# HYPOMIMIA IN PARKINSON’S DISEASE: AN AXIAL SIGN RESPONSIVE TO LEVODOPA

Ricciardi L1,2, De Angelis A2, Marsili L3, Faiman I4, Pradhan P4, Pereira EA2, Edwards MJ2, Morgante F2,5§\*and Bologna M6,7§

*1MRC Brain Network Dynamics Unit, Nuffield Department of Clinical Neurosciences, Oxford, UK*

*2Neurosciences Research Centre, Molecular and Clinical Sciences Research Institute, St George's University of London, London, UK*

*3Gardner Family Center for Parkinson's Disease and Movement Disorders, Department of Neurology, University of Cincinnati, Cincinnati, Ohio*

*4Clinical Neuropsychology Service, St George’s University Hospital NHS Foundation Trust, London, UK*

*5Department of Experimental and Clinical Medicine, University of Messina, Messina, Italy*

*6Department of Human Neurosciences, Sapienza University of Rome, Italy*

*7IRCCS Neuromed, Pozzilli (IS), Italy*

§ Dr Morgante and Dr Bologna share senior authorship

**Running title:** Hypomimia in Parkinson’s disease

**Character count title (spaces included):** 71

**Word count (abstract):** 186

**Word count (text):** 2690

**Tables:** 3; **Figure**s: 2

**Supplementary material:** 4 tables

**References:** 34

**Key words:** Parkinson’s disease, hypomimia, facial bradykinesia, non-motor symptoms, face

**Funding sources:** none

**\*Correspondence to:**

Dr. Francesca Morgante, MD, PhD

Neurosciences Research Centre, Molecular and Clinical Sciences Research Institute, St George's University of London, Cranmer Terrace, SW17 0RE, London, United Kingdom

e-mail: fmorgant@sgul.ac.uk

# ****ABSTRACT****

**Objective:**Hypomimia is a prominent clinical feature in people with Parkinson’s disease, though it remains under-investigated. We aimed here to examine the clinical correlates of hypomimia in Parkinson's disease and to test if this is a levodopa-responsive sign.

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

**Results:**Hypomimia occured in up to 70% of PD patients. Patients with hypomimia had worse UPDRS-III OFF scores, mainly driven by bradykinesia and rigidity sub-scores. Patients with hypomimia also had worse apathy than patients without hypomimia. Finally, we found that hypomimia is levodopa-responsive and its improvement mirrors the change in axial motor symptoms by levodopa.

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

# ****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]. Yet, it is unknown whether hypomimia is influenced by demographic features of patients, i.e. aging, 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 to axial signs (posture, gait and balance disorders) or to 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 to other parkinsonian signs [7], no clear information is available on the effects of levodopa on this clinical feature.**

**Given this background, we aimed here to investigate the following research questions: 1) is the severity of hypomimia in PD influenced by demographic features? 2) does hypomimia parallel the impairment of appendicular or axial or motor signs? 3) is hypomimia associated to non-motor symptoms of PD, including cognitive and psychiatric symptoms? 4) 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 related to degree 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 Advanced Movement Disorders Clinic at St George’s University Hospital (London, United Kingdom) were invited to participate in the study. The diagnosis of idiopathic PD was confirmed according to 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 following the Declaration of Helsinki, and the research ethics board approved the study (IRAS number 259146).

## Outcome measures

PD patients were assessed after a 12 hours overnight medication withdrawal in the “practically defined OFF condition” [10]. The last dose of prolonged release dopamine agonist medication was taken the morning before the test. They were also assessed in their best ON condition 60-90 minutes 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 (UPDRS) part III and the Hoehn and Yahr stage. Presence of hypomimia was defined according to a score ≥ 2 on 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 UPDRS-III: 18 (speech), 22 (rigidity of neck), 27 (arising from chair), 28 (posture), 29 (gait) and 30 (postural stability) [11]. Moreover, we computed the variable “appendicular signs score” as the sum of UPDRS-III tremor scores, bradykinesia scores and rigidity scores of right and left limbs. Dyskinesia were rated with the Rush Dyskinesia rating scale. The Non-Motor Symptoms Scale (NMSS) was employed 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 3 subscales evaluating difficulties with speech, swallowing disturbances, and drooling of saliva [13]. Gait impairment and falls were investigated with the self-administered Gait and fall 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 by means of the Parkinson’s disease questionnaire-39 items (PDQ-39) scale [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 was administered per each domain (See supplementary Table 1). Patients were categorized as normal cognition and mild cognitive impairment (MCI) according to the Level II International Parkinson and Movement Disorders Society criteria [19].

