











ORIGINAL ARTICLE

Clinical and structural brain correlates of hypomimia in early-stage Parkinson's disease

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Abstract

Background and purpose: Reduced facial expression of emotions is a very frequent symptom of Parkinson's disease (PD) and has been considered part of the motor features of the disease. However, the neural correlates of hypomimia and the relationship between hypomimia and other non-motor symptoms of PD are poorly understood.

Methods: The clinical and structural brain correlates of hypomimia were studied. For this purpose, cross-sectional data from the COPPADIS study database were used. Age, disease duration, levodopa equivalent daily dose, Unified Parkinson's Disease Rating Scale part III (UPDRS-III), severity of apathy and depression and global cognitive status were collected. At the imaging level, analyses based on gray matter volume and cortical thickness were used.

Results: After controlling for multiple confounding variables such as age or disease duration, the severity of hypomimia was shown to be indissociable from the UPDRS-III speech and bradykinesia items and was significantly related to the severity of apathy ($\beta = 0.595$; $p < 0.0001$). At the level of neural correlates, hypomimia was related to motor regions brodmann area 8 (BA 8) and to multiple fronto-temporo-parietal regions involved in the decoding, recognition and production of facial expression of emotions.

Conclusion: Reduced facial expressivity in PD is related to the severity of symptoms of apathy and is mediated by the dysfunction of brain systems involved in motor control and in the recognition, integration and expression of emotions. Therefore, hypomimia in PD may be conceptualized not exclusively as a motor symptom but as a consequence of a multidimensional deficit leading to a symptom where motor and non-motor aspects converge.

KEYWORDS

hypomimia, neural, neuroimage, non-motor symptoms, Parkinson's disease

INTRODUCTION

Hypomimia, a reduced degree of facial expression for spontaneous and emotional movements, is a classical and very frequent symptom of Parkinson's disease (PD) [1, 2]. Lack of or reduced facial expression of emotions has a substantial impact on patients, partners and caregivers. For all of them, hypomimia arises as a stigma that significantly impacts quality of life [3], social wellbeing and interpersonal relationships, and that gradually increases social isolation [2, 4, 5].

Hypomimia is typically considered to be a form of bradykinesia of the facial muscles and to be primarily mediated by motor basal ganglia dysfunction [4]. Accordingly, hypomimia is rated as a motor sign for which its gradation is associated with the severity of the disease [6, 7]. Therefore, hypomimia can improve with dopamine-replacement treatment, an effect possibly mirroring the changes observed in axial motor symptoms induced by treatment with levodopa [8]. However, the evolutionary particularities of human facial expression and the multiplicity of functions of facial muscles, compared to limb muscles, make facial muscle innervation and control unique [9, 10]. The mechanisms involved in involuntary

and voluntary facial expression of emotions are not comparable to other systems of motor control. Moreover, in contrast to limb bradykinesia, it has been suggested that hypomimia is not usually asymmetrical, although some studies found that the most expressive face side is usually the less affected body side in terms of bradykinesia [6, 11, 12].

Thus, the question arises as to whether hypomimia is a pure motor disorder [11, 13] or if, in contrast, this symptom is a consequence of a more complex set of defective neural, cognitive and affective mechanisms. Preliminary evidence supporting hypomimia as a non-motor symptom of PD comes from studies associating hypomimia to impairment in facial emotion recognition [14, 15]. Facial emotion recognition deficits are more pronounced in PD patients with apathy [16] and in PD patients with cognitive impairment [17]. Moreover, in PD there is also an association between impairment in posing facial expressions of emotions and deficits in facial emotion recognition [13]. A recent study showed that patients with hypomimia had more severe apathy and axial signs than patients without hypomimia, but that they did not differ in terms of depression, anxiety and neuropsychological performance [8].

Less is known about the association between hypomimia and cognition in PD. One recent study in a relatively small sample of patients observed that the severity of hypomimia was positively correlated with axial symptoms and negatively correlated with cognitive performance [11]. Similar results indicating that more severe hypomimia was associated with worse cognitive scores independently of motor severity were obtained using a larger sample of untreated PD patients from the Parkinson's Progression Markers Initiative [18].

