Title

Clinical and neuroimaging correlates of progression of mild parkinsonian signs in community-dwelling older adults

Permalink

https://escholarship.org/uc/item/1tc2x11q

Authors

Miller-Patterson, Cameron
Han, Jennifer
Yaffe, Kristine
et al.

Publication Date

2020-06-01

DOI

10.1016/j.parkreldis.2020.05.023

Peer reviewed

Clinical and neuroimaging correlates of progression of mild parkinsonian signs in community-dwelling older adults

Cameron Miller-Patterson, MD[1,*], **Jennifer Han, MD**[1], **Kristine Yaffe, MD**[2], **Andrea L Rosso, PhD, MPH**[3], **Lenore J Launer, PhD**[4], **Stephen B Kritchevsky, PhD**[5], **Robert M Boudreau, PhD**[3], **Caterina Rosano, MD, MPH**[3]

[1]University of Pittsburgh School of Medicine, Department of Neurology, 3550 Terrace St, Pittsburgh, PA 15213, USA

[2]University of California San Francisco School of Medicine, Department of Psychiatry, Neurology, and Epidemiology, 533 Parnassus Ave, San Francso, CA 94143, USA

[3]University of Pittsburgh School of Public Health, Department of Epidemiology, 130 De Soto St, Pittsburgh, PA 15213, USA

[4]National Institutes of Health, National Institute on Aging, 251 Bayview Blvd, Bethesda, MD 21224, USA

[5]Wake Forest University School of Medicine, Stricht Center for Healthy Aging and Alzheimer's Prevention, Winston-Salem, NC, USA

Abstract

Introduction—Mild parkinsonian signs (MPS) are associated with morbidity. Identification of MPS progression markers may be vital for preventive management, yet has not been pursued. This study aimed to ascertain clinical/neuroimaging features predictive of MPS progression.

Methods—205 participants in the Health ABC Study were included. MPS was defined using published guidelines. MPS progression was evaluated by determining UPDRS-III change between baseline and follow-up 2 years later. Standard brain MRI and DTI were obtained at baseline. Correlation coefficients between demographics, vascular risk factors, imaging markers, and UPDRS-III change were adjusted for follow-up time. Linear regression was used to adjust for possible confounders in the relationship between imaging markers and MPS progression.

Results—30% of participants had baseline MPS. Demographics and risk factors did not differ significantly between participants with MPS (MPS+) and without MPS (MPS−). Mean follow-up time was 3.8±0.8 years. Older age, male gender, diabetes were associated with faster rate of UPDRS-III change in MPS− but not MPS+ participants. Among MPS− participants, the only imaging marker associated with faster UPDRS-III progression was higher gray matter mean diffusivity (MD), widespread in various cortico-subcortical bihemispheric regions, independent of

*Corresponding Author, millerpatterson@gmail.com.

age, gender, diabetes. No imaging features were associated with UPDRS-III change among MPS+ participants.

Conclusions—Lower gray matter integrity predicted MPS progression in those who did not have baseline MPS. Microstructural imaging may capture early changes related to MPS development, prior to macrostructural change. Any future management promoting gray matter preservation may inhibit MPS development.

Keywords

diffusion tensor imaging; mild parkinsonian signs; mild parkinsonism; parkinsonian-like signs; Parkinson's disease

Introduction

Mild parkinsonian signs (MPS), also known as "parkinsonian-like signs" or "mild parkinsonism," are very common among elderly individuals and include bradykinesia, rigidity, tremor, and gait disturbance. Estimates of MPS prevalence range from 30% to 40%, with higher prevalence in older age [1]. However, MPS are not benign and are associated with an increased risk of dementia [1], depression [2], disability [3], and mortality [4]. The relationship between MPS and Parkinson's disease (PD) requires further investigation. While individuals with MPS are likely at higher risk for PD [5] [6], such that these signs represent prodromal disease in certain cases, they are not necessarily sensitive or specific for a future diagnosis [5].

Neuropathologic correlates of MPS have previously been evaluated. There appear to be complex contributions from cerebral microvascular disease [7], age-related degeneration of the nigrostriatal pathway [8], and other subclinical neurodegenerative processes such as Alzheimer's-type pathology [9]. However, while clinical factors such as hyposmia [10] and cardiovascular disease [11] have been associated with MPS progression, structural brain changes that contribute to progression have not been evaluated. Elucidation of such changes may provide a better understanding of the mechanisms underlying MPS and may be important for preventive management.

Since conventional T_1- and T_2-weighted MRI techniques have suggested distinct macrostructural changes associated with parkinsonian signs including bradykinesia and gait disturbance [12], these imaging modalities may provide biomarkers for MPS progression. However, information provided by these techniques is limited; diffusion tensor imaging (DTI) may additionally reveal an association between microstructural tissue damage and change in MPS. Our goal was to determine the relationship between neuroimaging markers and MPS progression, as well as between other clinical characteristics and MPS progression, over at least a 2-year time-frame.

