD ON, early LPD ON, early RPD OFF; early LPD OFF; advanced RPD ON; advanced LPD ON; advanced RPD OFF; advanced LPD OFF).

Legend: UPDRS: Unified Parkinson's Disease Rating Scale; SD: standard deviation; S&E: Schwab & England scale; H&Y: Hoehn & Yahr scale; DRT: dopa replacement therapy

Significant after FDR correction compared with OFF-DRT condition

2.2 Neuropsychological and psychiatric screening

As described in previous studies [19], a short neuropsychological and psychiatric battery was administered by a board-certified neuropsychologist (JAP) to the participants prior to the vocal emotion recognition sessions which were also administrated by JAP. This battery included the Mattis Dementia Rating Scale [MDRS; 34] and a series of tests assessing frontal executive functions, including Nelson's modified version of the Wisconsin Card Sorting Test [MCST; 35], the Trail Making Test [TMT; 36], the Categorical and Literal Fluency test [37], the Action (Verb) Fluency task [38], and the Stroop test [39]. Depression was assessed using the Montgomery-Asberg Depression Rating Scale [MADRS; 40]. The MADRS was chosen because of the predominance of cognitive items over somatic ones, thus limiting interference with Parkinson's symptoms. Finally, the State-Trait Anxiety Inventory [STAI; 41] was used to assess anxiety. Of note, the early PD patients only underwent the MDRS and STAI-A state in the OFF-DRT condition.

2.3 Vocal emotion recognition task and procedure

All participants were exposed to a set of vocal stimuli [4, 6, 42, 43], consisting of short pseudowords of meaningless speech composing pseudowords pseudoword # 1: [fɪ gœt laiʃ ʃɑ̃ kil gɔs tɛʁ], pseudoword # 2: [h'ɛt s' ɑ̃dik pr'ɒɑ̃g ŋj'y v'ɛntzi], obtained by concatenating different syllables found in Indo-European languages. Four categories of emotional prosody (anger, fear, happiness, and sadness), together with a neutral condition, were used in the present study. We selected utterances produced by 12 different actors (6 women and 6 men), each expressed with five different prosodies (anger, fear, happiness, neutral, and sadness). The set of vocal stimuli (pseudowords) comprised 60 stimuli (12 actors × 5 emotion conditions) and is extensively described elsewhere [42]. All stimuli were presented bilaterally via stereo headphones with an Authorware program designed especially for this study. Participants were required to listen to each stimulus, after which they were asked to rate its emotional content on a set of visual analogue scales ranging from “Not at all” to “Very much”, which were simultaneously displayed on the computer screen. More specifically, participants rated each stimulus on six scales: one scale for each featured emotion (anger, fear, happiness, and sadness), one for neutral, and one for the surprise emotion. Participants were told that they could listen again to each stimulus as many as six times, by clicking on a button on the computer interface (click counter). Participants were given two examples to familiarize themselves with the task.

As described elsewhere [19, 42], and to avoid a list effect between the ON and OFF DRT conditions in the early PD patient group, the targets were counterbalanced. In the ON condition, half of the early PD patients were assessed with Version A of the vocal emotion recognition task and half with Version B. In the OFF condition, the former was assessed with Version B and the latter with Version A. The entire protocol was completed in a single 90-min session. The early PD patients underwent a second session in the OFF (or ON) condition. The ON versus OFF DRT sessions were randomized.

2.4 Audiometric screening procedure

Each participant underwent a complete evaluation within the otolaryngology department of Rennes University Hospital, with the completion of a tonal and vocal audiogram, making it possible to determine the degree of hearing loss, as well as speech understanding. To ensure that the participants had normal hearing, a standard audiometric screening procedure (AT-II-B audiometric test) was administrated to measure tonal (measure the degree of hearing loss and to know the location from which this loss comes) and vocal sensitivity (to test the degree of speech understanding), making it possible to determine the degree of hearing loss, as well as speech understanding. None of the patients included in the study wore hearing aids or had a history of tinnitus or a hearing impairment.

2.5 Statistical analyses

We performed inter-group comparisons using non-parametric Kruskall–Wallis and Mann Whitney U tests, and intra-group comparisons using Wilcoxon matched U-tests. Benjamini-Hochberg False Discovery Rate corrections (FDR) were applied for all comparisons. Versions A and B of the emotional prosody recognition task were compared using the $\chi 2$ test. Finally, spearman correlations were performed to quantify the relationships between neuropsychological, sociodemographic, and clinical variables and the emotional prosody recognition variables. To avoid type I errors, we have opted to include in the correlation models only those variables that are significant in the context of inter- and intra-group comparisons.