**DATA SHARING**

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

# STATISTICAL ANALYSIS

After checking for normal distribution of the variables by Kolmogorov-Smirnov test, group comparisons were performed by either t-test or Mann Whitney-U test for continuous variables and Chi-square or Fisher exact test for categorical data. Bonferroni correction was used to account for multiple comparisons. To test the effect of levodopa response on hypomimia, we performed a repeated measure ANOVA with “group” as between group factor (2 levels: PD with hypomimia, PD without hypomimia) and “medication” as within group factor (2 levels: OFF medication, ON medication). Conditional on significant F-values, we employed post-hoc paired-wised comparisons within each group.

Univariable linear regression analyses were employed to explore the relationship between clinical variables such as age, gender, disease duration, dopaminergic therapy, severity of axial and appendicular signs and 1) the degree of reduced facial expression at baseline (UPDRS-III item 19); 2) the delta of change of UPDRS III 19 at the Levodopa challenge test. The parameters that were significantly associated with the outcomes in the univariable level were then included in multivariable models.

For all the 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 PD patients whose clinical and demographic data are showed in Supplementary Table 2. Fifty-seven (64%) PD patients were classified as PD with hypomimia (PD-HYP) and 32 patients (36%) as PD without hypomimia (PD-no-HYP). There was no difference in age, sex, disease duration, total LEDD, LEDD dopamine-agonists between groups (Table 1).

## Clinical correlates of hypomimia in PD

We found a significant between-groups difference in terms of severity of motor symptoms OFF medication. Specifically, PD-HYP had significantly worse UPDRS-III total score, body bradykinesia, rigidity and axial sub-scores compared to PD-no-HYP (Table 1). Conversely, there were no between-groups differences when evaluating tremor sub-scores and gait and balance symptoms as per GFQ. Non-motor symptoms (p=0.04) and apathy (p<0.0001) were more severe in PD-HYP compared to PD-no-HYP (Table 1) however non-motor symptoms did not survive after adjusting for multiple comparisons.

PD-HYP had worse orofacial symptoms and specifically higher difficulties with speech and drooling of saliva (ROMP total: p<0.0001; ROMP speech: p<0.0001; ROMP saliva: p=0.001). There was only a trend for the difficulty in swallowing (ROMP-Swallowing, p=0.05) (Figure 1, panel A).

Finally, PD-HYP reported worse quality of life at the PDQ-39 total score (p=0.03) and more specifically in the sub-scores activity of daily living, social support and communication (p= 0.001, 0.01 and <0.0001, respectively) (Figure 1, panel B).

To evaluate possible differences in the neuropsychological profile and in the frequency of mild cognitive impairment in PD-HYP and PD-no-HYP, 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 were PD-NC and 38 were PD-MCI. Distribution of PD-NC and PD-MCI in the 2 groups of patients with and without hypomimia were similar (p=0.5, Chi-square test). Following adjustment for multiple comparisons, performance on all neuropsychological tests was comparable between PD-HYP and PD-no-HYP (Supplementary Table 3).