Materials and Methods

Study Population

All participants were part of the Health, Aging, and Body Composition (Health ABC) ancillary study Healthy Brain Project (HBP), which was approved by the University of Pittsburgh Institutional Review Board. Inclusion criteria included ability to walk without an assistive device, ability to complete a 6-meter walk test, and eligibility to obtain a brain MRI. Written informed consent was obtained from all participants.

Of 1527 participants enrolled in Health ABC between 1996 and 1997 at the Pittsburgh site, 819 were alive and eligible for the ancillary study between 2006 and 2008. Of those, 315 met eligibility for an MRI at 3 Tesla (3T MRI), while 205 had complete Unified Parkinson's Disease Rating Scale (UPDRS) data both at baseline and at a second time-point at least 2 years after baseline, were not taking any medications that induce or inhibit parkinsonism, and did not have a diagnosis of PD or other neurologic disease at baseline or follow-up. A flowchart detailing inclusion/exclusion of participants is shown in Figure 1.

Measurement of MPS

The complete Unified Parkinson's Disease Rating Scale Part III (UPDRS-III) was used to identify bradykinesia, rigidity, tremor, and gait disturbance. MPS was considered present if an individual met the following minimum criteria on the UPDRS-III score based on protocol by Louis et al [1]: (1) 2 or more items with a score of 1, (2) 1 item with a score of 2 or more, or (3) a rest tremor score of 1. This protocol was applied both at baseline and follow-up in each participant to determine presence or absence of MPS. The total UPDRS-III score was used to quantify the severity of parkinsonian signs. MPS progression was measured as the change in UPDRS-III score between 2 time points over change in time (in years) using scores from baseline and a follow-up visit at least 2 years after the baseline visit (follow-up visits were performed annually). If a patient had multiple visits after 2 years, we used the most recent follow-up date with available UPDRS-III data to assess for MPS change. Therefore, only 1 follow-up visit was used to evaluate UPDRS-III progression since the baseline visit.

UPDRS-III subdomain scores were also calculated for participants at baseline and follow-up using the following criteria: bradykinesia score=sum of scores for UPDRS items 23–26, 31 (bradykinesia of arms/legs, body bradykinesia), rigidity score=sum of scores for UPDRS item 22 (rigidity of neck/arms/legs), tremor score=sum of scores for UPDRS items 20 and 21 (rest tremor of face/arms/legs, action tremor of arms), gait disturbance score=sum of scores for UPDRS items 28–30 (posture, gait, postural stability). Subdomain score progression was measured as the difference between the follow-up and baseline scores divided by time in years between the 2 visits.

Population Characteristics

Participants' age, gender, race, and education level were included. Cardiovascular disease and its risk factors (cholesterol, diabetes, hypertension, smoking history) were determined from participant interview and confirmed by medical record. Body mass index (BMI) was

calculated. All participants underwent the modified mini-mental status exam (3MS) [13]. Muscle strength was quantified by isokinetic dynamometer (Kincom) with peak torque as a summary measure.

MRI Techniques

Acquisition and processing protocols have been published [14]. Gray matter, white matter, and cerebrospinal fluid were segmented on skull-stripped T_1-weighted images in native anatomical space [15], and volumes were estimated by summing voxels classified as these tissue types. Total intracranial volume was computed as the volume inside the inner skull. The total gray matter volume (GMv) was adjusted for total intracranial volume, thereby representing a measure of gray matter atrophy. White matter hyperintensity volume (WMHv) was obtained from T_2-weighted fluid-attenuated inversion recovery images using an automated region-growing method [16] and the Johns Hopkins University Atlas [17], and normalized by brain volume. The fractional anisotropy (FA), which indicates the degree to which water molecule diffusion is unidirectional and is a marker of tract integrity, was measured in normal-appearing white matter. The mean diffusivity (MD), which indicates the magnitude of water molecule motion and is a marker of structural damage, was measured in gray matter. A neuroradiologist examined each MRI for abnormalities. Regions-of-interest were labeled using previously-published methods [18], and specific regions were chosen for analysis (see below under Statistical Analysis) based on findings of prior publications correlating particular anatomic brain regions with gait impairment in subjects with PD [19], subjects with small vessel disease [20], and community-dwelling older adults [12, 21].

Statistical Analysis

Pearson or Spearman correlations were used as appropriate to evaluate relationships between population characteristics, risk factors, imaging markers, and annualized UPDRS-III score change adjusted for follow-up time. Once an association between MPS and neuroimaging abnormalities was discovered, analysis was repeated after stratifying for presence of baseline MPS. Stepwise linear regression was used to adjust for possible confounders in the relationship between MPS progression and imaging measures. Coefficients were adjusted for demographics and for variables bivariately associated with UPDRS-III change either in the full cohort or an MPS subgroup. In order to further evaluate the relationship between MPS progression and neuroimaging abnormalities, stepwise linear regression was repeated by region-of-interest adjusted for demographics and covariates. SPSS version 22.0 was used (IBM-SPSS Inc, Chicago, IL).