3. Results

3.1 Motor evaluation (Table 1)

As expected, intragroup analyses revealed significant differences within both subgroups (LPD and RPD) between the ON and OFF-DRT conditions, both in the early and advanced stages of the disease for UPDRS III, S&E and H&Y (except for the S&E scores in the early stage of the disease which weren't significantly different between the OFF and ON-DRT conditions).

Intergroup analyses between LPD and RPD within the early and advanced stages did not reveal significant differences.

3.2 Neuropsychological and psychiatric assessments (Table 2)

Detailed intragroup and intergroup results as function of DRT, disease stage and motor symptom asymmetry are presented in Table 2.

	Early		**Advanced**		**HC**
	RPD ON-DRT **Mean ± *SD***	**LPD ON-DRT** **Mean ± *SD***	**RPD ON-DRT** **Mean ± *SD***	**LPD ON-DRT** **Mean ± *SD***	**Mean ± *SD***
MDRS (/144)	139.25 ± 4.53	139.86 ± 5.52	141.25 ± 2.31	140.43 ± 2.99	141.64 ± 2.17
Stroop Test - Interference	-3.95 ± 14.36	0.23 ± 8.53	7.82 ± 5.53	4.45 ± 8.44	5.13 ± 10.81
TMT A (seconds)	45.75 ± 13.34	38.86 ± 11.94	47.00 ± 19.06	39.00 ± 8.26	43.64 ± 16.53
TMT B (seconds)	127 ± 31.70	78.29 ± 22.77	98.88 ± 44.72	87.71 ± 34.3	99.21 ± 46.34
TMT B-A (seconds)	76.13 ± 26.64	39.43 ± 17.93	51.88 ± 30.06	48.71 ± 33.81	55.6 ± 38.05
Categorical fluency (2')	26.13 ± 5.62	26.43 ± 11.03	35.25 ± 12.03	31.71 ± 13.33	33.27 ± 8.80
Phonemic fluency (2 ')	20.63 ± 6.30	19.14 ± 9.03	23.75 ± 7.69	22.86 ± 6.39	21.20 ± 6.38
Action (Verb) Fluency (1')	13.88 ± 3.48	15.71 ± 6.87	18.25 ± 7.46	14.14 ± 7.65	19.33 ± 6.62
MCST - N of categories (/6)	5.50 ± 1.41	5.71 ± 0.76	5.88 ± 0.35	5.71 ± 0.49	5.93 ± 0.27
MCST - N of errors	5.88 ± 10.11	3.29 ± 4.61	3 ± 3.12	4.71 ± 4.64	2.36 ± 2.17
MCST - N of perseverations	2.88 ± 6.53	1.00 ± 1.53	0.75 ± 1.17	0.86 ± 1.46	0.36 ± 0.63
MADRS	5.33 ± 3.20	6.86 ± 6.44*	11.17 ± 10.28**	4.00 ± 2.45	1.83 ± 2.44
STAI-A State	37.93 ± 4.41**	39.71 ± 7.80**	39.06 ± 14.79	40.14 ± 12.72**	28.50 ± 8.52
STAI-A Trait	35.63 ± 10.03	42.86 ± 13.72	46.75 ± 13.54	38.71 ± 14.99	36.50 ± 9.39

Table 2. Neuropsychological performances and psychiatric symptoms as function of disease duration (early vs. advanced) and subgroups (LPD; RPD; HC) in ON-DRT condition.

Legend: LPD: patients with PD exhibiting predominantly left-sided motor symptoms; RPD: patients with PD exhibiting predominantly right-sided motor symptoms; HC: healthy controls; MDRS: Mattis Dementia Rating Scale; TMT: Trail Making Test; MCST: Modified

Wisconsin Card Sorting Test; ON-DRT: patient with (on) dopaminergic replacement therapy; *SD*: standard deviation; STAI: The Stait-Trait Anxiety Inventory.