Multivariable regression analysis showed that the degree of reduced facial expression (UPDRS-III item 19) was associated to 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 total, appendicular, axial and hypomimia UPDRS-III scores. For UPDRS-III total score, there was a main effect of the factor “group” [F(1,87)=23.1, p <0.0001], where PD-HYP had significantly higher UPDRS-III total score than PD-no-HYP. In 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 pattern for the appendicular signs 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 of UPDRS-III 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 expression in 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 PD-no-HYP (N=51) (supplementary table 4). 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 sub-scores (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 the univariable level, there was a significant association between the improvement in facial expression (delta UPDRS-III item 19) and the improvement in total UPDRS-III score, appendicular sub-scores and axial score. In the multivariable regression model, the improvement in facial expression was associated with the improvement of the axial score only [B=0.6, C.I (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. Here 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 is levodopa responsive and the extent of its improvement with medication is mainly associated with the reduction of axial symptoms. This association occurred independently from 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 in the UPDRS has been previously reported [4], in line with previous clinical observations of lesser 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 current study, PD with hypomimia had 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]. Yet, 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 had 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 due 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 individualised approach to the treatment of these symptoms.

Another relevant finding of our 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 symptoms severity. This supports the hypothesis that reduced facial expression in PD should be considered a levodopa responsive symptoms similar to other motor symptoms [3, 32, 33].

Our data also highlight that a reduction in facial expression is associated with a worse quality of life, especially related 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 wellbeing, which certainly require further investigations [5, 6, 34].

We acknowledge limitations of our study. First, the lack of an objective method to quantify the facial expression; second, we evaluated only one aspect of the facial impairment in PD whereas we did not include measures of emotional facial expression. Finally, all patients taking dopamine-agonists used prolonged release formulations, which were lastly taken the morning before the test. Yet, we could not rule out a complete wash-out from these medications.

In conclusion, we provide here novel information on the clinical correlates of hypomimia in PD as well as data for its responsiveness to levodopa administration. Our results indicate that hypomimia is a common clinical feature in PD that deserves attention during the 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 due to decreased central dopaminergic tone and it 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.

# ACKNOWLEDGEMENTS

We are grateful to all the patients taking part in this study.

**LEGENDS TO FIGURES**

**Figure 1:** **Differences between PD with hypomimia and PD without hypomimia in orofacial symptoms and quality of life**. PD patients with hypomimia had higher scores in ROMP total score, ROMP speech and ROMP saliva sub-scores (panel A) and reported worse quality of life as per PDQ-39 total score and sub-scores activity of daily living, social support and communication (panel B).

**Figure 2: Differences between PD with hypomimia and PD without hypomimia in motor symptoms severity:** PD patients with hypomimia had a significant higher score at UPDRS-III total score (panel A), and facial expression, appendicular and axial sub-scores (panel B-C-D respectively).

**ETHICAL COMPLIANCE STATEMENT**

Institutional ethics approval was obtained (IRAS number 259146) and approved by the ethical Committee. The study was conducted in accordance with the Declaration of Helsinki. Each participant provided written informed consent before study participation.

We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

**CONFLICT OF INTERESTS**

This study did not receive any industry funding.

**FULL FINANCIAL DISCLOSURE FOR THE PREVIOUS 12 MONTHS**

* Lucia Ricciardi: Research support from UK’s Medical Research Council (MRC), Clinical Academic Research Partnerships.
* Francesca Morgante: Speaking honoraria from Abbvie, Medtronic, Zambon, Bial, Merz; Travel grants from the International Parkinson’s disease and Movement Disorder Society; Advisory board fees from Merz; Consultancies fees from Merz and Bial; Research support from Boston Scientific, Merz and Global Kynetic; Royalties for the book “Disorders of Movement” from Springer; member of the editorial board of Movement Disorders, Movement Disorders Clinical Practice, European Journal of Neurology.
* Mark J Edwards: Honoraria from Merz Pharma and Boeringer Ingleheim. Royalties from the Oxford University Press.
* The other authors do not have any disclosure to declare.

