Title

Multiple modality biomarker prediction of cognitive impairment in prospectively followed de novo Parkinson disease

Journal

PLOS ONE, 12(5)

ISSN

1932-6203

Authors

Caspell-Garcia, Chelsea
Simuni, Tanya
Tosun-Turgut, Duygu
et al.

Publication Date

2017

DOI

10.1371/journal.pone.0175674

Peer reviewed

PLOS ONE

RESEARCH ARTICLE

Multiple modality biomarker prediction of cognitive impairment in prospectively followed de novo Parkinson disease

Chelsea Caspell-Garcia[1], Tanya Simuni[2], Duygu Tosun-Turgut[3], I-Wei Wu[3], Yu Zhang[3], Mike Nalls[4], Andrew Singleton[4], Leslie A. Shaw[5], Ju-Hee Kang[5,6], John Q. Trojanowski[5], Andrew Siderowf[7], Christopher Coffey[1], Shirley Lasch[8], Dag Aarsland[9,10], David Burn[11], Lana M. Chahine[12], Alberto J. Espay[13], Eric D. Foster[1], Keith A. Hawkins[14], Irene Litvan[15], Irene Richard[16], Daniel Weintraub[12,17,18,19]*, the Parkinson's Progression Markers Initiative (PPMI)[¶]

1 Department of Biostatistics, College of Public Health, University of Iowa, Iowa City, IA, United States of America, **2** Feinberg School of Medicine, Northwestern University, Chicago, IL, United States of America, **3** University of California, San Francisco, San Francisco, CA, United States of America, **4** Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, MD, United States of America, **5** Department of Pathology and Laboratory Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, United States of America, **6** Department of Pharmacology & Clinical Pharmacology, Inha University School of Medicine, Incheon, Republic of Korea, **7** Avid Radiopharmaceuticals, Philadelphia, PA, United States of America, **8** Institute for Neurodegenerative Disorders (IND) and Molecular NeuroImaging, LLC (MNI), New Haven CT, United States of America, **9** Department of Old Age Psychiatry, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, England, **10** Centre for Age-Related Medicine, Stavanger University Hospital, Stavanger, Norway, **11** Institute for Ageing and Health, Newcastle University, Newcastle, England, **12** Department of Neurology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, United States of America, **13** Department of Neurology, University of Cincinnati Academic Health Center, Cincinnati, OH, United States of America, **14** Department of Psychiatry, Yale School of Medicine, New Haven, CT, United States of America, **15** UCSD Movement Disorder Center, Department of Neurosciences, University of California San Diego, San Diego, CA, United States of America, **16** Departments of Neurology and Psychiatry, University of Rochester School of Medicine and Dentistry, Rochester, NY, United States of America, **17** Department of Psychiatry, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, United States of America, **18** Parkinson's Disease Research, Education and Clinical Center (PADRECC and MIRECC), Philadelphia Veterans Affairs Medical Center, Philadelphia, PA, United States of America, **19** Mental Illness Research, Education and Clinical Center (MIRECC), Philadelphia Veterans Affairs Medical Center, Philadelphia, PA, United States of America

¶ Complete membership of the author group can be found in the acknowledgments section.
* Daniel.Weintraub@uphs.upenn.edu

Citation: Caspell-Garcia C, Simuni T, Tosun-Turgut D, Wu I-W, Zhang Y, Nalls M, et al. (2017) Multiple modality biomarker prediction of cognitive impairment in prospectively followed de novo Parkinson disease. PLoS ONE 12(5): e0175674. https://doi.org/10.1371/journal.pone.0175674

Editor: Stephen D. Ginsberg, Nathan S Kline Institute, UNITED STATES

Received: December 28, 2016

Accepted: March 29, 2017

Published: May 17, 2017

Data Availability Statement: The data underlying this study are third party data. Interested researchers may apply for access to these data at the following link: http://www.ppmi-info.org/access-data-specimens/download-data/. The authors confirm that they do not have special access privileges to these data and that interested researchers may apply to access these data in the manner described.

Funding: Michael J Fox Foundation for Parkinson's Research (michaeljfox.org) – study design, data

Abstract

Objectives

To assess the neurobiological substrate of initial cognitive decline in Parkinson's disease (PD) to inform patient management, clinical trial design, and development of treatments.