Differential effects between conditions are reported

* *p* <. 050 when compared with HC group

** Significant after FDR ($p < .017$) correction when compared with HC group

3.3 Recognition of vocal emotions (Table 3)

3.3.1 Version A vs. B comparisons

No significant difference was found between the percentages of correct responses for Versions A and B, $\chi^2(7) = 8.00$, $p = .200$, in the HC group.

3.3.2 Vocal emotion recognition as a function of motor symptom asymmetry

For early LPD (ON-DRT) vs. early RPD (ON-DRT) vs. HC, analyses revealed a significant difference on the non-target scale Neutral, when the target emotion was anger ($H = 8.08$, $p = .018$); and on the non-target scale Neutral, when the target emotion was neutral ($H = 6.1$, $p = .047$). Two-by-two group comparisons revealed a significant difference between early LPD ON and the HC groups for the scale Neutral, when the target emotion was anger ($z = -2.68$, $p = .007$); and for the Neutral scale, when the target emotion was neutral ($z = -2.32$, $p = .017$).

For early LPD (OFF-DRT) vs. early RPD (OFF-DRT) vs. HC, intergroup analysis revealed a significant difference on the non-target scale Sadness, when the target emotion was neutral ($H = 9.19$, $p = .011$); on the non-target scale Happiness, when the target emotion was neutral ($H = 6.98$, $p = .030$); and on the non-target scale Sadness, when the target emotion was fear ($H = 6.38$, $p = .041$). Two-by-two tests revealed a significant difference between the early RPD OFF and the early LPD OFF groups for two contrasts (z = 2.66, p = .008), for Sadness/neutral; z = 2.37, p = .017, for Sadness/fear).

For advanced LPD (ON-DRT) vs. advanced RPD (ON-DRT) vs. HC, analyses revealed a significant difference on the non-target scale Anger, when the target emotion was neutral (H = 6.11, p = .047); as well as on the non-target Fear, when the target emotion was neutral (H = 7.14, p = .027). Two-by-two tests revealed a significant difference between advanced LPD ON and the advanced RPD ON groups for the scale Anger, when the target emotion was neutral (z = -2.20, p = .021); as well as between advanced LPD ON and HC groups on the non-target Fear, when the target emotion was neutral (z = -2.93, p = .002), suggesting in both cases a greater misattribution effect for the advanced LPD ON group.

All other comparisons were non-significant after FDR correction (*all p's* > .32).

3.3.3 Vocal emotion recognition as a function of stage of disease and motor symptom asymmetry

Early LPD (ON-DRT) vs. advanced LPD (ON-DRT) vs. HC. For LPD intergroup comparisons, analyses revealed a significant difference on the non-target scale Neutral, when the target emotion was anger (H = 8.74, p = .013); on the non-target scale Fear, when the target emotion was neutral (H = 7.75, p = .021); and on the non-target scale Neutral, when the target emotion was neutral (H = 6.5, p = .039) (see Figure 1). Two-by-two tests revealed significant differences between advanced LPD ON and HC, for the scale Neutral, when the target emotion was fear (z = -2.89, p = .004); as well as between early LPD and the advanced LPD groups for the scale Neutral, when the target emotion was neutral (z = -2.04, p = .041).

All other comparisons were non-significant after FDR correction (*all p's* > .27).

3.3.4 Vocal emotion recognition as function of DRT and motor symptom asymmetry

For early LPD, intragroup analysis between ON-DRT versus OFF-DRT conditions revealed a significant difference on the non-target scale Sadness, when the target emotion was fear (z = 2.2, p = .028); where LPD misattributed significantly more of a fear stimulus with Sadness in the ON-DRT condition, compared to the OFF-DRT condition (see Figure 1).

For early RPD, intragroup analysis between ON-DRT versus OFF-DRT conditions revealed a significant difference on the non-target scale Sadness, when the target emotion was fear (z = 2.1, p = .036) (see Figure 1).

All other results were non-significant after FDR correction (*all p's* > .26).