Results

Cohort characteristics are summarized in Table 1. In this sample of 205 participants, MPS were present (MPS+) in 62 participants (30%) at the time of baseline testing. The overall mean age at time of MRI was 82.7±2.6 years, and it did not differ significantly between MPS+ and MPS− participants. Other demographic features were also similar between the 2 groups. Risk factor rates including those for cardiovascular disease, diabetes, hypertension, and smoking status were not significantly different, nor were quadriceps strength or 3MS scores.

The mean UPDRS-III score at baseline for the entire cohort was 1.5±2.8. Mean follow-up time was 3.8±0.8 years for the entire cohort. The mean rate of UPDRS-III change was 0.6±1.0 points per year for a mean total of 2.29 points from baseline to follow-up, and this change was significantly higher in the MPS− group compared to the MPS+ group. Baseline bradykinesia, rigidity, tremor, gait disturbance scores for the full cohort were 0.83±2.03, 0.05±0.50, 0.14±0.50, 0.24±0.70, respectively. Mean rates of bradykinesia, rigidity, tremor, gait disturbance change were 0.01±0.67, 0.05±0.27, 0.25±0.49, 0.12±0.38 points per year, respectively. While 205 participants had a 3T MRI brain, only 185 had DTI (FA and MD) performed. As indicated in Table 1, the proportions of participants with and without MPS in this cohort were similar to those seen in the full cohort. On baseline MRI, MPS− participants had higher GMv and FA than MPS+ participants.

Bivariate analyses for the full cohort as well as each MPS subgroup are shown in Table 2. In the full cohort, older age, male gender, and lower baseline UPDRS-III score were significantly associated with a higher increase in UPDRS-III score during follow-up. Male gender and presence of diabetes were associated with faster increase in UPDRS-III within the MPS− group but not the MPS+ group. Other factors related to cardiovascular disease, including total cholesterol, high density lipoprotein, and systolic blood pressure, were not significantly associated with UPDRS-III change in the full cohort (data not shown). Conversely, lower muscle strength was associated with faster increase in UPDRS-III within the MPS+ group but not the MPS− group. Lower baseline UPDRS-III was correlated with a greater change in UPDRS-III score in the full cohort and MPS+ group. Figure 2 shows that average change in UPDRS score was greater for MPS− participants compared to MPS+ participants, and even larger for males compared to females. As shown in Supplementary Figure, while nearly all MPS− participants' UPDRS-III scores worsened or remained unchanged at follow-up, the UPDRS-III score for a portion of MPS+ participants improved; 73 MPS− participants met criteria for MPS at follow-up, while 14 MPS+ participants no longer met criteria.

As shown in Table 2, lower GMv and higher MD were significantly associated with faster rate of UPDRS-III increase in the full cohort, while WMHv and FA were not. Stratification by baseline MPS status revealed the imaging findings were significant in the MPS− group but not the MPS+ group. Also shown in Table 2, a significant association between MD and UPDRS-III progression remained when adjusted for age, gender, and diabetes status in the MPS− group, while the association between GMv and UPDRS-III progression did not remain significant. The adjusted association with MD was driven by several brain regions, included in Supplementary Table. Standardized coefficients >0.30 were seen for the bilateral precentral gyri, right superior frontal gyrus, right middle frontal gyrus, left supplementary motor area, and left inferior parietal gyrus. A significant negative association was seen for the left putamen.

Discussion

In this study, lower gray matter integrity as measured by lower GMv and higher MD predicted progression of parkinsonian signs, particularly among those without MPS at baseline. The role of gray matter integrity in relation to MPS severity has been suggested by

a previous Health ABC cohort study, which showed that bradykinesia and gait disturbance have non-overlapping spatial distributions of focal gray matter atrophy [12]. However, while the association of UPDRS-III change with MD was robust to adjustment for covariates, the association with GMv was not. This suggests that lower gray matter integrity at the microstructural as opposed to macrostructural level is a more sensitive marker for MPS development, likely because it reflects earlier change in brain structure.

The association between neuroimaging markers of gray matter integrity and MPS progression was present only for those participants who were free of MPS at baseline. As shown in Supplementary Figure, a significant portion of UPDRS-III scores in the MPS+ group actually improved at follow-up, likely contributing to the lack of observed association in this group. This may have been due to subjectivity in the rating scale, so that it is easier to accurately distinguish absence from presence of parkinsonism (as in the MPS− group at baseline compared to follow-up) compared to subsequent small changes in parkinsonism severity. MPS may also be reversible in certain individuals, possibly due to neural plasticity [11]. A ceiling effect could have also contributed to UPDRS-III change in the MPS+ group, in that the progression of parkinsonian signs secondary to structural degeneration occurs at a faster rate earlier rather than later after the initial development of such signs. This rationale is supported by the fact that lower baseline UPDRS-III in the full cohort and MPS+ group is associated with a higher rate of UPDRS-III change, as shown in Table 2. This would parallel the clinical course of PD; in a cohort of PD patients evaluated over a 5-year time-frame, the steepest change in Movement Disorders Society UPDRS occurred within the first year [22]. Such a ceiling effect could have been compounded by the fact that participants who went on to develop PD and/or were started on medications for parkinsonism were excluded, as well as by the fact that many individuals with worsening parkinsonism who had MPS to begin with may not have returned for follow-up at all.