In the present study, associations between hypomimia, motor symptoms, apathy and cognition in a large observational cohort study of already treated non-demented PD patients were examined, and the neural correlates of the severity of hypomimia as assessed by multimodal magnetic resonance imaging (MRI) acquisitions were further assessed.

MATERIALS AND METHODS

Sample and assessments

Cross-sectional data from the Cohort of Patients with Parkinson's Disease in Spain (COPPADIS) study (database released in May 2019) were used [19]. Details regarding the methods used in the COPPADIS study can be found in the original publications [19]. A total of 506 PD participants were included for whom the following variables were available: age, disease duration, levodopa equivalent daily dose (LEDD), the Unified Parkinson's Disease Rating Scale part III (UPDRS-III) [7], the apathy item of the Neuropsychiatric Inventory (NPI) [20], Beck's Depression Inventory [21] and the Parkinson's Disease—Cognitive Rating Scale (PD-CRS) [22].

The severity of hypomimia was rated through the UPDRS-III facial expression item which grades eye-blink frequency, masked facies or loss of facial expression, spontaneous smiling, and parting of lips from 0, normal, to 1, slight; 2, mild; 3, moderate; and 4, severe. Global motor status was rated with all the components of the UPDRS-III. To further explore the association between hypomimia and other clinical and imaging parameters controlling the effect of other motor symptoms, a secondary motor score derived from the total Movement Disorder Society UPDRS-III score minus the facial expression score was also computed. The bradykinesia subscore of the UPDRS was also computed (sum of items 2, 4–9 and 14) [23].

The severity of apathetic symptoms and the severity of depressive symptoms were respectively rated with the apathy item of the NPI and Beck's Depression Inventory. Global cognitive status was rated with the PD-CRS. Cut-off scores for mild cognitive impairment (PD-MCI) and for dementia (PDD) were used to identify participants with normal cognition, PD-MCI or PDD [22, 24]. The frontal-subcortical and posterior-cortical PD-CRS summary scores and the scores from performance in each PD-CRS subtest were also collected.

Statistical analyses

First, simple correlational analyses were performed to explore the association between hypomimia and age, disease duration, LEDD, UPDRS-III scores, depressive symptoms, apathy and cognitive performance. To more deeply address the association between hypomimia and all the other UPDRS-III items, a univariate regression analysis was first performed between the facial expression item and the total UPDRS-III score minus facial expression, using disease duration and LEDD as covariates. In a second step, to better disentangle the specific items of the UPDRS-III associated with hypomimia, the data were subjected to a second univariate regression analysis including all the UPDRS-III items as fixed factors and using disease duration, age and LEDD as covariates.

To explore the association between hypomimia and other clinical variables, separate univariate regression analyses were conducted between hypomimia and depression, apathy and cognitive status, using as covariates all the UPDRS-III items minus those that appeared to be indissociable from hypomimia in the previous analysis. Finally, a binary logistic regression analysis was performed with participants classified as with and without clinically relevant apathetic symptoms (NPI apathy ≥ 2) [25] and hypomimia, age, disease duration, LEDD and UPDRS-III items minus those involved in hypomimia as predictors. Given that previous studies have supported that asymmetry of facial expression occurs in PD and is related to asymmetry of motor impairment [12, 13], the analyses were repeated after controlling for motor laterality. For these analyses, the SPSS statistical package was used, and $p < 0.05$ was considered significant.

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Neuroimaging add-on study

A subset of 132 patients had T1-MRI available. These data were used to explore the structural neuroimaging correlates of facial expression in PD. Details about the image acquisition protocols in the COPPADIS cohort have been reported previously [19].

Regarding neuroimaging preprocessing, two procedures were applied to quantify gray matter integrity. On the one hand, to assess cortical atrophy, a standard surface-based cortical thickness (Cth) pipeline using FreeSurfer 6.0 was used to obtain vertexwise Cth data for each patient. These Cth maps were normalized to a standard fsaverage space and smoothed using a Gaussian kernel of 15 mm full-width at half-maximum (FWHM).