	Early LPD OFF condition					
Emotion	**Anger scale**	**Fear scale**	**Happiness scale**	**Neutral scale**	**Sadness scale**	**Surprise scale**
Anger	48.50 (± 19.05)	7.95 (± 6.33)	0.19 (± 0.11)	13.79 (± 20.21)	1.38 (± 1.66)	8.63 (± 8.08)
Fear	6.62 (± 9.42)	41.38 (± 15.72)	3.68 (± 7.04)	10.07 (± 21.50)	5.33 (± 7.09) @ “”	18.21 (± 9.93)
Happiness	7.74 (± 7.97)	8.20 (± 6.13)	29.13 (± 12.17)	13.50 (± 19.47)	4.77 (± 5.54)	19.69 (± 13.27)
Neutral	0.77 (± 1.04)	1.53 (± 1.88)	1.24 (± 1.64)	50.55 (± 25.12)	0.41 (± 0.79) @	9.09 (± 12.31)
Sadness	2.03 (± 1.33)	4.20 (± 3.47)	0.19 (± 0.16)	26.60 (± 12.63)	36.24 (± 17.92)	2.18 (± 3.41)
	Early RPD OFF condition					
Emotion	**Anger scale**	**Fear scale**	**Happiness scale**	**Neutral scale**	**Sadness scale**	**Surprise scale**
Anger	52.4 (± 15.02)	13.36 (± 11.86)	0.67 (± 1.07)	5.06 (± 3.91)	2.86 (± 2.82)	15.95 (± 14.65)
Fear	18.55 (± 14.40)	38.43 (± 16.36)	3.89 (± 4.27)	3.76 (3.71)	18.41 (± 11.03)	17.32 (± 14.54)
Happiness	12.43 (± 10.14)	12.77 (± 12.52)	27.94 (± 8.88)	3.26 (± 6.11)	10.59 (± 8.25)	24.78 (± 13.39)
Neutral	2.26 (± 4.00)	2.43 (± 2.97)	8.22 (± 5.58) *	38.95 (± 19.20)	6.56 (± 9.09)	15.22 (± 7.87)
Sadness	1.12 (± 3.82)	12.47 (± 9.69)	1.00 (± 1.87)	28.11 (± 13.57)	39.66 (± 18.71)	6.22 (± 6.76)

	Early LPD ON condition					
Emotion	**Anger scale**	**Fear scale**	**Happiness scale**	**Neutral scale**	**Sadness scale**	**Surprise scale**
Anger	54.8 (± 19.43)	4.61 (± 4.53)	0.99 (± 2.08)	15.66 (± 9.89) *	1.61 (± 2.66)	8.67 (± 6.17)
Fear	12.74 (± 14.02)	39.72 (± 17.80)	0.92 (± 1.20)	4.36 (±5.69)	10.75 (± 12.12) #	17.98 (± 11.22)
Happiness	12.60 (± 14.61)	6.57 (± 6.80)	28.92 (± 11.05)	7.87 (± 11.23)	8.24 (± 10.85)	22.92 (± 10.08)
Neutral	1.33 (± 3.02)	0.56 (± 1.03)	2.23 (± 3.62)	59.46 (± 26.44) *	2.08 (± 2.15)	8.60 (± 7.19)
Sadness	2.02 (± 3.14)	7.78 (± 4.18)	0.27 (± 0.20)	27.53 (± 11.20)	37.56 (± 19.94)	5.97 (± 5.78)
	Early RPD ON condition					
Emotion	**Anger scale**	**Fear scale**	**Happiness scale**	**Neutral scale**	**Sadness scale**	**Surprise scale**
Anger	52.63 (± 19.42)	11.48 (± 15.04)	0.58 (± 1.13)	7.82 (± 5.20)	2.48 (± 6.04)	12.21 (± 17.18)
Fear	12.10 (± 8.85)	32.81 (± 19.05)	4.06 (± 6.56)	4.21 (± 4.64)	11.94 (± 8.63)#	18.27 (± 18.48)
Happiness	9.98 (± 10.28)	7.25 (± 7.61)	30.92 (± 10.50)	4.02 (± 3.59)	8.29 (± 9.72)	19.69 (± 12.93)
Neutral	0.56 (± 1.11)	0.93 (± 1.23)	4.86 (± 6.24)	38.38 (± 15.36)	2.03 (± 3.12)	13.36 (± 17.25)
Sadness	2.23 (± 4.04)	11.05 (± 13.17)	0.56 (± 1.02)	21.84 (± 11.31)	37.04 (± 21.55)	6.32 (± 10.52)
	Advanced LPD ON condition					
Emotion	**Anger scale**	**Fear scale**	**Happiness scale**	**Neutral scale**	**Sadness scale**	**Surprise scale**
Anger	40.10 (± 15.46)	3.39 (± 3.14)	0.27 (± 0.20)	7.48 (± 3.50)	3.53 (± 3.87)	7.35 (± 5.65)
Fear	5.46 (± 5.95)	24.89 (± 16.12)	1.68 (± 2.16)	11.37 (± 11.28) *	11.37 (± 10.48)	13.72 (± 5.51)
Happiness	4.43 (± 4.25)	5.06 (± 3.57)	26.27 (± 10.14)	7.46 (± 10.87)	3.45 (± 2.80)	16.44 (± 9.31)
Neutral	1.83 (± 2.84) *@	0.39 (± 0.34)	2.34 (± 2.34)	32.66 (± 15.54)	2.59 (± 3.14)	12.91 (± 4.19)
Sadness	0.37 (± 0.38)	10.70 (± 5.97)	0.36 (± 0.49)	19.25 (± 15.59)	30.26 (± 10.07)	2.69 (± 2.99)
	Advanced RPD ON condition					
Emotion	**Anger scale**	**Fear scale**	**Happiness scale**	**Neutral scale**	**Sadness scale**	**Surprise scale**
Anger	50.15 (± 11.58)	6.19 (± 5.59)	1.72 (± 2.88)	6.11 (± 4.09)	0.43 (± 0.36)	8.78 (± 8.95)

