Hypomimia in Parkinson's disease: an axial sign responsive to levodopa

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Background and purpose: Hypomimia is a prominent clinical feature in people with Parkinson's disease (PD), but it remains under-investigated. We aimed to examine the clinical correlates of hypomimia in PD and to determine whether this is a levodopa-responsive sign.

Methods: We included 89 people with PD. Hypomimia was assessed from digital video recordings by movement disorder specialists. Clinical evaluation included use of the Unified Parkinson's Disease Rating Scale part III (UPDRS-III), and assessment of motor and non-motor symptoms using standardized clinical scales. The relationships between hypomimia and other clinical data were analysed using Mann–Whitney *U*-tests and regression analysis.

Results: Hypomimia occurred in up to 70% of patients with PD. Patients with hypomimia had worse UPDRS-III 'off-medication' scores, mainly driven by bradykinesia and rigidity subscores. Patients with hypomimia also had worse apathy than patients without hypomimia. Finally, we found that hypomimia was levodopa-responsive and its improvement mirrored the change by levodopa in axial motor symptoms.

Conclusion: Our study provides novel information regarding the clinical correlates of hypomimia in people with PD. A better understanding of hypomimia may be relevant for improving treatment and quality of life in PD.

Introduction

People with Parkinson's disease (PD) often manifest severe loss of facial expression, referred to as hypomimia [1,2]. However, despite being one of the hallmark features of PD, hypomimia has been characterized in a relatively limited number of clinical and neurophysiological studies [3,4].

Well-defined data on the prevalence of hypomimia in PD are also lacking. Together with other orofacial symptoms (speech and swallowing impairment, sialorrhoea), hypomimia has been associated with more severe motor symptoms [4]. However, it is not known whether hypomimia is influenced by the demographic features of patients, that is, age, gender and disease duration. It is also unclear whether hypomimia parallels the severity of appendicular cardinal motor signs (bradykinesia and rigidity) or, rather, is associated with axial signs (posture, gait and balance disorders) or non-motor features such as cognitive and psychiatric symptoms. Moreover, data on the impact of hypomimia on quality of life and social well-being of PD patients are limited [5,6]. Finally, although hypomimia seems to be a better predictor of basal ganglia dopaminergic denervation compared with other

parkinsonian signs [7], no clear information is available on the effects of levodopa on this clinical feature.

Given this background, we aimed to address the following research questions: (i) is the severity of hypomimia in PD influenced by demographic features?; (ii) does hypomimia parallel the impairment of appendicular, axial or motor signs?; (iii) is hypomimia associated with non-motor symptoms of PD, including cognitive and psychiatric symptoms? and (iv) is hypomimia levodopa-responsive?

Accordingly, we tested possible correlations between patients' hypomimia and their demographic and clinical features. We evaluated other clinical correlates of hypomimia by analysing its relationship with appendicular or axial motor signs (orofacial, speech and gait). We also extensively assessed non-motor symptoms, such as cognitive and neuropsychiatric deficits and we tested whether they were related to the severity of hypomimia. Finally, we assessed the effect of levodopa on hypomimia and compared it to changes in other parkinsonian signs after a levodopa challenge test.

Methods

Patients

Consecutive patients with PD attending the Movement Disorders Clinic at St George's University Hospital (London, UK) were invited to participate in the study. The diagnosis of idiopathic PD was confirmed according to Movement Disorder Society (MDS) clinical diagnostic criteria [8]. We excluded patients with dementia as per clinical assessment. We also excluded patients with a history of Bell's palsy, maxillofacial deficits, or injection of botulinum toxin in facial muscles for cosmetic or therapeutic purposes which could interfere with facial movements.

Demographic and clinical data were gathered including gender, age, age at disease onset and disease duration. Information about PD medications was collected and the total levodopa equivalent daily dose (LEDD) and LEDD dopamine agonists were calculated for each patient [9]. All patients provided written informed consent to participate according to the Declaration of Helsinki, and the research ethics board approved the study (IRAS number 259146).

Outcome measures

Patients with PD were assessed after a 12-h overnight medication withdrawal in the practically defined 'off-medication' (OFF) condition [10]. The last dose of prolonged-release dopamine agonist medication was taken the morning before the test. The patients were also assessed in their best 'on-medication' (ON) condition 60–90 min after taking a dose of levodopa corresponding to their usual morning LEDD plus 50% (supramaximal dose = 150%).