On the other hand, subcortical differences in gray matter volume (GMV) were assessed by a standard GMV voxel-based morphometry pipeline using the SPM12 toolbox. Briefly, voxelwise GMV maps were obtained by probabilistic tissue-based segmentation normalized to the standard MNI space and smoothed using an isotropic kernel of 8 mm FWHM. This voxel-based morphometry analysis was restricted to subcortical regions.

Neuroimaging regression analyses were performed to study the GMV and Cth correlates of facial expression, using age as a nuisance covariate. To do this, a global map was first obtained from the regression using the UPDRS-III total score. For the latter neuroimaging analyses, only the set of clusters surviving $p < 0.05$ and multiple comparison correction (Monte Carlo with 10,000 repeats for Cth and small-volume random field theory for GMV) were considered significant.

The sets of GMV and Cth maps obtained were then used to explore the specific association between hypomimia and distinct clusters of GMV and Cth. Thus, to delimit those clusters in association with hypomimia without the collinear contribution of the other UPDRS-III items, LEDD or disease duration, a univariate regression analysis was conducted using hypomimia and related UPDRS-III items as dependent variables and all the other UPDRS-III scores, age, disease duration and LEDD as covariates.

RESULTS

The sample was composed of 506 PD participants from the COPPADIS study with mean age 62.3 ± 9.1 years, mean disease duration 5.5 ± 4.3 years and mean UPDRS-III = 23.4 ± 11.4 . Table 1 shows the sociodemographic and clinical characteristics of the sample. Bradykinesia was found to be more severe on the left side ($t(506) = -2.6$; $p = 0.008$). In the sample, according to the PD-CRS total score, 71.1% ($n = 360$) were cognitively preserved, 22.1% ($n = 112$) were classified as PD-MCI and 6.7% ($n = 34$) were classified as PDD.

TABLE 1 Clinical and sociodemographic characteristics of the sample

	Mean (SD)	Range
Age (years)	62.2 (9.1)	30–75
Disease duration	5.5 (4.3)	0–30
UPDRS-III total	23.4 (11.4)	2–78
Hypomimia	1.2 (0.7)	0–3
Bradykinesia	8.9 (5.1)	0–28
Left side	4.6 (3.2)	0–14
Right side	4.2 (2.9)	0–14
LEDD	576.4 (418.5)	0–2220
BDI-II	9.5 (7.3)	0–37
NPI–Apathy	1.3 (2.3)	0–12
PD-CRS total	91.1 (16.3)	44–141
Frontal-subcortical	63.6 (14.8)	25–111
Posterior-cortical	27.4 (3.4)	11–38

Abbreviations: BDI-II, Beck's Depression Inventory; LEDD, levodopa equivalent daily dose; NPI, Neuropsychiatric Inventory; PD-CRS, Parkinson's Disease–Cognitive Rating Scale; UPDRS-III, Unified Parkinson's Disease Rating Scale part III.

In a simple correlational analysis, the direct association between hypomimia and age, disease duration, LEDD, UPDRS-III scores, depressive symptoms, apathy and cognitive performance was explored. As expected, associations were found between hypomimia and disease duration ($r = 0.167$; $p < 0.0002$), LEDD ($r = 0.223$; $p < 0.0001$) and UPDRS-III (hypomimia item excluded) ($r = 0.516$; $p < 0.0001$). Significant associations were also found between hypomimia and severity of depressive symptoms ($r = 0.139$; $p = 0.002$), apathy ($r = 0.169$; $p < 0.0001$) and cognitive status as measured with the PD-CRS total score ($r = -0.233$; $p < 0.0001$).

Focusing on the exploration of the association between hypomimia and other motor symptoms, a univariate regression analysis was performed using disease duration and LEDD as covariates. This first step showed a moderate association between hypomimia and UPDRS-III minus hypomimia score ($r^2 = 0.349$; $F_{(1,53)} = 3.83$; $p < 0.0001$).