Methods

We longitudinally assessed, up to 3 years, 423 newly diagnosed patients with idiopathic PD, untreated at baseline, from 33 international movement disorder centers. Study outcomes were four determinations of cognitive impairment or decline, and biomarker predictors were baseline dopamine transporter (DAT) single photon emission computed tomography

collection, decision to publish, preparation of manuscript. PPMI – a public-private partnership – is funded by the Michael J. Fox Foundation for Parkinson's Research and funding partners, including Abbvie, Avid Radiopharmaceuticals, Biogen, Bristol-Myers Squibb, Covance, GE Healthcare, Genentech, GlaxoSmithKline, Lilly, Lundbeck, Merck, Meso Scale Discovery, Pfizer, Piramal, Roche, Servier, and UCB. Dr. Andrew Siderowf is an employee of Avid Radiopharmaceuticals. Avid Radiopharmaceuticals provided support in the form of salary for Dr. Siderowf, but did not have any additional role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. Dr. Siderowf's specific role is articulated in the 'author contributions' section. Also supported by NINDS P50 NS053488 (Trojanowski JQ-PI). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: Alberto J. Espay: Dr. Espay has received grant support from NIH, Great Lakes Neurotechnologies and the Michael J Fox Foundation; personal compensation as a consultant/scientific advisory board member for Abbvie, TEVA, Impax, Merz, Acadia, Cynapsus, Lundbeck, and USWorldMeds; publishing royalties from Lippincott Williams & Wilkins, Cambridge University Press, and Springer; and honoraria from Abbvie, UCB, USWorldMeds, Lundbeck, Acadia, the American Academy of Neurology, and the Movement Disorders Society. He serves as Associate Editor of the Journal of Clinical Movement Disorders and on the editorial board of Parkinsonism and Related Disorders. Andrew Siderwof: Dr. Siderowf is a full-time employee of Avid Radiopharmaceuticals, a wholly owned subsidiary of Eli Lilly and Company. Dag Aarsland, MS: Dr. Aarsland has received research support and/or honoraria from Astra-Zeneca, H. Lundbeck, Novartis Pharmaceuticals and GE Health, and serves as paid consultant for H. Lundbeck and Axovant. Irene Litvan: Dr. Litvan has been a member of the Cynapsus, Lundbeck, Biogen and Bristol-Myers Squibb Advisory Boards. She is a member of the Biotie/Parkinson Study Group Medical Advisory Board. She is an investigator in NIH Grants: 5P50 AG005131-31, 5T35HL007491, 1U01NS086659 and 1U54NS092089-01; Parkinson Study Group, Michael J Fox Foundation, AVID Pharmaceuticals, C2N Diagnostics and Bristol-Myers Squibb. She receives her salary from the University of California San Diego. John G. Trojanowski: Dr. Trojanowski may accrue revenue in the future on patents submitted by the University of Pennsylvania wherein he is co-Inventor and he

(SPECT) scan, structural magnetic resonance imaging (MRI; volume and thickness), diffusion tensor imaging (mean diffusivity and fractional anisotropy), cerebrospinal fluid (CSF; amyloid beta [Aβ], tau and alpha synuclein), and 11 single nucleotide polymorphisms (SNPs) previously associated with PD cognition. Additionally, longitudinal structural MRI and DAT scan data were included. Univariate analyses were run initially, with false discovery rate = 0.2, to select biomarker variables for inclusion in multivariable longitudinal mixed-effect models.

Results

By year 3, cognitive impairment was diagnosed in 15–38% participants depending on the criteria applied. Biomarkers, some longitudinal, predicting cognitive impairment in multivariable models were: (1) dopamine deficiency (decreased caudate and putamen DAT availability); (2) diffuse, cortical decreased brain volume or thickness (frontal, temporal, parietal, and occipital lobe regions); (3) co-morbid Alzheimer's disease Aβ amyloid pathology (lower CSF Aβ 1–42); and (4) genes (*COMT* val/val and *BDNF* val/val genotypes).

Conclusions

Cognitive impairment in PD increases in frequency 50–200% in the first several years of disease, and is independently predicted by biomarker changes related to nigrostriatal or cortical dopaminergic deficits, global atrophy due to possible widespread effects of neurodegenerative disease, co-morbid Alzheimer's disease plaque pathology, and genetic factors.

Introduction

In Parkinson disease (PD) cognitive impairment can occur in a range of cognitive domains[1], dementia (PDD) affects up to 80% of patients long-term[2], mild cognitive impairment (PD-MCI) occurs in 25–30% of non-demented patients[1] and is a risk factor for dementia[3], and cognitive deficits are present in some patients at the time of diagnosis[4].