Our region-of-interest analyses suggest that the association between MD and UPDRS-III progression in MPS− participants has a selective spatial distribution. Involved areas included bihemispheric prefrontal regions, suggesting that increasing deficits in executive function and attention may be associated with progressive motor and gait impairment; this is consistent with what has been described in subjects with small vessel disease cross-sectionally [20]. Of note, in our prior study of community-dwelling older adults a correlation was only observed in the left hemisphere [21]. While the left prefrontal cortex has a well-established role in executive control [21], which in turn may play a role in mobility [23], lesions of the right prefrontal cortex have also been associated with poor planning [24]. We also found significant associations with bilateral supplementary motor areas, pre- and postcentral gyri, inferior parietal areas, and left thalamus. Consistent with prior research [25], this suggests that both motor and somatosensory networks play an important role in functional control of movement. Interestingly, among basal ganglia structures, no areas were positively associated with UPDRS-III change, while left putamen MD was negatively correlated with such change. A possible explanation is a floor effect, whereby a more rapid rate of neuronal cell death is seen earlier on simply due to greater volume, correlating with a more rapid progression of parkinsonism.

UPDRS-III scores also worsened more rapidly in older males and diabetics who at baseline did not have MPS. While we have previously shown that diabetes is associated with worse MD [26], the present study suggests that the relationship between MD and UPDRS-III change is independent of diabetes, as discussed above. Alternatively, since the relationship between GMv and parkinsonism progression did not remain significant after adjustment for age, gender, and diabetes, it is possible that such characteristics drive macrostructural rather than microstructural gray matter change more robustly. Risk factor modification to preserve gray matter integrity in aging adults may help to prevent MPS progression and associated morbidity. Of note, while one prior study found an association between cardiovascular disease and MPS development in MPS− participants [11], this was not observed in ours. This may be due to differing sensitivity of the criteria used to define MPS in the prior study, since the authors classified MPS as present if a participant scored 1 on 1 of 7 UPDRS-III items [11].

A significant strength of the study includes the evaluation of longitudinal UPDRS data, as most studies on MPS are limited by their cross-sectional nature. Furthermore, the inclusion of DTI measures as markers of microstructural integrity complemented standard MRI techniques. To our knowledge, only one other study has investigated DTI in MPS, which demonstrated a higher risk in subjects whose imaging showed severe loss of microstructural integrity within white matter lesions regardless of overall white matter lesion volume [7]. Notably, this study did not investigate gray matter changes. Lastly, while our study incorporated the same diagnostic protocol proposed by Louis et al [1], the entire UPDRS-III was used to evaluate participants instead of the abbreviated 10-item version that has been utilized previously [1]. Therefore, our study may have benefited from greater sensitivity in identifying MPS compared to prior ones.

There are several limitations of this study that may have impacted the results. First, individuals were recruited on a volunteer basis and were required to follow up at least 11 years after initial enrollment in Health ABC, which may have attracted a healthier cohort on average compared to the actual community-dwelling population. MRI ineligibility as well as other MRI criteria may have further excluded less healthy adults. This may have fostered selection against MPS+ participants; in prior studies, they have been older and have had more vascular risk factors compared to MPS− participants [4, 27], whereas in our study there were no significant differences in these characteristics between the 2 groups. Second, while the rater was trained in UPDRS evaluation, it is possible that assessment by a clinician with specialized movement disorders training would have led to more accurate results, and potentially the elucidation of a significant association between imaging features and progression in MPS+ participants in addition to MPS− participants. Third, it is possible that our sample size was too small to detect a significant association between UPDRS-III change and white matter abnormalities. The fact that MPS progression was not associated with white matter disease is consistent with some studies but not with others. In the wider body of literature on mobility limitations in the elderly, associations of mobility with both white matter changes [28, 29] and gray matter changes [20, 21, 25] have been reported. Fourth, many participants were lost to follow-up, resulting in the relatively small sample size in this study and a potential survivor effect. Fourth, it should also be noted that our cohort may have included participants with prodromal or undiagnosed PD. However, this would be

unlikely to significantly influence outcomes, given that the prevalence of PD is estimated to be about 2% in the population over age 80 [30]. Fifth, while participants with neurologic disease were excluded, we did not assess for presence of musculoskeletal disease, which may have confounded the evaluation for motor parkinsonism. Lastly, while this study found associations between structural brain changes and subsequent parkinsonism development, follow-up imaging was not assessed. Therefore, we did not evaluate for a correlation between progressive neurodegeneration at either the macrostructural or microstructural level and progressive parkinsonism.