In both OFF and ON conditions, motor symptom severity and disease stage were evaluated using the Unified Parkinson's Disease Rating Scale part III (UPDRS-III) and the Hoehn and Yahr stage. Presence of hypomimia was defined according to a score ≥ 2 on the UPDRS-III, item 19 ('slight but definitely abnormal diminution of facial expression'). Bradykinesia score was calculated as the sum of the sub-items finger taps (left and right), hand movement (left and right), rapid alternate movements of hands (right and left), leg agility (right and left), and body bradykinesia of the UPDRS-III (items 23–26). Axial motor features were expressed in terms of 'axial score', which was calculated as the sum of the following items of the UPDRS-III: 18 (speech), 22 (rigidity of neck), 27 (arising from chair), 28 (posture), 29 (gait) and 30 (postural stability) [11]. In addition, we computed the variable 'appendicular score' as the sum of UPDRS-III tremor , bradykinesia and rigidity scores of right and left limbs. Magnitude of change after levodopa was calculated for UPDRS-III item 19, axial and appendicular scores as follows: delta = (score OFF-score ON)/score OFF.

Dyskinesia was rated with the Rush Dyskinesia rating scale. The Non-Motor Symptoms Scale was used to evaluate severity of non-motor symptoms [12].

Orofacial symptoms were measured using the Radboud Oral Motor Inventory for PD (ROMP), a self-administered questionnaire that encompasses three subscales evaluating difficulties with speech, swallowing disturbances, and drooling of saliva [13]. Gait impairment and falls were investigated with the self-administered Gait and Falls Questionnaire (GFQ) [14].

Mood and psychiatric symptoms were explored using the Hamilton Anxiety [15] and Depression Rating Scale [16] and Apathy Evaluation Scale [17]. Quality of life was measured using the 39-item Parkinson's Disease Questionnaire (PDQ-39) [18].

All PD patients underwent an extensive neuropsychological test battery, including tests to assess attention, executive functions, language, memory, and visuospatial functions. A minimum of two tests were administered for each domain (Table S1). Patients were categorized as having normal cognition or mild cognitive impairment (MCI) according to the Level II International Parkinson and Movement Disorders Society criteria [19].

Statistical analysis

After checking for normal distribution of the variables by Kolmogorov–Smirnov test, group comparisons

Table 1 Comparison of demographic and clinical characteristics of Parkinson's disease patients with and without hypomimia

	No hypomimia (N = 32)	Hypomimia (N = 57)	P
Age, years	60.3 ± 6.75	61.8 ± 6.5	0.2
Women, n	15	18	0.1
Disease duration, years	9.5 ± 3.6	11.2 ± 4.9	0.1
Age at onset, years	51.1 ± 7.7	50.6 ± 7.6	0.9
Total LEDD	938 ± 470.9	1028.4 ± 371.6	0.3
Dopamine agonists LEDD	206.5 ± 150.1	189.3 ± 167.3	0.5
UPDRS-I score	1.8 ± 2.1	2.3 ± 2.1	0.1
UPDRS-II score	14.1 ± 6.1	18.5 ± 7.2	0.01
UPDRS-III - OFF score	34.6 ± 15.0	51.4 ± 13.9	**<0.0001**
Bradykinesia OFF subscore	13.6 ± 6.3	19.8 ± 6.5	**<0.0001**
Rigidity OFF subscore	7.4 ± 3.8	12.1 ± 4.8	**<0.0001**
Tremor OFF subscore	6.1 ± 5.2	5.7 ± 5.5	0.5
Axial OFF subscore	7.2 ± 4.5	10.4 ± 4.5	**0.001**
UPDRS-IV score	5.83 ± 3.392	6.2 ± 3.6	0.9
RDRS score	3.63 ± 3.586	3.9 ± 3.9	0.8
% improvement at levodopa challenge test	59.1 ± 15.9	52.9 ± 19.7	0.2
GFQ score	16.9 ± 12.9	20.1 ± 14.6	0.4
NMSS total score	58.3 ± 31.5	76.9 ± 43.4	0.04
HDRS score	6.7 ± 4.3	8.1 ± 7.0	0.7
HARS score	9.4 ± 6.8	10.6 ± 10.2	0.9
Apathy evaluation scale score	5.8 ± 6.5	11.2 ± 7.1	**<0.0001**