A range of demographic and clinical correlates or potential risk factors for cognitive decline have been identified, including increasing age and duration of PD, male sex, specific motor features (postural instability gait disorder [PIGD] subtype), and a range of non-motor symptoms (e.g., visual hallucinations, apathy, depression, and rapid eye movement (REM) sleep behaviour disorder)[5].

Cortical Lewy body disease (LBD) pathology appears to be the major contributing pathology to cognitive decline in PD[6], but Alzheimer disease (AD)-related changes are also present in a significant percentage of patients[7]. A range of neurotransmitter deficits have been implicated, including in acetylcholine[8], dopamine[9], and norepinephrine systems[10]. Genetic influences have been identified in some studies, including apolipoprotein E4 [*ApoE4*] status[11] and SNPs in brain-derived neurotrophic factor (*BDNF*) val^{66}met[12], catechol-O-methyl-transferase (*COMT*) val^{158}met[13], and microtubule-associated protein tau (*MAPT*) [14]. Finally, diffuse (primarily medial temporal lobe, parietal lobe and prefrontal cortex) gray matter atrophy and white matter changes have been associated with cognitive decline in PD [15, 16].

The research on the neural substrates of the initial stages of cognitive decline in PD, starting with disease onset, are limited, with previous studies often characterized by single site participation, relatively small sample sizes, cross-sectional design, or a limited biomarker assessment.

received revenue from the sale of Avid to Eli Lily as co-inventor on imaging related patents submitted by the University of Pennsylvania. Mike Nalls, PhD: Dr. Nalls is supported by a consulting contact between Kelly Services and the National Institute of Aging, NIH, Bethesda, MD, USA> Tanya Simuni, MD: Dr. Simuni has served as a consultant received consulting fees from Acadia, Abbvie, Allergan, Anavex, Avid, GE Medical, Eli Lilly and Company, Harbor, Ibsen, IMPAX, Lundbeck, Merz, Inc., the National Parkinson Foundation, Navidea, Pfizer, TEVA Pharmaceuticals, UCB Pharma, Voyager, US World Meds, and the Michael J. Fox Foundation for Parkinson's Research; Dr. Simuni has served as a speaker and received an honorarium from Acadia, IMPAX, Lundbeck, TEVA Pharmaceuticals, and UCB Pharma; Dr Simuni is on the Scientific advisory board for Anavex, Sanofi, MJFF. Dr. Simuni sits on the Advisory Board for IMPAX; Dr. Simuni has received research funding from the NINDS, MJFF, NPF, TEVA Pharmaceuticals, Auspex, Biotie, Civitas, Acorda, Lundbeck, Neuroderm, NINDS, National Institutes of Health, Northwestern Foundation, and the Michael J. Fox Foundation for Parkinson's Research; Dr. Simuni received funding support for educational programs from GE Medical, TEVA, and Lundbeck. Dr. Siderowf is an employee of Avid Radiopharmaceuticals. Avid Radiopharmaceuticals provided support in the form of salary for Dr. Siderowf, but did not have any additional role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. Mike A. Nalls' participation is supported by a consulting contract between dataconsult.io LLC and the National Institute on Aging, NIH, Bethesda, MD, USA. As a possible conflict of interest, Dr. Nalls also consults for Illumina Inc, the Michael J. Fox Foundation and University of California Healthcare. These do not alter our adherence to PLOS ONE policies on sharing data and materials.

The Parkinson's Progression Markers Initiative (PPMI) is an ongoing, prospective, longitudinal, biomarker-rich observational study of disease progression in early PD[17]. The biomarkers obtained in the PPMI study include dopamine transporter (DAT) SPECT imaging, brain structural MRI, CSF and blood biomarkers as well as DNA for genotyping. The goals of these analyses were to evaluate which baseline and longitudinal biomarkers may predict cognitive impairment in early PD.

Materials and methods

Participants

Newly diagnosed, untreated PD patients (N = 423) were enrolled in PPMI from June 2010—May 2013 out a cohort of 489 screened patients. At baseline PD participants were required to: (1) have a recent idiopathic PD diagnosis; (3) be untreated for PD; (4) have a dopamine transporter (DAT) deficit on imaging; and (5) not have dementia as determined by the site investigator. The aims and methodology of the study have been published elsewhere[17] and are available at www.ppmi-info.org/study-design. The overall study was approved by the Research Subjects Review Board at the University of Rochester, and the study was approved by the institutional review board at each site, and participants provided written informed consent. Clinical data out to three years post-baseline was utilized. Data was downloaded on September 21, 2015; at the time of data download 38 PD patients had discontinued study participation (9.0% discontinuation).