**DOCUMENTATION OF AUTHOR ROLES**

1.       Research project: A. Conception, B. Organization, C. Execution;

2.       Statistical Analysis: A. Design, B. Execution, C. Review and Critique;

3.       Manuscript: A. Writing of the first draft, B. Review and Critique;

**AUTHORS CONTRIBUTION:**

Lucia Ricciardi: 1A, 1B, 1C, 2A, 2B, 2C, 3A, 3B

De Angelis A: 1C, 2C, 3B

Marsili L: 1C, 2C, 3B

Faiman I: 1C, 2C, 3B

Pradhan P: 1C, 2C, 3B

Pereira EA: 1C, 2C, 3B

Edwards MJ: 1C, 2C, 3B

Francesca Morgante: 1A, 1B, 2C, 3B

Matteo Bologna: 1A, 2B, 2C, 3B

# REFERENCES

[1]. Bologna M, Fabbrini G, Marsili L, Defazio G, Thompson PD, Berardelli A. Facial bradykinesia. *JNeurolNeurosurgPsychiatry*. 2013 **84:** 681-685.

[2]. Ricciardi L, Bologna M, Morgante F*, et al.* Reduced facial expressiveness in Parkinson's disease: A pure motor disorder? *JNeurol Sci*. 2015 **358:** 125-130.

[3]. Karson CN. Spontaneous eye-blink rates and dopaminergic systems. *Brain*. 1983 **106 (Pt 3):** 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. *ParkinsonismRelat 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 (Vienna)*. 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. *JIntNeuropsycholSoc*. 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.

**Table 1: Comparison between PD patients with and without hypomimia for demographical and clinical variables**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **No-Hypomimia**  **(N=32)** | **Hypomimia**  **(N=57)** | **p value** |
| **Age (years)** | 60.3 ± 6.75 | 61.8 ± 6.5 | 0.2 |
| **Gender** | 15 F | 18 F | 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** | 1.8 ± 2.1 | 2.3 ± 2.1 | 0.1 |
| **UPDRS II** | 14.1 ± 6.1 | 18.5 ± 7.2 | **0.01** |
| **UPDRS III - OFF** | 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** | 5.83 ± 3.392 | 6.2 ± 3.6 | 0.9 |
| **RDRS** | 3.63 ± 3.586 | 3.9 ± 3.9 | 0.8 |
| **% improvement at LCT** | 59.1 ± 15.9 | 52.9 ± 19.7 | 0.2 |
| **GFQ** | 16.9 ± 12.9 | 20.1 ± 14.6 | 0.4 |
| **NMSS total score** | 58.3 ± 31.5 | 76.9 ± 43.4 | **0.04** |
| **HDRS** | 6.7 ± 4.3 | 8.1 ± 7.0 | 0.7 |
| **HARS** | 9.4 ± 6.8 | 10.6 ± 10.2 | 0.9 |
| **Apathy evaluation scale** | 5.8 ± 6.5 | 11.2 ± 7.1 | **<0.0001** |

Values are mean ± standard deviation. Abbreviations: ADL: activity of daily living; F: female; GFQ: gait and freezing of gait questionnaire; HARS: Hamilton Anxiety Rating Scale; HDRS: Hamilton Depression Rating Scale; LCT: levodopa challenge test; LEDD: levodopa equivalent daily dose; MOCA: Montreal Cognitive assessment; NMSS: Non Motor Symptoms Scale; PDQ-39: the 39-item PD questionnaire; RDRS= Rush Dyskinesia Rating scale; ROMP: the Radboud Oral Motor Inventory for Parkinson’s Disease ; UPDRS: Unified Parkinson’s Disease Rating Scale.

p-value corrected for multiple comparisons=0.002

Table 2: Univariable and multivariable regression analysis with hypomimia (by UPDRS III 19) as dependent variable

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Univariable Analysis | | | | |
|  | **Beta** | **95% CI - LB** | **95% CI - UB** | **p-value** |
| 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 | | | | |
|  | **Beta** | **95% CI - LB** | **95% CI - UB** | **p-value** |
| 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; LB = lower bound; LEDD: levodopa equivalent daily dose; UB = upper bound. \*significant values are bolded.

Table 3: Univariable and multivariable regression analysis with delta of change of UPDRS III 19 at the Levodopa challenge test as dependent variable in the PD-HYP group.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Univariable Analysis | | | | |
|  | **Beta** | **95% CI - LB** | **95% CI - UB** | **p-value** |
| 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 | | | | |
|  | **Beta** | **95% CI - LB** | **95% CI - UB** | **p-value** |
| 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 |

CI= confidence interval; LB = lower bound; Δ: delta change in score after levodopa challenge test; UB = upper bound UPDRS: Unified PD Rating Scale.