Values are mean ± SD, unless otherwise indicated. P value corrected for multiple comparisons 0.002. ADL, activities of daily living; GFQ, Gait and Fall Questionnaire; HARS, Hamilton Anxiety Rating Scale; HDRS, Hamilton Depression Rating Scale; LEDD, levodopa equivalent daily dose; MOCA, Montreal Cognitive assessment; NMSS, Non-Motor Symptoms Scale; OFF, off-medication; ON, on-medication; PDQ-39, 39-item Parkinson's Disease questionnaire; RDRS, Rush Dyskinesia Rating Scale; ROMP, Radboud Oral Motor Inventory for Parkinson's Disease; UPDRS, Unified Parkinson's Disease Rating Scale. Significant values are shown in bold.

were performed using either a t-test or Mann–Whitney U-test for continuous variables and a chi-squared or Fisher's exact test for categorical data. Bonferroni correction was used to account for multiple comparisons. To test the effect of levodopa on hypomimia, we performed a repeated-measure ANOVA with 'group' as between-group factor (two levels: PD with hypomimia, PD without hypomimia) and 'medication' as a within-group factor (two levels: OFF, ON). Conditional on significant F values, we used *post hoc* pairwise comparisons within each group.

Univariable linear regression analyses were performed to explore the relationship between facial expression at baseline (as per UPDRS-III item 19) and the following variables: age, gender, disease duration, LEDD, axial and appendicular scores of UPDRS-III.. To explore the association between the response to levodopa of facial expression and demographical and clinical variables, we employed univariable linear regression analysis with delta value of UPDRS-III item 19 as dependent variable. The variables that were significantly associated with outcomes at the univariable level were included in the multivariable models.

For all statistical procedures we used SPSS Statistics version 25 and the significance level was set as $P < 0.05$ in all tests.

Results

We included 89 patients with PD whose clinical and demographic data are shown in Table S2. Fifty-seven (64%) patients with PD were classified as having PD with hypomimia (PD-HYP group) and 32 patients (36%) as having PD without hypomimia (PD-no-HYP group). There was no difference in age, sex, disease duration, total LEDD or LEDD dopamine agonists between the groups (Table 1).

Clinical correlates of hypomimia in PD

We found a significant between-group difference in terms of severity of motor symptoms in the OFF condition. Specifically, the PD-HYP group had significantly worse UPDRS-III total score, body bradykinesia, rigidity and axial subscores compared to the PD-no-HYP group (Table 1). Conversely, there were no between-group differences when evaluating tremor subscores and gait and balance symptoms as per the GFQ. Non-motor symptoms ($P = 0.04$) and apathy ($P < 0.0001$) were more severe in the PD-HYP group compared to the PD-no-HYP group (Table 1), however, non-motor symptoms did not survive after adjusting for multiple comparisons.
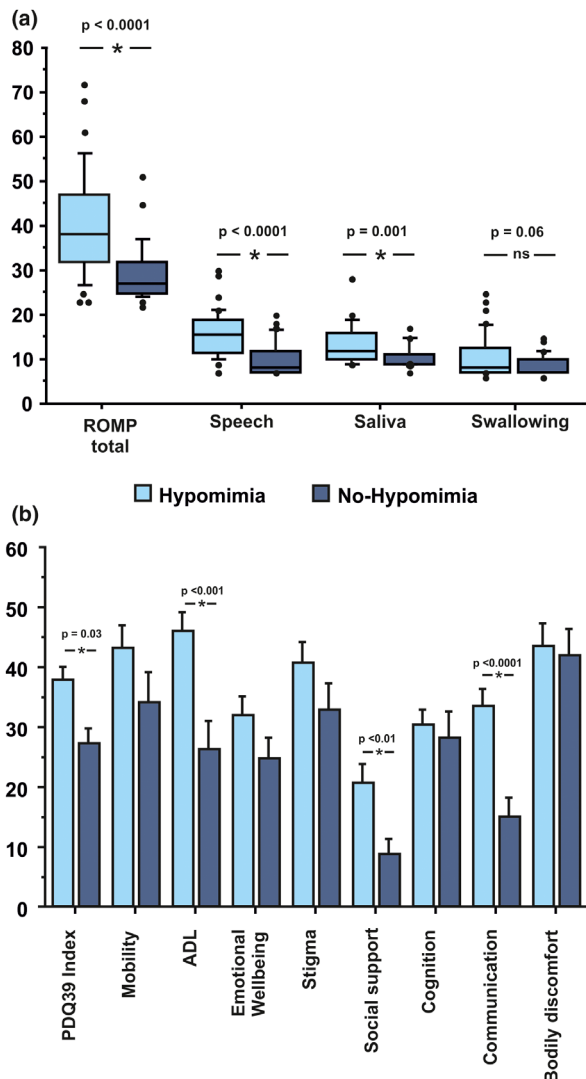
Figure 1 Differences between Parkinson's disease (PD) with hypomimia and PD without hypomimia in orofacial symptoms and quality of life. PD patients with hypomimia had higher Radboud Oral Motor Inventory for Parkinson's Disease (ROMP) total score, and higher ROMP speech and ROMP saliva subscores (a) and reported worse quality of life according to 39-item Parkinson's Disease Questionnaire (PDQ-39) total score and PDQ-39 activities of daily living (ADL), social support and communication subscores (b).