Fear	9.08 (± 6.90)	41.86 (± 12.71)	3.36 (± 2.65)	3.42 (± 4.44)	9.48 (± 10.57)	7.20 (± 9.86)
Happiness	7.48 (± 5.08)	6.28 (± 4.56)	35.60 (± 12.63)	0.99 (± 1.58)	5.14 (± 4.97)	16.38 (± 12.72)
Neutral	0.15 (± 0.09)	0.58 (± 0.74)	8.74 (± 6.84)	34.44 (± 17.03)	1.17 (± 2.03)	13.98 (± 10.75)
Sadness	1.53 (± 3.03)	6.70 (± 5.71)	1.90 (± 3.87)	23.88 (± 9.04)	33.88 (± 18.63)	2.31 (± 3.96)
	Healthy controls					
Emotion	**Anger scale**	**Fear scale**	**Happiness scale**	**Neutral scale**	**Sadness scale**	**Surprise scale**
Anger	54.99 (± 10.02)	3.64 (± 4.05)	0.59 (± 1.10)	5.34 (± 5.27)	0.88 (± 1.42)	5.72 (± 3.80)
Fear	8.88 (± 8.90)	41.63 (± 12.09)	0.96 (± 2.70)	1.86 (± 2.24)	10.22 (± 6.82)	11.19 (± 10.48)
Happiness	9.15 (± 6.59)	8.13 (± 4.29)	29.24 (± 10.50)	1.10 (± 1.47)	8.74 (± 7.92)	15.99 (± 10.40)
Neutral	0.17 (± 0.11)	1.14 (± 1.26)	4.95 (± 9.16)	32.52 (± 15.95)	1.84 (± 2.77)	14.86 (± 8.42)
Sadness	2.23 (± 2.73)	8.82 (± 4.52)	0.77 (± 2.22)	18.08 (± 9.80)	34.77 (± 11.74)	1.58 (± 2.59)

Table 3. Mean ratings and standard deviations [minimum 0; maximum 100] of pseudoword stimuli in emotion prosody task for patients with PD, according to disease stage and motor symptom asymmetry.

Legend: LPD: patients with PD exhibiting predominantly left-sided motor symptoms; RPD: patients with PD exhibiting predominantly right-sided motor symptoms; HC: healthy controls.

“ (p < .05) when compared with advanced PD group

* Significant after FDR (in early PD: *p* <.017; in advanced PD: *p* < .050) correction when compared with HC group

@ Significant after FDR (intergroup in the OFF-DOPA and ON-DOPA conditions: *p* <.025) correction when compared with RPD group

“” Significant after FDR (*p* < .050) correction when compared with Advanced PD group