In a second step, to better disentangle the specific items of the UPDRS-III associated with hypomimia, the data were subjected to a second univariate regression analysis including all the UPDRS-III items as fixed factors and using disease duration, age and LEDD as covariates. This analysis showed that the main UPDRS-III items associated with hypomimia were speech ($F_{(1,53)} = 20.05$; $p < 0.0001$) and bradykinesia-hypokinesia ($F_{(1,53)} = 4.01$; $p = 0.003$). Thus, these two factors (speech and bradykinesia-hypokinesia) were assumed not as confounders but as inherent to hypomimia.

Thirdly, the association between hypomimia and other clinical symptoms that appeared as directly correlated in the simple correlational analysis was explored. A separate univariate regression analysis was conducted between hypomimia and depression, apathy and cognitive status, using as covariates all the UPDRS-III items minus those assumed to be hypomimia or part of them (speech and bradykinesia-hypokinesia), disease duration and LEDD. This analysis showed an absence of association between depression, cognitive status and hypomimia, but a significant, albeit relatively low, association between hypomimia and apathy severity ($F_{(1,53)} = 2.01$; $p = 0.043$). Following this finding, a binary logistic regression analysis was performed with participants classified as presenting with and without clinically relevant apathetic symptoms (NPI apathy severity ≥ 2) and hypomimia, age, disease duration, LEDD and UPDRS-III items minus those involved in hypomimia as predictors. This analysis showed a strong association between hypomimia and clinically relevant apathy ($\beta = 0.595$; $p < 0.0001$). These associations remained significant after controlling for motor asymmetry. To further explore the possible relationship between the severity of hypomimia and the laterality of bradykinesia, another binary logistic regression analysis was performed. No significant relationship was found between laterality of bradykinesia and severity of hypomimia.

In the neuroimaging analysis, a whole series of cortical and GMV maps was obtained. The obtained maps represented the main neuro-anatomical correlates of the whole UPDRS-III scores. Then, to delimit those clusters in association with hypomimia without the collinear contribution of the other UPDRS-III items, LEDD or disease duration, a univariate regression analysis was conducted using hypomimia,

speech and bradykinesia-hypokinesia as independent variables of interest and all the other UPDRS-III scores, age, disease duration and LEDD as covariates. This analysis showed an independent association of hypomimia and lower Cth in the left rostral middle frontal cortex ($r = -0.257$; $p = 0.004$), in the left superior frontal gyrus ($r = -0.208$; $p = 0.020$), in the left superior parietal gyrus ($r = -0.250$; $p = 0.005$), left middle temporal cortex ($r = -0.201$; $p = 0.025$), the right rostral middle frontal gyrus ($r = -0.212$; $p = 0.018$) and the right inferior parietal gyrus ($r = -0.210$; $p = 0.019$). Equivalent associations were found between all these brain regions and the other UPDRS-III items that appeared as contributors to hypomimia such as speech and bradykinesia-hypokinesia. Specifically, a significant association was found between the left ($r = 0.317$; $p < 0.001$) and right ($r = 0.258$; $p = 0.004$) rostral middle frontal gyrus thickness and the bradykinesia-hypokinesia score. Regarding the analysis of subcortical GMV, the only region that showed a significant correlation with hypomimia was the posterior portion of the mesencephalon ($r = -0.192$; $p = 0.028$). The neuroimaging correlates of hypomimia were not significantly altered after controlling for motor laterality (Figure 1).

DISCUSSION

The main results of the present study indicate a relationship of hypomimia with few and specific motor and non-motor symptoms of PD. The correlates of hypomimia with other motor symptoms, neuropsychiatric symptoms, cognitive performance as well as neuroimaging data were addressed in a prospective sample of PD patients in the early stages. Although hypomimia represents a very frequent symptom of PD, there are few studies that have explored the clinical and neural correlates of this symptom in a representative sample.