The PD-HYP group had worse orofacial symptoms and, specifically, higher difficulty with speech and drooling of saliva scores (ROMP total score: $P < 0.0001$; ROMP speech subscore: $P < 0.0001$; ROMP saliva subscore: $P = 0.001$). There was only a trend for difficulty in swallowing [ROMP swallowing subscore, $P = 0.06$ (Fig. 1a)].

Finally, the PD-HYP group reported worse quality of life, as measured by the PDQ-39 total score ($P = 0.03$) and, more specifically, the subscores for

Table 2 Univariable and multivariable regression analysis with hypomimia (assessed by UPDRS III, facial expression score) as dependent variable.

	β	95% CI, lower bound	95% CI, upper bound	P
Univariable analysis				
Axial score OFF	0.509	0.067	0.142	**<0.0001**
Appendicular score OFF	0.517	0.026	0.054	**<0.0001**
Gender	0.107	−0.196	0.599	0.317
Age (years)	0.205	−0.001	0.058	0.059
Disease duration	0.169	−0.011	0.078	0.141
LEDD	0.144	0	0.001	0.218
Multivariable analysis				
Age (years)	0.214	0.005	0.055	**0.02**
Axial score OFF	0.256	0.004	0.101	**0.033**
Appendicular score OFF	0.366	0.01	0.047	**0.003**

CI, confidence interval; LEDD, levodopa equivalent daily dose; OFF, off-medication; ON, on-medication. Significant values are shown in bold.

activities of daily living, social support and communication [$P = 0.001$, $P = 0.01$ and $P < 0.0001$, respectively (Fig. 1b)].

To evaluate possible differences in neuropsychological profile and in frequency of MCI in the PD-HYP and PD-no-HYP groups, we classified all patients as cognitively intact, i.e. normal cognition (PD-NC) or MCI (PD-MCI) [19]. Of the 89 PD patients recruited, 51 had PD-NC and 38 had PD-MCI. The distribution of PD-NC and PD-MCI in the two groups of patients with and without hypomimia was similar ($P = 0.5$, chi-squared test). After adjustment for multiple comparisons, performance on all neuropsychological tests was similar in the PD-HYP and PD-no-HYP groups (Table S3).

Multivariable regression analysis showed that the degree of reduced facial expression (UPDRS-III item 19) was associated with age, severity of axial and appendicular signs after correcting for disease duration, gender and dopaminergic therapy (Table 2).