Significant after FDR correction (p < .050) when compared with OFF-DRT condition

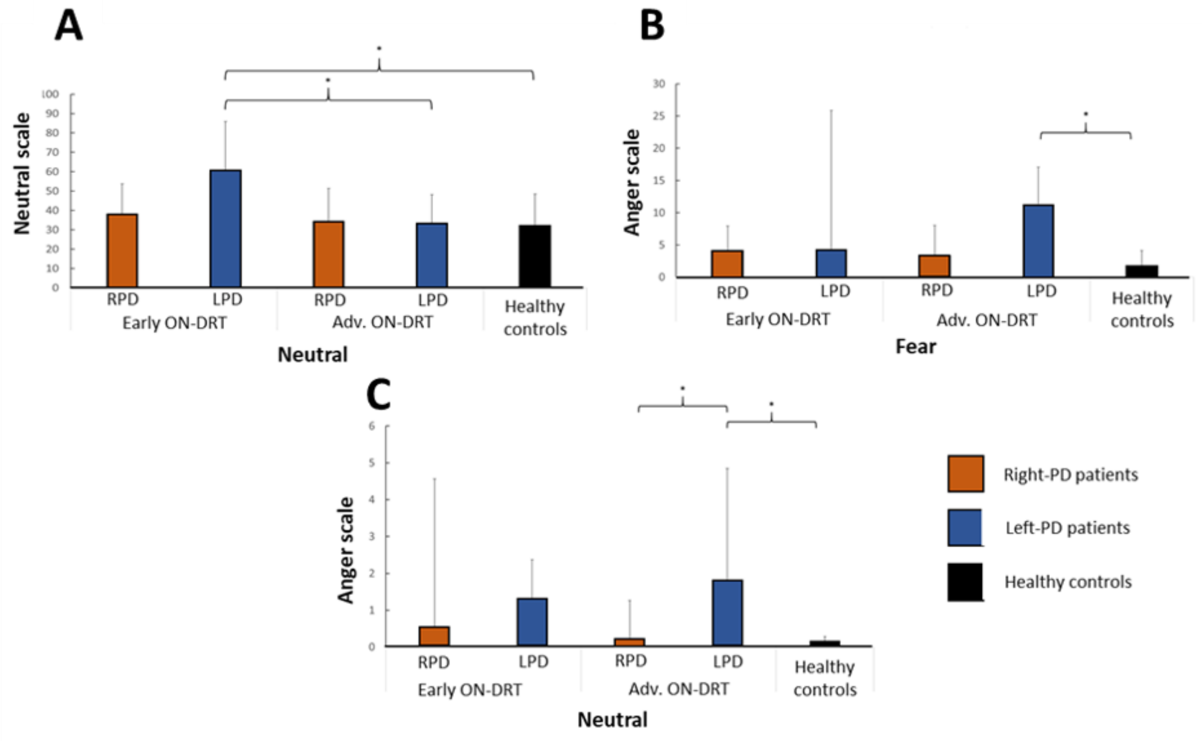

Figure 1. Mean ratings (and standard deviations) for significant emotional prosody recognition according to disease stage (early and advanced) and motor symptom asymmetry (LDP and RPD), as well as for healthy controls. A) Neutral scales when the stimulus was Neutral. B) Anger scales when the stimulus was fear. C) Anger scales when the stimulus was neutral.

**significant after FDR correction

3.4 Relationships between vocal emotion recognition performances and secondary variables

To avoid type I errors, we have opted to include in the correlation models only those variables that are significant in the context of inter- and intra-group comparisons.

A significant moderate negative correlation, was observed between the ratings on the Neutral scales when participants listened to fear and MADRS (R = - 0.44, t = -2.33, p = .029).

A significant weak negative correlation was observed between the ratings on the Neutral scales when participants listened to neutral and disease duration [in years] (R = - 0.38, t = -2.19, p = .037), as well as a moderate negative correlation with DRT [in mg/ml] (R = - 0.51, t = - 3.08, p = .005) (see Figure 2).