The results highlight different facets that deserve to be considered. First, as anticipated, the severity of hypomimia appeared inseparable from the severity of other motor symptoms. It is to be

expected that patients do not present a single motor symptom but a combination of these symptoms whose severity is related. In this sense, collinearity between motor symptoms will always be a common finding. Nevertheless, our results indicate that, regardless of age, disease duration and pharmacological treatment, the severity of hypomimia specifically correlates with a few specific motor items of the UPDRS-III, namely speech and bradykinesia-hypokinesia. This relationship was not considered to be the result of a collinearity effect since it is maintained by controlling for the effect of all the other motor symptoms. In contrast, it is considered that it may reflect the expression of the same cluster of symptoms whose causal mechanisms could be the same. Secondly, no relationship between the severity of hypomimia and the severity of anxiety or cognitive impairment was found. Moreover, the clinical and neuroimaging correlates of hypomimia were not significantly influenced by motor laterality. In contrast, a clear relationship between the severity of hypomimia and the severity of apathy was observed, as well as between the severity of hypomimia and the frequency with which patients express apathy in a clinically significant range. These results do not allow the directionality of this relationship to be clarified. Previous studies have shown a relationship between predominantly rigid-akinetic phenotypes of PD and a higher prevalence of apathy [26, 27]. In this sense, it could be considered that patients with more rigid-akinetic symptomatology and who therefore score higher on bradykinesia-hypokinesia will have not only more severe hypomimia but also more severe apathy.

Another possibility has to do with the effect that apathy itself could have as a modulator of the intensity of facial expression. Apathy in PD is a common and multidimensional symptom characterized by a decrease in goal-oriented behaviors, often accompanied by emotional flattening, loss of initiative and reactivity, and decreased self-activation. As an accompanying feature, several studies have pointed to disturbances of facial expression in patients with apathy, with lack of emotional expression being the most representative feature. Interestingly, facial emotion recognition is also significantly

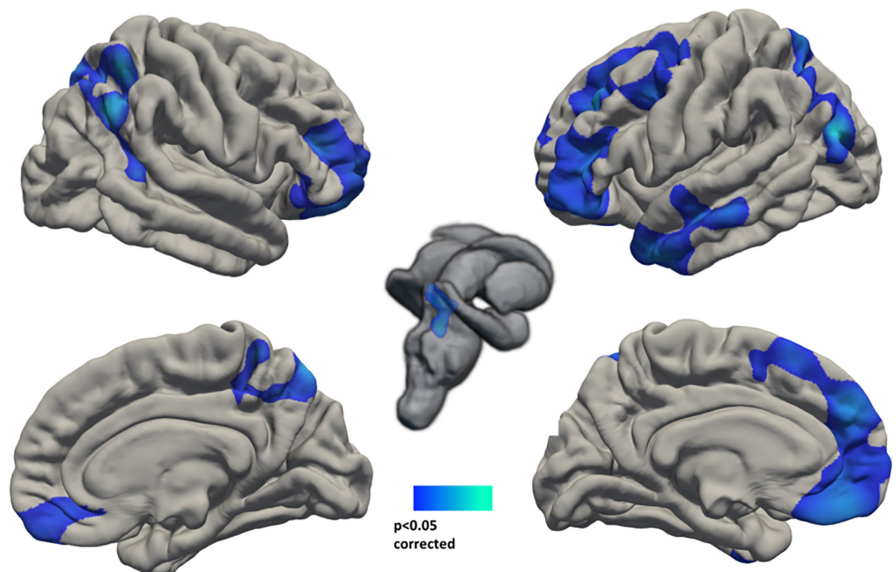


FIGURE 1 Regions exhibiting a significant pattern of cortical thinning and reduced subcortical gray matter volume in association with hypomimia

impaired in PD with isolated apathy compared to non-apathetic patients [28]. Taken together, these data point to the possible involvement of mechanisms and processes related to the expression and recognition of facial emotions in the genesis of hypomimia and related apathetic symptoms in PD.

From a neuroimaging perspective, with the exception of the middle frontal gyrus at the intersection with the precentral gyrus forming the frontal eye fields (BA 8), the regions that appear most closely related to the severity of hypomimia were not regions that play a central role in motor control. All the other fronto-temporo-parietal regions highlighted in the analysis are known to participate both in the recognition and production of facial expressions of emotions [29, 30]. Specifically, the middle and superior frontal cortex, and proximal territories such as the dorsal-lateral prefrontal cortex and the frontal pole, appeared previously associated with the expression and imitation of different types of facial expressions. Similarly, superior parietal and middle temporal regions strongly contribute to decoding and processing facial expressions [29, 30]. In this sense, it would be interesting to explore the role of these structures in the context of hypomimia associated with PD in studies based on dynamic facial expression and recognition processes, and not only in a static context as in the present study.