\*significant values are bolded.

A screenshot of a cell phone

Description automatically generated

A screenshot of a cell phone

Description automatically generated

Supplementary Table 1: Neuropsychological tests used to estimate functioning on each cognitive domain.

|  |  |
| --- | --- |
| Cognitive Domain | Neuropsychological Test |
| Attention and working memory | WAIS-IV Digit Span Forwards |
|  | WAIS-IV Digit Span Backwards  Trial Making Test - A |
|  | Symbol Digit Modalities Test |
| Executive function | D-KEFS Phonemic Fluency |
|  | Trial Making Test - B |
|  | Stroop color-word test |
| Language | Graded Naming Test |
|  | D-KEFS Semantic Fluency |
|  | WAIS-IV Similarities |
| Memory | Rey’s Auditory Verbal Learning Test (RAVLT) immediate and delayed recall |
|  | Birt Memory and Information Processing Battery (BMIPB) form 1; Story Memory delayed recall |
|  | Birt Memory and Information Processing Battery (BMIPB) form 1; Complex Figure delayed recall  Rey’s Complex Figure immediate and delayed recall |
|  | Camden Topographical Recognition Memory, delayed recall |
| Visuospatial function | RBANS Line Orientation |
|  | VOSP Shilouettes |
|  | Birt Memory and Information Processing Battery (BMIPB) form 1; Complex Figure copy  Rey’s Complex Figure copy |
|  | MOCA Cube/clock drawing |

|  |  |
| --- | --- |
| Age (years) | 61.3±6.5 |
| Gender (M/F) | 56/33 |
| Disease duration (years) | 10.6 ± 4.5 |
| Age at onset (years) | 50.8 ± 7.6 |
| Total LEDD | 997.1 ± 407.9 |
| Dopamine-agonists LEDD | 195.1 ± 160.9 |
| UPDRS I | 2.1 ± 2.1 |
| UPDRS II - OFF | 17 ± 7.1 |
| UPDRS III - OFF | 45.3 ± 16.4 |
| UPDRS-III 18 (Speech) OFF | 1.2 ± 0.7 |
| UPDRS-III 19 (Facial Expression) OFF | 1.8 ± 0.91 |
| UPDRS IV | 6.0 ± 3.4 |
| AIMS | 3.8 ± 3.7 |
| Gait and Falls questionnaire | 18.9 ± 14.0 |
| ROMP - scale TOTAL | 35.6 ± 11.4 |
| ROMP - SPEECH | 13.5 ± 5.5 |
| ROMP - SALIVA | 12.2 ± 4.2 |
| ROMP - SWALLOWING | 9.6 ± 4.1 |
| NMSS total score | 70.4 ± 40.5 |
| HDRS | 7.5 ± 6.1 |
| HARS | 10.1 ± 9.0 |
| Apathy evaluation scale | 9.3 ± 7.3 |
| MOCA | 26.2 ± 3.6 |
| PDQ 39 | 51.5 ± 29.6 |

Supplementary Table 2: Demographic and clinical data of the study population

Values are mean ± standard deviation.

HARS: Hamilton Anxiety Rating Scale; HDRS: Hamilton Depression Rating Scale; LEDD: levodopa equivalent daily dose; MOCA: Montreal Cognitive assessment; NMSS: Non Motor Symptoms Scale; PDQ-39: the 39-item PD questionnaire; ROMP: the Radboud Oral Motor Inventory for Parkinson’s Disease; UPDRS: Unified Parkinson’s Disease Rating Scale.