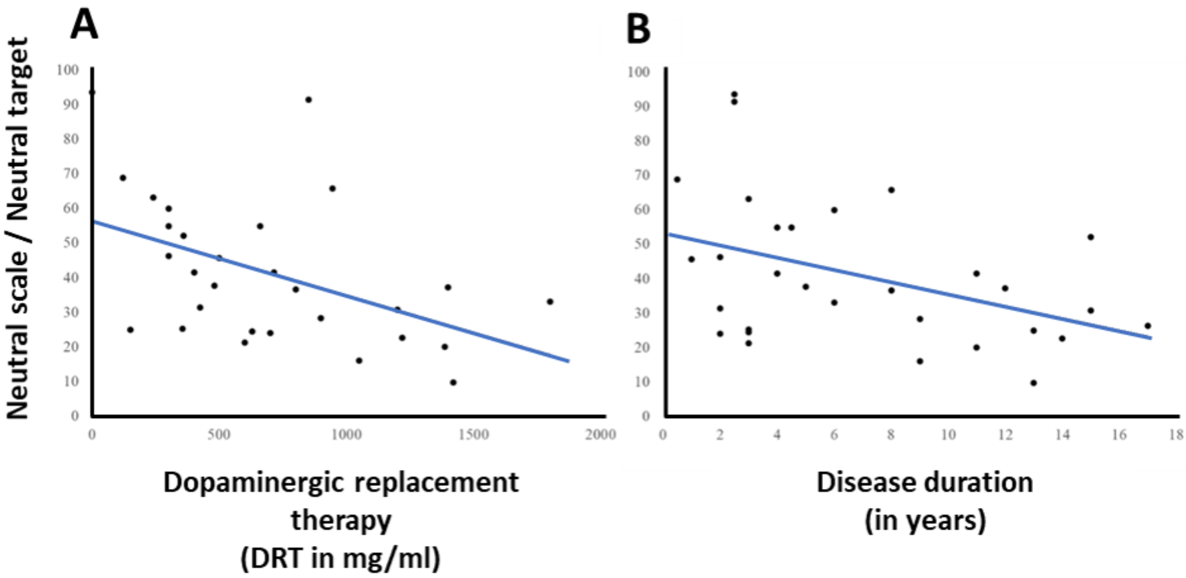

Figure 2. Correlations between neutral emotion and neutral emotion scales performances with secondary variables (dopaminergic replacement therapy [mg/ml] and disease duration). A. The higher the dopaminergic replacement therapy (mg/ml), the worse the recognition of neutral prosody. B. The higher the disease duration (years), the worse the recognition of neutral prosody.

4. Discussion

The aim of the present study was to investigate the differential effects of motor symptom asymmetry, DRT and stages of the disease on emotion prosody recognition in PD. Our findings revealed two primary patterns of results.

First, as hypothesized, LPD patients exhibited greater deficits in emotion recognition compared to both RPD patients and healthy controls, particularly for the recognition of fear and neutral emotions. This supports the theory of right hemisphere dominance in essential emotion recognition mechanisms. Specifically, advanced LPD patients showed a higher rate of misattribution on the Neutral scale when anger was the target emotion, as well as reduced accuracy in recognizing neutral stimuli compared to controls—patterns not observed in RPD patients. These results suggest that LPD may experience greater degradation in right meso-limbic dopaminergic pathways, which are crucial for emotional prosody recognition. However, this hypothesis must be tempered by the interaction between DRT and disease duration, as our findings suggest a more complex effect of DRT on emotional processing than initially predicted.

Contrary to our hypothesis, early RPD patients benefited from DRT in emotion recognition, particularly for fear, while early LPD patients showed a decline in performance under DRT, especially for recognizing anger. This indicates that DRT had a positive effect on emotional prosody recognition in early-stage RPD patients, while it had a detrimental impact on early LPD patients. One possible explanation is that RPD patients, despite initial asymmetry, may experience more pronounced bilateral denervation, reducing the risk of a dopaminergic overdose effect on the right hemisphere. Conversely, LPD patients may be more susceptible to a dopaminergic overdose effect in the ON-DRT condition, particularly in the ipsilateral (left) hemisphere, due to less severe neurodegeneration. This could impair emotional processing by overstimulating areas involved in emotion recognition.

These findings help explain the inconsistencies in previous studies on the effects of DRT on emotion recognition in PD, where motor symptom asymmetry was not considered [44]. In our data, some results were consistent with our predictions: for instance, LPD patients overestimated the intensity of neutral stimuli under DRT, as has been observed in prior studies. These findings, aligned with embodiment theories [45], suggest that reduced emotional expressiveness in PD (hypomimia or aprosody) may lead to both a decrease in emotional reactivity and an increased recognition of neutral stimuli. Our results reinforce the hypothesis that DRT may alter meso-limbic pathways involved in embodiment processes, with a possible right-hemisphere dominance for these functions.