As limitations of the study, it should be noted that it is a cross-sectional study that does not allow conclusions to be drawn regarding the possible causal relationship between hypomimia and the risk of cognitive impairment. In this sense, longitudinal studies are needed to answer this question. A main limitation of this study is the use of a single-item-based scoring of hypomimia and apathy. Future work using more comprehensive scales should delve into the characterization of their subdomains. Finally, it is evident that some of the associations found at the level of correlation analysis are weak and their replication deserves to be taken into account in future studies.

Taken together, these results confirm that, in addition to being a rigid-akinetic symptom, hypomimia in PD may be partly mediated by the dysfunction of brain systems involved in the recognition, integration and expression of emotions. Consequently, hypomimia in PD may be conceptualized not exclusively as a motor symptom but as a consequence of a multidimensional deficit involving motor-action control deficits and dysfunction of high-order cognitive processes related to the expression and recognition of emotions. Therefore, the mechanisms participating in the development of hypomimia are partially overlapping with those contributing to the expression and recognition of emotion and mood, providing a biologically plausible explanation regarding the association between hypomimia and apathy in PD. Further prospective and longitudinal research should explore whether hypomimia should be taken as an early indicator of apathy in PD.

AUTHOR CONTRIBUTIONS

Frederic Sampedro: Data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); validation (equal); visualization (equal); writing – original draft (equal); writing – review

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The protocol and the statistical analysis plan are available on request. De-identified participant data are not available for legal and ethical reasons.

ETHICAL APPROVAL

All procedures were performed in accordance with the standards of the Ethics Committee at each study site, and in accordance with the 1964 Declaration of Helsinki and its later amendments. For this study, approval was received from the Comité de Ética de la Investigación Clínica de Galicia from Spain (2014/534; 02/DEC/2014). Written informed consent from all participants in this study were obtained before the start of the study. COPPADIS-2015 was classified by the AEMPS (Agencia Española del Medicamento y Productos Sanitarios) as a post-authorization prospective follow-up study with the code COH-PAK-2014-01.

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REFERENCES

- Goetz CG. The history of Parkinson's disease: early clinical descriptions and neurological therapies. *Cold Spring Harb Perspect Med*. 2011;1:a008862.
- Jankovic J. Parkinson's disease: clinical features and diagnosis. *J Neurol Neurosurg Psychiatry*. 2008;79:368-376.
- Ma HI, Gunnery SD, Stevenson MT, Saint-Hilaire M, Thomas CA, Tickle-Degnen L. Experienced facial masking indirectly compromises quality of life through stigmatization of women and men with Parkinson's disease. *Stigma Health*. 2019;4:462-472.
- Bologna M, Fabbrini G, Marsili L, Defazio G, Thompson PD, Berardelli A. Facial bradykinesia. *J Neurol Neurosurg Psychiatry*. 2013;84:681-685.
- 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.
- Fereshtehnejad SM, Skogar O, Lökk 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.
- Goetz CG, Tilley BC, Shaftman SR, et al. Movement Disorder Society-sponsored revision of the unified Parkinson's disease rating scale (MDS-UPDRS): scale presentation and clinimetric testing results. *Mov Disord*. 2008;23:2129-2170.
- Ricciardi L, De Angelis A, Marsili L, et al. Hypomimia in Parkinson's disease: an axial sign responsive to levodopa. *Eur J Neurol*. 2020;27:2422-2429.
- Cattaneo L, Pavesi G. The facial motor system. *Neurosci Biobehav Rev*. 2014;38:135-159.
- Erickson K, Schulkin J. Facial expressions of emotion: a cognitive neuroscience perspective. *Brain Cogn*. 2003;52:52-60.
- Maycas-Cepeda T, Lopez-Ruiz P, Feliz-Feliz C, et al. Hypomimia in Parkinson's disease: what is it telling us? *Front Neurol*. 2020;11:603582.
- Ricciardi L, Visco-Comandini F, Erro R, et al. Emotional facedness in Parkinson's disease. *J Neural Transm (Vienna)*. 2018;125:1819-1827.
- 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.
- Baggio HC, Segura B, Ibarretxe-Bilbao N, et al. Structural correlates of facial emotion recognition deficits in Parkinson's disease patients. *Neuropsychologia*. 2012;50:2121-2128.
- Jacobs DH, Shuren J, Bowers D, Heilman KM. Emotional facial imagery, perception, and expression in Parkinson's disease. *Neurology*. 1995;45:1696-1702.
- Martinez-Corral M, Pagonabarraga J, Llebaria G, et al. Facial emotion recognition impairment in patients with Parkinson's disease and isolated apathy. *Parkinsons Dis*. 2010;2010:930627.