Effect of levodopa on hypomimia

Figure 2 shows the effects of levodopa administration in patients with and without hypomimia for UPDRS-III total, appendicular, axial and facial expression-scores. For UPDRS-III total score, there was a main effect of the factor 'group' [$F(1,87) = 23.1$, $P < 0.0001$], with the PD-HYP group having a significantly higher score than the PD-no-HYP group. In the presence of a 'medication' effect [$F(1,87) = 332.1$, $P < 0.0001$], the two groups differed by magnitude of response to levodopa ('group' by 'medication' interaction: $F(1,87) = 11.8$; $P = 0.0009$). We found a similar
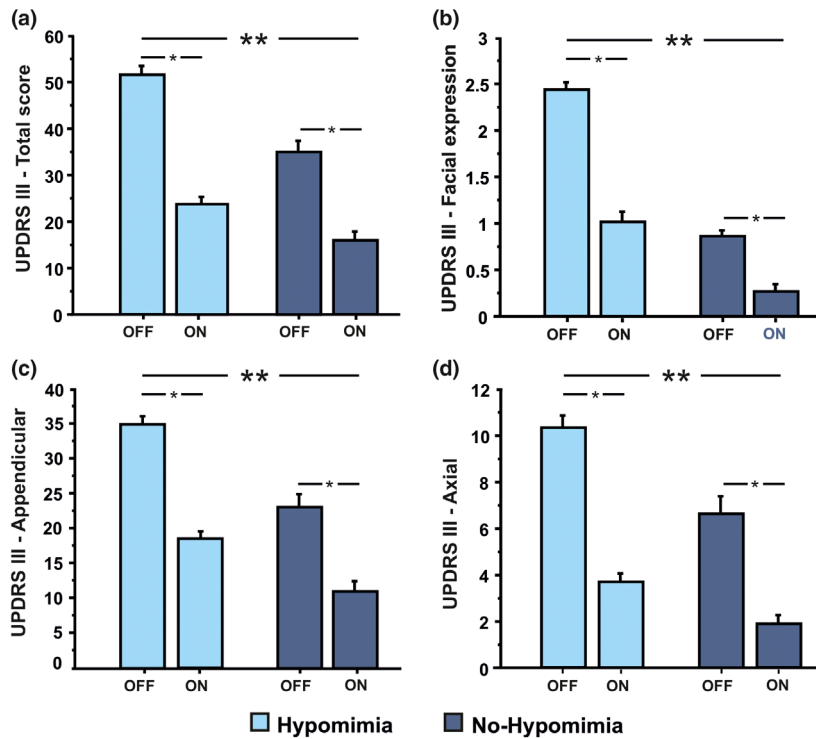
Figure 2 Differences between Parkinson's disease (PD) with hypomimia and PD without hypomimia in motor symptoms severity. PD patients with hypomimia had a significant higher score at Unified Parkinson's Disease Rating Scale part III (UPDRS-III) total score (a), facial expression (b), appendicular (c) and axial sub-scores (d). OFF, off-medication; ON, on-medication.

pattern for the appendicular score, with a main effect of 'medication' [F(1,87) = 366.9, P <0.0001] and 'group' [F(1,87) = 24.1, P <0.0001] and a significant medication by group interaction [F(1,87) = 9.2, P = 0.03]. Similarly, levodopa managed to improve the axial score in both groups, albeit to a different extent [effect of group: F(1,87) = 17.8, P < 0.0001; effect of medication: F(1,87) = 217.1, P < 0.0001; group by medication interaction: F(1,87) = 6.02, P = 0.02]. Finally, levodopa improved facial expressionin both groups [effect of group: F(1,87) = 122.8, P < 0.0001; effect of medication: F(1,87) = 156.7, P < 0.0001; group by medication interaction: F(1,87) = 26.7, P < 0.0001].

We then analysed the response of hypomimia to a levodopa challenge only in the PD-HYP group (N = 51; Table S4). There was a mean improvement of 60.4 ± 30.4% in UPDRS-III item 19 (facial expression) after levodopa intake (P < 0.0001 at Wilcoxon test) along with a significant improvement in UPDRS-III total score and all UPDRS-III subscores (all P < 0.0001). Regression analysis was performed to test which variables were associated with the improvement of facial expression by levodopa (Table 3). At univariable level, there was a significant association

Table 3 Univariable and multivariable regression analysis with delta of UPDRS-III item 19 as dependent variable in the group of patients with Parkinson's disease and hypomimia

	β	95% CI, lower bound	95% CI, upper bound	P
Univariable analysis				
Age (years)	−0.5	−1.9	0.8	0.4
Gender	−16.6	−34.6	1.3	0.06
Disease duration (years)	0.1	−1.7	1.9	0.8
Δ Axial score UPDRS-III	0.6	0.3	0.9	**<0.0001**
Δ Appendicular score UPDRS-III	0.4	0.0	0.8	**0.04**
Multivariable analysis				
Δ Axial score UPDRS-III	0.6	0.3	0.9	**<0.0001**
Δ Appendicular score UPDRS-III	0.09	−0.3	0.5	0.6

UPDRS-III, Unified Parkinson's Disease Rating Scale, part III; Δ = delta (see methods for details). Significant values are shown in bold.

between the improvement in facial expression and the improvement in total, appendicular and axial UPDRS-III scores. In the multivariable regression model, the improvement in facial expression was associated with the improvement of the axial score only [β = 0.6 95% confidence interval= 0.3–0.9);

P <0.0001]. We found no association between facial expression improvement and age, gender and disease duration.