**Supplementary Table 3: Comparison between PD with and without hypomimia in neuropsychological tests**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  | **PD-no-HYP** | **PD-HYP** | **p value** |
| **Screening test** | **MOCA** | 26.0 ± 3.1 | 26.3 ± 3.9 | 0.4 |
| **Attention/working memory** |  |  |  |  |
|  | **DIGIT SPAN** | 24.0 ± 5.6 | 25.3 ± 6.3 | 0.6 |
|  | **SPAN FORWARD** | 8.9 ± 1.9 | 9.9 ± 2.5 | 0.1 |
|  | **SPAN BACKWARD** | 7.7 ± 1.7 | 7.9 ± 2.3 | 0.9 |
|  | **TMT A** | 43.1 ± 20.0 | 47.7 ± 26.2 | 0.5 |
|  | **Symbol/digit modalities test** | 42.6 ±11.9 | 38.2 ± 14.2 | 0.3 |
| **Executive functions** |  |  |  |  |
|  | **Phonemic Fluency** | 38.6 ± 14.3 | 43.5 ± 14.9 | 0.1 |
|  | **TMT B** | 114.7 ± 78.6 | 102.8 ± 56.0 | 0.5 |
|  | **Stroop interference** | 89.1 ± 24.9 | 79.9 ± 27.5 | 0.1 |
| **Language** |  |  |  |  |
|  | **Semantic Fluency** | 18.8 ± 6.6 | 19.2 ± 5.2 | 0.6 |
|  | **Graded Naming Test** | 19.3 ± 6.3 | 20.5 ± 6.3 | 0.3 |
|  | **WAIS-IV Similarities** | 23 ± 5.0 | 22.7 ± 5.2 | 0.9 |
| **Memory** |  |  |  |  |
|  | **RAVLT Total words over 5 trials** | 44.3 ± 11.0 | 43.5 ± 10.9 | 0.9 |
|  | **RAVLT Delayed Recall** | 9.6 ± 3.5 | 8.1 ± 4.5 | 0.2 |
|  | **RAVLT Recognition** | 14.1 ± 1.2 | 13.9 ± 1.4 | 0.8 |
|  | **Story Memory immediate recall** | 23.9 ±7.2 | 22.2 ± 10.1 | 0.3 |
|  | **Story Memory delayed recall** | 21.0 ± 7.9 | 19.8 ± 9.9 | 0.5 |
|  | **REY FIGURE IMMEDIATE RECALL** | 59.2 ± 31.0 | 51.8 ± 27.6 | 0.2 |
|  | **REY FIGURE DELAYED RECALL** | *58.1 ± 30.6* | *45.3 ± 23.5* | *0.03* |
|  | **Topographic memory-Camden test** | 25.7 ± 3.5 | 26.5 ± 10.8 | 0.9 |
| **Visuo-spatial functions** |  |  |  |  |
|  | **Line orientation RBANS** | 17.0 ± 2.4 | 15.7 ± 3.7 | 0.2 |
|  | **VOSP Silhouettes** | 23.3 ± 3.1 | 21.7 ± 4.3 | 1 |

Values are mean ± 1 standard deviation. p-value corrected for multiple comparisons=0.002. Abbreviations: MOCA: Montreal Cognitive assessment; RAVLT: Rey Auditory Verbal Learning Test; TMT= trail making test; WAIS-IV: Wechsler Adult Intelligence Scale-Fourth Edition ; VOSP: Visual Object and Space Perception Battery.

Supplementary Table 4: motor scores before and after levodopa challenge test in the PD-HYP group.

|  |  |  |  |
| --- | --- | --- | --- |
|  | OFF med | ON med | p-value |
| UPDRS III total score | 51.3 ± 13.9 | 23.5 ± 11.6 | **<0.0001** |
| UPDRS III item 19 | 2.4 ± 0.5 | 1 ± 0.7 | **<0.0001** |
| Axial score | 10.0 ± 4.4 | 4.4 ± 2.7 | **<0.0001** |
| Appendicular score | 34.9 ± 10.0 | 16.9 ± 8.9 | **<0.0001** |
| Bradykinesia score | 23.9 ± 8.06 | 10.6 ± 6.2 | **<0.0001** |
| Rigidity score | 12.3 ± 4.8 | 7.4 ± 4.5 | **<0.0001** |
| Tremor score | 5.3 ± 5.5 | 0.8 ± 1.1 | **<0.0001** |