In summary, lower gray matter integrity, especially at the microstructural level, may be an important prognostic biomarker for the development of MPS, which has been associated with increased morbidity and mortality in the elderly. Future studies with larger sample sizes are needed to further explore the associations we found. As gray matter loss appears to be linked to MPS development, any future management linked to gray matter preservation may have a role in prevention of MPS and its associated morbidity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

References

1. Louis ED, Tang MX, Mayeux R: Parkinsonian signs in older people in a community-based study: risk of incident dementia. Arch Neurol 2004, 61(8):1273–1276. [PubMed: 15313847]

2. Uemura Y, Wada-Isoe K, Nakashita S, Nakashima K: Depression and cognitive impairment in patients with mild parkinsonian signs. Acta Neurol Scand 2013, 128(3):153–159. [PubMed: 23397887]

3. Murray AM, Bennett DA, Mendes de Leon CF, Beckett LA, Evans DA: A longitudinal study of parkinsonism and disability in a community population of older people. J Gerontol A Biol Sci Med Sci 2004, 59(8):864–870. [PubMed: 15345740]

4. Louis ED, Tang MX, Schupf N: Mild parkinsonian signs are associated with increased risk of dementia in a prospective, population-based study of elders. Mov Disord 2010, 25(2):172–178. [PubMed: 20077482]

5. Berg D, Godau J, Seppi K, Behnke S, Liepelt-Scarfone I, Lerche S, Stockner H, Gaenslen A, Mahlknecht P, Huber H et al.: The PRIPS study: screening battery for subjects at risk for Parkinson's disease. Eur J Neurol 2013, 20(1):102–108. [PubMed: 22852790]

6. Mahlknecht P, Stockner H, Marini K, Gasperi A, Djamshidian A, Willeit P, Kiechl S, Willeit J, Rungger G, Poewe W et al.: Midbrain hyperechogenicity, hyposmia, mild parkinsonian signs and risk for incident Parkinson's disease over 10 years: A prospective population-based study. Parkinsonism Relat Disord 2020, 70:51–54. [PubMed: 31864071]

7. de Laat KF, van Norden AG, van Oudheusden LJ, van Uden IW, Norris DG, Zwiers MP, de Leeuw FE: Diffusion tensor imaging and mild parkinsonian signs in cerebral small vessel disease. Neurobiol Aging 2012, 33(9):2106–2112. [PubMed: 22000858]

8. Buchman AS, Shulman JM, Nag S, Leurgans SE, Arnold SE, Morris MC, Schneider JA, Bennett DA: Nigral pathology and parkinsonian signs in elders without Parkinson disease. Ann Neurol 2012, 71(2):258–266. [PubMed: 22367997]

9. Liu Y, Stern Y, Chun MR, Jacobs DM, Yau P, Goldman JE: Pathological correlates of extrapyramidal signs in Alzheimer's disease. Ann Neurol 1997, 41(3):368–374. [PubMed: 9066358]

10. Wilson RS, Arnold SE, Buchman AS, Tang Y, Bennett DA: Odor identification and progression of parkinsonian signs in older persons. Exp Aging Res 2008, 34(3):173–187. [PubMed: 18568978]

11. Mahoney JR, Verghese J, Holtzer R, Allali G: The evolution of mild parkinsonian signs in aging. J Neurol 2014, 261(10):1922–1928. [PubMed: 25047763]

12. Rosano C, Bennett DA, Newman AB, Venkatraman V, Yaffe K, Harris T, Kritchevsky S, Aizenstein HJ: Patterns of focal gray matter atrophy are associated with bradykinesia and gait disturbances in older adults. J Gerontol A Biol Sci Med Sci 2012, 67(9):957–962. [PubMed: 22367436]

13. Teng EL, Chui HC: The Modified Mini-Mental State (3MS) examination. J Clin Psychiatry 1987, 48(8):314–318. [PubMed: 3611032]

14. Venkatraman VK, Aizenstein HJ, Newman AB, Yaffe K, Harris T, Kritchevsky S, Ayonayon HN, Rosano C: Lower Digit Symbol Substitution Score in the Oldest Old is Related to Magnetization Transfer and Diffusion Tensor Imaging of the White Matter. Front Aging Neurosci 2011, 3:11. [PubMed: 21991255]

15. Zhang Y, Brady M, Smith S: Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm. IEEE Trans Med Imaging 2001, 20(1):45–57. [PubMed: 11293691]

16. Wu M, Rosano C, Butters M, Whyte E, Nable M, Crooks R, Meltzer CC, Reynolds CF 3rd, Aizenstein HJ: A fully automated method for quantifying and localizing white matter hyperintensities on MR images. Psychiatry Res 2006, 148(2–3):133–142. [PubMed: 17097277]

17. Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, Watkins KE, Ciccarelli O, Cader MZ, Matthews PM et al.: Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. Neuroimage 2006, 31(4):1487–1505. [PubMed: 16624579]

18. Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, Mazoyer B, Joliot M: Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage 2002, 15(1):273–289. [PubMed: 11771995]

19. Taylor KI, Sambataro F, Boess F, Bertolino A, Dukart J: Progressive Decline in Gray and White Matter Integrity in de novo Parkinson's Disease: An Analysis of Longitudinal Parkinson Progression Markers Initiative Diffusion Tensor Imaging Data. Front Aging Neurosci 2018, 10:318. [PubMed: 30349475]

20. de Laat KF, Reid AT, Grim DC, Evans AC, Kotter R, van Norden AG, de Leeuw FE: Cortical thickness is associated with gait disturbances in cerebral small vessel disease. Neuroimage 2012, 59(2):1478–1484. [PubMed: 21854857]

21. Rosano C, Aizenstein HJ, Studenski S, Newman AB: A regions-of-interest volumetric analysis of mobility limitations in community-dwelling older adults. J Gerontol A Biol Sci Med Sci 2007, 62(9):1048–1055. [PubMed: 17895446]

22. Simuni T, Siderowf A, Lasch S, Coffey CS, Caspell-Garcia C, Jennings D, Tanner CM, Trojanowski JQ, Shaw LM, Seibyl J et al.: Longitudinal Change of Clinical and Biological Measures in Early Parkinson's Disease: Parkinson's Progression Markers Initiative Cohort. Mov Disord 2018, 33(5):771–782. [PubMed: 29572948]

23. Kuo HK, Leveille SG, Yu YH, Milberg WP: Cognitive function, habitual gait speed, and late-life disability in the National Health and Nutrition Examination Survey (NHANES) 1999–2002. Gerontology 2007, 53(2):102–110. [PubMed: 17090975]

24. Goel V, Vartanian O, Bartolo A, Hakim L, Ferraro AM, Isella V, Appollonio I, Drei S, Nichelli P: Lesions to right prefrontal cortex impair real-world planning through premature commitments. Neuropsychologia 2013, 51(4):713–724. [PubMed: 23266766]

25. Callisaya ML, Beare R, Phan TG, Chen J, Srikanth VK: Global and regional associations of smaller cerebral gray and white matter volumes with gait in older people. PLoS One 2014, 9(1):e84909. [PubMed: 24416309]

26. Falvey CM, Rosano C, Simonsick EM, Harris T, Strotmeyer ES, Satterfield S, Yaffe K, Health ABCS: Macro- and microstructural magnetic resonance imaging indices associated with diabetes among community-dwelling older adults. Diabetes Care 2013, 36(3):677–682. [PubMed: 23160721]

27. Rosso AL, Bohnen NI, Launer LJ, Aizenstein HJ, Yaffe K, Rosano C: Vascular and dopaminergic contributors to mild parkinsonian signs in older adults. Neurology 2018, 90(3):e223–e229. [PubMed: 29247072]

28. Rosario BL, Rosso AL, Aizenstein HJ, Harris T, Newman AB, Satterfield S, Studenski SA, Yaffe K, Rosano C, Health ABCS: Cerebral White Matter and Slow Gait: Contribution of Hyperintensities and Normal-appearing Parenchyma. J Gerontol A Biol Sci Med Sci 2016, 71(7):968–973. [PubMed: 26755683]

29. van der Holst HM, Tuladhar AM, Zerbi V, van Uden IWM, de Laat KF, van Leijsen EMC, Ghafoorian M, Platel B, Bergkamp MI, van Norden AGW et al.: White matter changes and gait decline in cerebral small vessel disease. Neuroimage Clin 2018, 17:731–738. [PubMed: 29270357]

30. Pringsheim T, Jette N, Frolkis A, Steeves TD: The prevalence of Parkinson's disease: a systematic review and meta-analysis. Mov Disord 2014, 29(13):1583–1590. [PubMed: 24976103]

- Several risk factors are associated with faster UPDRS-III change in MPS– subjects