Discussion

Hypomimia is a well-recognized feature of PD, but its clinical correlates have not been fully explored. In the present study, we identified that people with hypomimia had a more severe burden of motor symptoms, including orofacial symptoms. They also had worse apathy, but did not differ in terms of depression, anxiety and cognitive profile. Finally, we demonstrated that hypomimia was levodopa-responsive and the extent of its improvement with medication was mainly associated with reduction of axial symptoms. This association occurred independently of age, gender and disease duration.

Our data confirm that hypomimia is a frequent sign of PD [4], occurring in up to 70% of patients in our sample. Indeed, it is an underestimated and neglected sign, mainly due to a lack of clinical rating instruments and kinematic and neurophysiological measures, which may rate the different aspects of PD-related facial impairment, including emotional dysfunction [20,21].

The association between hypomimia and worse severity of motor scores on the UPDRS has been previously reported [4], in line with previous clinical observations of lower fluidity of movement, speed of talking, blinking, gesturing and vocal expressivity in PD with hypomimia [22]. At an experimental level, kinematic measures of posed smiling and voluntary grinning in PD have been correlated with severity of global dysfunction [21] and severity of motor symptoms of one body side, correlated with reduction of expressivity of emotions in the ipsilateral hemi-face in PD patients [23]. Accordingly, a common pathophysiological substrate for hypomimia and motor symptoms in PD has been hypothesized, in that hypomimia in PD is likely to reflect the abnormal activation of the primary motor and pre-motor frontal areas by dysfunctional basal ganglia [1,24].

A novel finding of the present study was that PD with hypomimia was associated with more severe axial and orofacial symptoms (speech, swallowing dysfunction, and sialorrhea). Indeed, drooling tested with clinical [25] or instrumental measures [13] has been previously correlated with hypomimia, supporting the view that sialorrhea in PD is mainly caused by an impairment of orofacial and swallowing muscles [26].

Impairment of facial expression was not related to cognitive impairment in our cohort of patients, as performance in several neuropsychological tests was comparable between the two groups. This finding implies that PD with reduced facial expression can have normal cognition [27]. Also, we did not find a higher burden of depression and anxiety in PD-HYP, in line with several neuropsychological reports documenting hypomimia in non-depressed PD patients [27,28]. This finding might be surprising when considering the previously documented association between depression and reduced facial expression of emotions in psychiatric patients [29]. However, it highlights the different pathophysiological basis of spontaneous facial activity and facial expression of emotions. Normal or even better expression of facial emotions (especially negative emotions) has been shown in patients with major depressive disorders [30].

When considering non-motor symptoms, PD with hypomimia was associated with worse apathy, a sign associated with reduced striatal dopamine transporter levels, independent of motor disability and depression in PD patients without cognitive abnormalities [31]. The relationship we found between hypomimia and apathy in PD possibly suggests a common pathophysiological background for the two abnormalities, likely attributable to altered interaction between the basal ganglia, prefrontal cortex and limbic system. Hence, our findings support the view of face as a body region where mechanisms related to different motor behaviour converge. From a clinical standpoint it is well known that apathy is a common abnormality in PD and that can severely affect the quality of life of both patients and caregivers. Insight into the relationship between hypomimia and apathy in PD could possibly be relevant in guiding a more individualized approach to the treatment of these symptoms.

Another relevant finding of the present study is that hypomimia is primarily related to low dopaminergic activity and it is a levodopa-responsive symptom. Indeed, facial expression improved significantly after levodopa intake, paralleling the improvement in limb and axial motor symptom severity. This supports the hypothesis that reduced facial expression in PD should be considered a levodopa-responsive symptom similar to other motor symptoms [3,32,33].

Our data also highlight that a reduction in facial expression is associated with worse quality of life, especially with regard to communication and activities of daily living. This relationship has not previously been identified. With relevance to this finding, some recent observations based on relatively small case studies, indicate complex interrelationships between hypomimia, depression and social and subjective well-being, which certainly require further investigation [5,6,34].