Beyond emotional recognition, the cognitive and psychiatric variables measured also revealed intriguing patterns. Early RPD patients performed significantly worse than both early LPD and HC on global cognitive efficiency (measured by the MDRS) in the OFF-DRT condition, but showed no significant differences in the ON-DRT condition, suggesting a potential normalizing effect of DRT on left hemisphere dopaminergic networks in early PD [46]. Moreover, we observed greater cognitive decline in RPD patients, possibly indicating a vulnerability to long-term cognitive deterioration and dementia [31, 47], which could be related to the bilateralization of motor symptoms [31]. In terms of psychiatric symptoms, advanced RPD patients displayed higher levels of depression compared to controls, echoing findings of cognitive and affective deficits in later stages of the disease. It remains unclear whether the reduced emotional prosody recognition observed in advanced LPD patients is due to disease progression or the effects of DRT, necessitating further investigation.

Our results suggest that alterations in emotional prosody recognition are present throughout the course of PD and evolve over time, influenced by motor symptom asymmetry and DRT. These findings support the model proposed by Péron, Frühholz [2], which highlights the role of lateralized dopaminergic pathways in emotion and cognitive processing.

Importantly, our study introduces the novel consideration of motor symptom asymmetry as a critical factor in the effectiveness of DRT on emotional processing. In the early stages of PD, RPD patients, contrary to the hypothesis of dopaminergic overdoses, appear to benefit from DRT in terms of emotional prosody and cognitive performance, potentially due to greater bilateralization of symptoms [48, 49]. LPD patients, however, seem to be more vulnerable to DRT-induced declines in emotion recognition, possibly due to greater degeneration of the right hemisphere and the risk of dopaminergic overdose. These findings also suggest that the progression of motor symptoms toward bilateralization could increase the risk of major cognitive decline, particularly in RPD patients [31], warranting further study. Additionally, future research should investigate not only motor asymmetry but also the type of dopaminergic medication used, as some studies suggest that dopaminergic antagonists may impair emotion recognition more than levodopa Lawrence, Goerendt [21]. This is further evidenced by Takahashi, Yahata [50] in functional magnetic resonance imaging of reduced activity of limbic regions following the injection of dopaminergic antagonists. Understanding these differences could lead to more targeted treatment strategies.

This study has several limitations. First, the small sample size limits the generalizability of our findings, although it provides a foundation for future research. Additionally, we did not assess emotion prosody recognition in advanced PD patients in the OFF-DRT condition, limiting our ability to fully understand the effects of disease progression. Ethical concerns about withholding medication from advanced PD patients contributed to this decision. Moreover, the lack of longitudinal follow-up prevents us from analyzing changes over time between early and advanced stages of PD. Another limitation is the absence of significant age differences between the early and advanced PD groups, suggesting that the advanced group may have had an earlier onset of PD. This could mean that advanced patients developed more emotional symptoms over time, a hypothesis aligned with studies on the effects of age on social cognition. Future studies should investigate the impact of age and disease onset on emotional and cognitive processing.

5. Conclusion

Our findings highlight the importance of considering motor symptom asymmetry when evaluating the effects of DRT on emotion prosody recognition and cognition in PD. For the first time, our results suggest an interaction between motor asymmetry and DRT, pointing to the involvement of lateralized dopaminergic pathways in emotional and cognitive functions. While these exploratory findings are based on a small sample, they pave the way for future research into the role of motor asymmetry and DRT in the emotional domain, with potential implications for more personalized patient management strategies.

6. Acknowledgements

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7. Statement of Ethics

After the participants had been given a complete description of the study, they all provided their written informed consent, and the study was conducted in accordance with the Declaration of Helsinki. The study protocol was reviewed and approved by the ethics committee of the Rennes University Hospital where all the data were acquired (Neurology Unit of Pontchaillou Hospital, Rennes University Hospital, France, Prof. M. Vérin) with the authorisation 05045 S granted to the Neurology Department of the CHU of Rennes.

8. Conflict of Interest Statement

The authors have nothing to disclose.

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10. Authors Contributions

PV: writing—original draft preparation; data curation; formal analysis

DG: investigation; resources; writing—review and editing

SD: investigation; resources; writing—review and editing

DD: investigation; resources; writing—review and editing

MV: investigation; resources; project administration; writing—review and editing; funding acquisition

JP: formal analysis; data curation; resources; investigation; project administration; writing—review and editing; funding acquisition

11. Data availability

The data that support the findings of this study are not publicly available due to containing information that could compromise the privacy of research participants but are available from corresponding author [JAN] upon reasonable request.

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