- MD is independently associated with faster UPDRS-III change in MPS– subjects

- Microstructural imaging may capture early changes related to MPS development

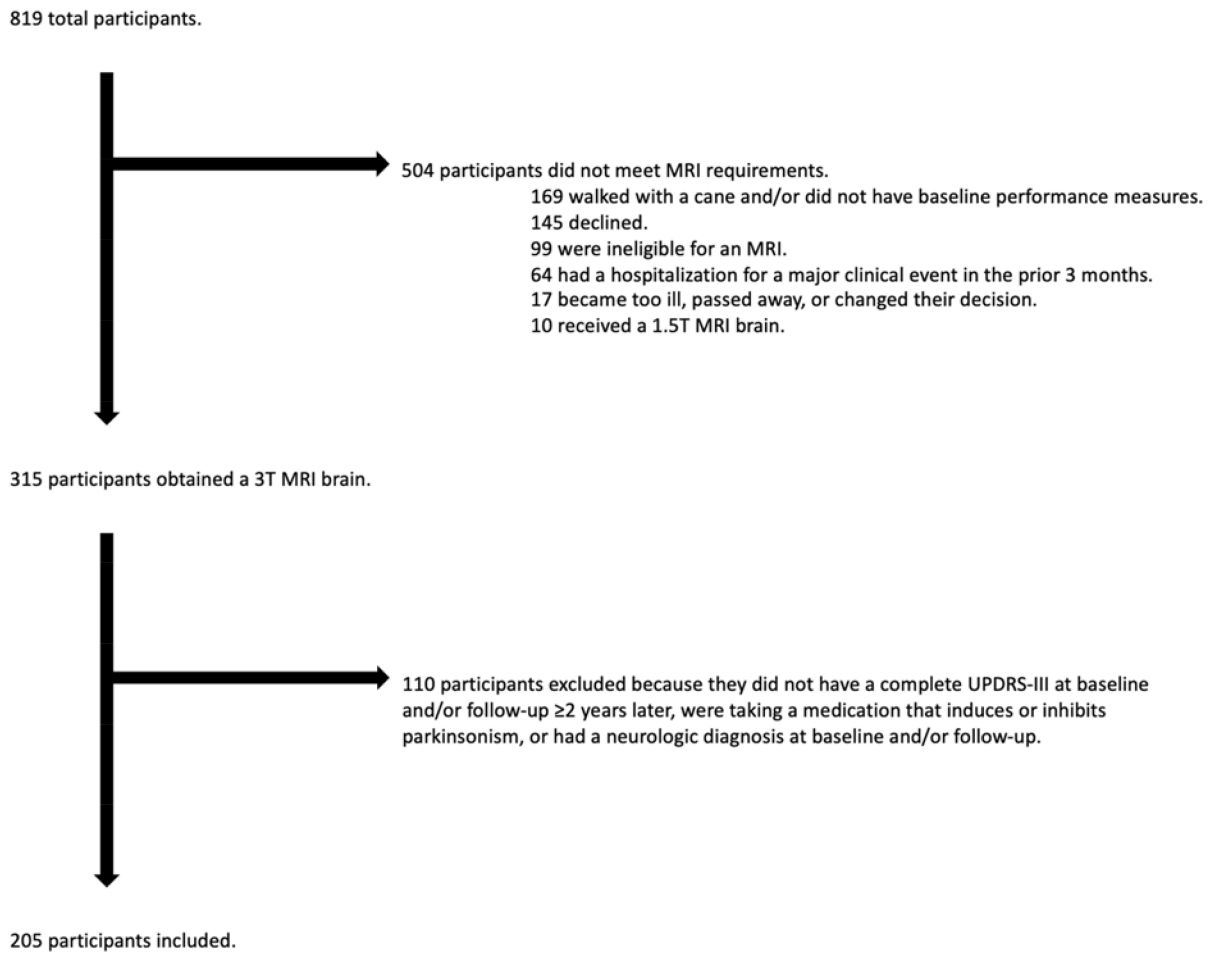- Interventions targeting gray matter integrity may reduce MPS development

819 total participants.

504 participants did not meet MRI requirements.
    169 walked with a cane and/or did not have baseline performance measures.
    145 declined.
    99 were ineligible for an MRI.
    64 had a hospitalization for a major clinical event in the prior 3 months.
    17 became too ill, passed away, or changed their decision.
    10 received a 1.5T MRI brain.

315 participants obtained a 3T MRI brain.

110 participants excluded because they did not have a complete UPDRS-III at baseline and/or follow-up ≥2 years later, were taking a medication that induces or inhibits parkinsonism, or had a neurologic diagnosis at baseline and/or follow-up.

205 participants included.

Figure 1. Inclusion/Exclusion of Study Participants
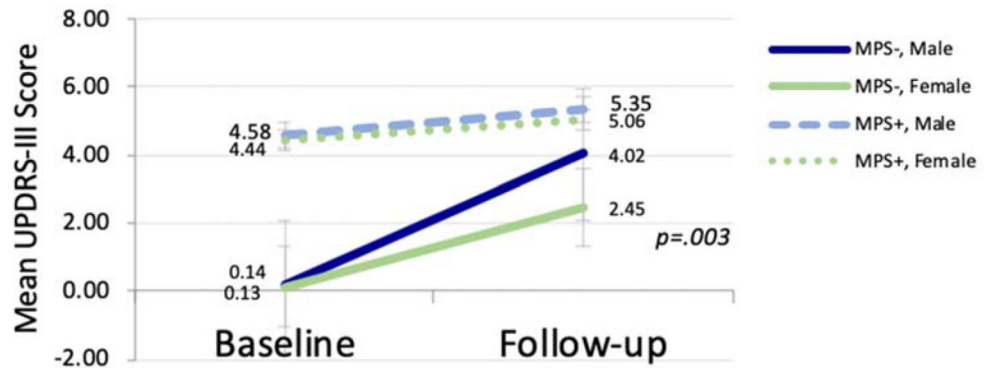Abbreviations: UPDRS-III=Unified Parkinson's Disease Rating Scale Part III.