17. Argaud S, Verin M, Sauleau P, Grandjean D. Facial emotion recognition in Parkinson's disease: a review and new hypotheses. *Mov Disord*. 2018;33:554-567.
18. Gasca-Salas C, Urso D. Association between hypomimia and mild cognitive impairment in de novo Parkinson's disease patients. *Can J Neurol Sci*. 2020;47:855-857.
19. Santos-Garcia D, Mir P, Cubo E, et al. COPPADIS-2015 (Cohort of patients with Parkinson's Disease in Spain, 2015), a global—clinical evaluations, serum biomarkers, genetic studies and neuroimaging—prospective, multicenter, non-interventional, long-term study on Parkinson's disease progression. *BMC Neurol*. 2016;16:26.
20. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The neuropsychiatric inventory: comprehensive assessment of psychopathology in dementia. *Neurology*. 1994;44:2308-2314.
21. Schrag A, Barone P, Brown RG, et al. Depression rating scales in Parkinson's disease: critique and recommendations. *Mov Disord*. 2007;22:1077-1092.
22. Pagonabarraga J, Kulisevsky J, Llebaria G, Garcia-Sanchez C, Pascual-Sedano B, Gironell A. Parkinson's disease-cognitive rating scale: a new cognitive scale specific for Parkinson's disease. *Mov Disord*. 2008;23:998-1005.
23. Li X, Xing Y, Martin-Bastida A, Piccini P, Auer DP. Patterns of grey matter loss associated with motor subscores in early Parkinson's disease. *Neuroimage Clin*. 2018;17:498-504.
24. Fernandez-Bobadilla R, Martinez-Horta S, Marin-Lahoz J, Horta-Barba A, Pagonabarraga J, Kulisevsky J. Development and validation of an alternative version of the Parkinson's disease-cognitive rating scale (PD-CRS). *Parkinsonism Relat Disord*. 2017;43:73-77.
25. Kulisevsky J, Pagonabarraga J, Pascual-Sedano B, Garcia-Sanchez C, Gironell A, Trapecio Group S. Prevalence and correlates of neuropsychiatric symptoms in Parkinson's disease without dementia. *Mov Disord*. 2008;23:1889-1896.
26. Kann SJ, Chang C, Manza P, Leung HC. Akinetic rigid symptoms are associated with decline in a cortical motor network in Parkinson's disease. *NPJ Parkinsons Dis*. 2020;6:19.
27. Moretti R, Torre P, Antonello RM, et al. Apathy: a complex symptom specific to the clinical pattern of presentation of Parkinson's disease? *Am J Alzheimers Dis Other Demen*. 2012;27:196-201.
28. Robert G, Le Jeune F, Dondaine T, et al. Apathy and impaired emotional facial recognition networks overlap in Parkinson's disease: a PET study with conjunction analyses. *J Neurol Neurosurg Psychiatry*. 2014;85:1153-1158.
29. Sarkheil P, Goebel R, Schneider F, Mathiak K. Emotion unfolded by motion: a role for parietal lobe in decoding dynamic facial expressions. *Soc Cogn Affect Neurosci*. 2013;8:950-957.
30. Kitada R, Okamoto Y, Sasaki AT, et al. Early visual experience and the recognition of basic facial expressions: involvement of the middle temporal and inferior frontal gyri during haptic identification by the early blind. *Front Hum Neurosci*. 2013;7:7.

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PD: Parkinson's Disease