We acknowledge some limitations of the present study. First, there was no objective method by which to quantify facial expression. Second, we evaluated only one aspect of facial impairment in PD, and we did not include measures of emotional facial expression. Third, all patients taking dopamine agonists used prolonged-release formulations, which were last taken the morning before the test. Therefore, we could not rule out a complete wash-out from these medications.

In conclusion, in the present study, we provide novel information on the clinical correlates of hypomimia in PD as well as data on its responsiveness to levodopa administration. Our results indicate that hypomimia is a common clinical feature in PD that deserves attention during clinical examination because it can have a negative impact in terms of the quality of life of patients. The results also have some important pathophysiological implications in that they support the hypothesis that hypomimia is mainly attributable to decreased central dopaminergic tone and is mainly associated with motor symptoms and apathy. Future studies are necessary to clarify to what extent hypomimia could also serve as a useful predictor of the clinical course of PD and to shed light on the relationship between hypomimia and impaired facial expression of emotions in PD.

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Disclosure of conflicts of interest

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Data sharing

The data from this study are available from the corresponding author upon reasonable request.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Neuropsychological tests used to estimate functioning on each cognitive domain.

Table S2. Demographic and clinical data of the study population.

Table S3. Comparison between Parkinson's disease with and without hypomimia in neuropsychological tests.

Table S4. Motor scores before and after levodopa challenge test in the PD-HYP group.

References

1. Bologna M, Fabbrini G, Marsili L, Defazio G, Thompson PD, Berardelli A. Facial bradykinesia. *J Neurol Neurosurg Psychiatry* 2013; **84:** 681–685.
2. Ricciardi L, Bologna M, Morgante F, et al. Reduced facial expressiveness in Parkinson's disease: a pure motor disorder? *J Neurol Sci* 2015; **358:** 125–130.
3. Karson CN. Spontaneous eye-blink rates and dopaminergic systems. *Brain* 1983; **106:** 643–653.
4. Fereshtehnejad SM, Skogar O, Lokk J. Evolution of orofacial symptoms and disease progression in idiopathic Parkinson's disease: longitudinal data from the Jonkoping Parkinson registry. *Parkinsons Dis* 2017; **2017:** 7802819.
5. Kang J, Derva D, Kwon DY, Wallraven C. Voluntary and spontaneous facial mimicry toward other's emotional expression in patients with Parkinson's disease. *PLoS One* 2019; **14:** e0214957.
6. Gunnery SD, Habermann B, Saint-Hilaire M, Thomas CA, Tickle-Degnen L. The Relationship between the experience of hypomimia and social wellbeing in people with Parkinson's disease and their care partners. *J Parkinsons Dis* 2016; **6:** 625–630.
7. Makinen E, Joutsa J, Jaakkola E, et al. Individual parkinsonian motor signs and striatal dopamine transporter deficiency: a study with [I-123]FP-CIT SPECT. *J Neurol* 2019; **266:** 826–834.
8. Postuma RB, Berg D, Stern M, et al. MDS clinical diagnostic criteria for Parkinson's disease. *Mov Disord* 2015; **30:** 1591–1601.
9. Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. *Mov Disord* 2010; **25:** 2649–2653.
10. Defer GL, Widner H, Marie RM, Remy P, Levivier M. Core assessment program for surgical interventional therapies in Parkinson's disease (CAPSIT-PD). *Mov Disord* 1999; **14:** 572–584.

11. Bejjani BP, Gervais D, Arnulf I, et al. Axial parkinsonian symptoms can be improved: the role of levodopa and bilateral subthalamic stimulation. *J Neurol Neurosurg Psychiatry* 2000; **68:** 595–600.

12. Chaudhuri KR, Martinez-Martin P, Brown RG, et al. The metric properties of a novel non-motor symptoms scale for Parkinson's disease: Results from an international pilot study. *Mov Disord* 2007; **22:** 1901–1911.

13. Kalf JG, Munneke M, van den Engel-Hoek L, et al. Pathophysiology of diurnal drooling in Parkinson's disease. *Mov Disord.* 2011; **26:** 1670–1676.

14. Giladi N, Shabtai H, Simon ES, Biran S, Tal J, Korczyn AD. Construction of freezing of gait questionnaire for patients with Parkinsonism. *Parkinsonism Relat Disord* 2000; **6:** 165–170.