Figure 2. Change in UPDRS-III Stratified by Absence/Presence of Baseline MPS and Gender
Abbreviations: UPDRS-III=Unified Parkinson's Disease Rating Scale Part III, MPS=Mild
Parkinsonian Signs.

Table 1.

Population Characteristics Stratified by Absence/Presence of Baseline MPS

			Baseline MPS Status	
		Full Cohort	**MPS−**	**MPS+**
Number		205	143	62
Demographic	Age in Years, Mean (SD)	82.7 (2.6)	82.6 (2.5)	83.1 (2.8)
	Women, Number (%)	113 (55)	77 (54)	36 (58)
	Black, Number (%)	85 (42)	60 (42)	45 (40)
	Education Beyond High School, Number (%)	169 (82)	121 (85)	48 (77)
	BMI, Mean (SD)	27.3 (4.3)	27.5 (4.0)	28.5 (5.0)
Risk Factor	Previous or Current Smoker, Number (%)	94 (46)	67 (47)	27 (44)
	Presence of Diabetes, Number (%)	51 (25)	36 (25)	15 (24)
	Presence of Hypertension, Number (%)	140 (68)	94 (66)	46 (74)
	Presence of Cardiovascular Disease, Number (%)	54 (26)	40 (28)	14 (23)
Overall Function	Quadriceps Strength, Mean (SD)	83.6 (29.8)	85.7 (30.1)	78.5 (28.5)
	3MS, Median (IQR)	95 (91–98)	96 (92–98)	95 (90–97)
UPDRS-III	UPDRS-III at Baseline, Mean (SD)	1.46 (2.81)	0.13[*] (0.34)	4.50 (3.54)
	Change in UPDRS-III per Year, Mean (SD)	0.60 (1.00)	0.80[*] (0.82)	0.14 (1.22)
	Follow-Up Time, Mean (SD)	3.81 (0.80)	3.87 (0.76)	3.69 (0.87)
Imaging	White Matter Hyperintensitiesx100, Median (IQR)	2.741 (0.080–0.703)	0.265 (0.077–0.663)	0.338 (0.138–0.712)
	Gray Matter Volume, Mean (SD)	0.385 (0.241)	0.387[*] (0.023)	0.379 (0.027)
	Fractional Anisotropy of White Matter, Mean (SD)[**]	0.360 (0.132)	0.362[*] (0.013)	0.357 (0.013)
	Mean Diffusivity of Gray Matterx100, Mean (SD)[**]	0.129 (0.010)	0.129 (0.010)	0.131 (0.011)

Abbreviations: MPS=Mild Parkinsonian Signs, SD=Standard Deviation, BMI=Body Mass Index, 3MS=Modified Mini-Mental, IQR=Interquartile Ratio, UPDRS-III=Unified Parkinson's Disease Rating Scale Part III.

[*]
p-value of between-group comparisons is <0.05.

[**]
130 MPS− and 55 MPS+ participants included in analysis.

Table 2.

Correlations between Population Characteristics and Longitudinal UPDRS-III Change Stratified by Absence/Presence of Baseline MPS

		UPDRS-III Change Adjusted for Follow-Up Time		
		Full cohort	**MPS−**	**MPS+**
Number		205	143	62
Demographic	Age	0.176[*]	0.214[*]	0.207
	Female Gender	−0.172[*]	−0.251[**]	−0.036
Risk Factor	Previous or Current Smoker	0.072	0.115	−0.013
	Presence of Diabetes	0.124	0.207[*]	−0.050
	Presence of Hypertension	−0.004	0.054	−0.048
	Presence of Cardiovascular Disease	0.090	0.162	−0.074
Overall Function	Quadriceps Strength	−0.095	−0.162	−0.281[*]
	3MS	−0.045	−0.016	−0.098
UPDRS-III	UPDRS-III at Baseline	−0.254[**]	0.160	−0.301[*]
	UPDRS-III at Follow-Up	0.732[**]	0.993[**]	0.779[**]
Imaging	White Matter Hyperintensities	0.047	0.142	−0.081
	Gray Matter Volume	−0.188[*]	−0.259[**]	−0.217
	Fractional Anisotropy of White Matter[***]	0.140	0.116	0.063
	Mean Diffusivity of Gray Matter[***]	0.200[**]	0.306[**]	0.143
Imaging Adjusted for Age, Gender, Diabetes	Gray Matter Volume	−0.085	−0.076	−0.212
	Mean Diffusivity of Gray Matter[***]	0.124	0.193[*]	0.123

Data presented as standardized coefficients, using Spearman or Pearson partial correlations as appropriate. Abbreviations: MPS=Mild Parkinsonian Signs, 3MS=Modified Mini Mental, UPDRS-III=Unified Parkinson's Disease Rating Scale Part III.

[*] p-value of correlation is <0.05.

[**] p-value of correlation is <0.005.

[***] 130 MPS− and 55 MPS+ participants included in analysis.