15. Leentjens AF, Dujardin K, Marsh L, et al. Anxiety rating scales in Parkinson's disease: critique and recommendations. *Mov Disord* 2008; **23:** 2015–2025.

16. Schrag A, Barone P, Brown RG, et al. Depression rating scales in Parkinson's disease: critique and recommendations. *Mov Disord* 2007; **22:** 1077–1092.

17. Marin RS, Biedrzycki RC, Firinciogullari S. Reliability and validity of the apathy evaluation scale. *Psychiatry Res* 1991; **38:** 143–162.

18. Jenkinson C, Fitzpatrick R, Peto V, Greenhall R, Hyman N. The Parkinson's disease questionnaire (PDQ-39): development and validation of a Parkinson's disease summary index score. *Age Ageing* 1997; **26:** 353–357.

19. Litvan I, Goldman JG, Troster AI, et al. Diagnostic criteria for mild cognitive impairment in Parkinson's disease: movement disorder society task force guidelines. *Mov Disord* 2012; **27:** 349–356.

20. Ricciardi L, Visco-Comandini F, Erro R, et al. Facial emotion recognition and expression in Parkinson's disease: an emotional mirror mechanism? *PLoS One* 2017; **12:** e0169110.

21. Marsili L, Agostino R, Bologna M, et al. Bradykinesia of posed smiling and voluntary movement of the lower face in Parkinson's disease. *Parkinsonism Relat Disord* 2014; **20:** 370–375.

22. Tickle-Degnen L, Lyons KD. Practitioners' impressions of patients with Parkinson's disease: the social ecology of the expressive mask. *Soc Sci Med* 2004; **58:** 603–614.

23. Ricciardi L, Visco-Comandini F, Erro R, et al. Emotional facedness in Parkinson's disease. *J Neural Transm* 2018; **125:** 1819–1827.

24. Bologna M, Berardelli I, Paparella G, et al. Altered kinematics of facial emotion expression and emotion recognition deficits are unrelated in Parkinson's disease. *Front Neurol* 2016; **7:** 230.

25. Karakoc M, Yon MI, Cakmakli GY, et al. Pathophysiology underlying drooling in Parkinson's disease: oropharyngeal bradykinesia. *Neurol Sci* 2016; **37:** 1987–1991.

26. Morgante F, Bavikatte G, Anwar F, Mohamed B. The burden of sialorrhoea in chronic neurological conditions: current treatment options and the role of incobotulinumtoxinA (Xeomin(R)). *Ther Adv Neurol Disord* 2019; **12:** 1756286419888601.

27. Smith MC, Smith MK, Ellgring H. Spontaneous and posed facial expression in Parkinson's disease. *J Int Neuropsychol Soc* 1996; **2:** 383–391.

28. Katsikitis M, Pilowsky I. A study of facial expression in Parkinson's disease using a novel microcomputer-based method. *J Neurol Neurosurg Psychiatry* 1988; **51:** 362–366.

29. Schwartz GE, Fair PL, Salt P, Mandel MR, Klerman GL. Facial muscle patterning to affective imagery in depressed and nondepressed subjects. *Science* 1976; **192:** 489–491.

30. Lautenbacher S, Bar KJ, Eisold P, Kunz M. Understanding facial expressions of pain in patients with depression. *J Pain.* 2017; **18:** 376–384.

31. Santangelo G, Vitale C, Picillo M, et al. Apathy and striatal dopamine transporter levels in de-novo, untreated Parkinson's disease patients. *Parkinsonism Relat Disord* 2015; **21:** 489–493.

32. Fetoni V, Genitrini S, Monza D, et al. Variations in axial, proximal, and distal motor response to L-dopa in multisystem atrophy and Parkinson's disease. *Clin Neuropharmacol* 1997; **20:** 239–244.

33. Umemura A, Toyoda T, Yamamoto K, Oka Y, Ishii F, Yamada K. Apraxia of eyelid opening after subthalamic deep brain stimulation may be caused by reduction of levodopa. *Parkinsonism Relat Disord* 2008; **14:** 655–657.

34. Wootton A, Starkey NJ, Barber CC. Unmoving and unmoved: experiences and consequences of impaired non-verbal expressivity in Parkinson's patients and their spouses. *Disabil Rehabil* 2019; **41:** 2516–2527.