Experimental design

Cognitive abilities. Cognition was assessed at baseline and annually. Global cognition was assessed with the Montreal Cognitive Assessment (MoCA). In addition, a detailed cognitive battery, as previously described and referenced[18], assessing the following domains was administered: memory (Hopkins Verbal Learning Test-Revised [HLVT-R]); visuospatial function (Benton Judgment of Line Orientation [JOLO]) 15-item (split-half) version; processing speed-attention (Symbol-Digit Modalities Test [SDMT]); and executive function and working memory (Letter-Number Sequencing [LNS] and semantic fluency [animals, vegetables and fruits]). Level II PD-MCI criteria[19] were not applicable given the lack of a separate language assessment or 10 cognitive tests across 5 domains. Published norms for each test were applied.

Definitions of cognitive impairment. For the purposes of these analyses cognitive impairment was defined three different ways:

1. The recommended MoCA cut-off for PD of <26 was applied[20]. Additionally, MoCA score was also examined as a continuous variable.
2. Using the detailed cognitive battery, cognitive impairment was defined as at least two test scores >1.5 standard deviations below the standardized mean score, a level of impairment within the recommend range (>1.0–2.0) of standard deviations below the mean to support a PD-MCI diagnosis[19]. Single scores were generated for each test, except for the HVLT-T, for which two scores were used (immediate free recall and recognition discrimination).
3. The site investigator's clinical diagnosis of cognitive impairment (PD-MCI or PDD) versus no cognitive impairment was made annually. Each site investigator was provided an instruction sheet that outlined how to assess cognitive decline, functional impairment, and general interpretation of cognitive tests to make a diagnosis of PD-MCI[19] or PDD[21]. As previously described [18], the site investigator's annual determination of cognitive impairment was introduced after some participants already had completed their baseline

and year 1 visits (106/423 [25.1%] of available patients had this assessment performed at baseline, and 271/395 [68.6%] at year 1).

Secondary analyses examined only incident cognitive impairment, including only those participants who did not meet one of the three criteria for cognitive impairment at the baseline visit (N = 394).

Biomarkers. Details about the biospecimen collection and analysis has been published[17].

1. DAT SPECT imaging (DaTscan^{TM}) was obtained at baseline and annually. Ipsilateral (i.e., brain hemisphere on *same* side as predominant motor symptoms) and contralateral (i.e., brain hemisphere on *opposite* side as predominant motor symptoms) caudate and putamen values were used.

2. CSF was obtained at baseline, month 6, year 1, and then annually using collection steps as described [22]. At the time of data download, values were available only for the baseline visit. Reported are levels of alpha synuclein (α-synuclein), total tau, p-tau181, beta-amyloid 1–42 (Aβ42), t-tau:Aβ42 ratio, p-tau181:Aβ42 ratio, and p-tau181:total tau ratio. These CSF biomarkers were measured in centralized laboratories using the xMAP INNO-BIA AlzBio3 immunoassay (Fujirebio, Ghent Belgium) for total tau, p-tau181 and beta-amyloid 1–42 (Aβ42) at the UPenn Biomarker Research Laboratory) or with commercially available ELISA kits (Covance laboratory, Dedham, MA) as described in detail elsewhere[22].

3. Structural MRI with minimum requirements for these analyses were obtained at baseline and annually, and were available for a subset of participants at baseline (N = 160). These participants were enrolled at 10 PPMI sites that used a standardized protocol for 3 Tesla machines (all Siemens Healthcare, USA). A 3D magnetization prepared rapid gradient echo (MPRAGE) sequence was used for imaging brain anatomy (176 axial slices, repetition time = 2300 ms, echo time = 2.98 ms, flip angle = 9˚, voxel size $1 \times 1 \times 1$ mm^3). The images were centrally processed at UCSF for cortical and subcortical morphometric measurements using FreeSurfer version 5.1[23]. FreeSurfer is a suite of algorithmic tools that automatically creates models of most anatomical brain structures on MRI based on a subject-independent probabilistic brain atlas in combination with nonlinear image registration of individual images to obtain subject-specific measurements. FreeSurfer version 5.1 uses a longitudinal workflow that estimates brain morphometry unbiased toward the chronological scan order by building first a template image from all time points as an unbiased prior distribution for each subject before computing morphometric deformations for every time point. This strategy reduces the random variation in the processing procedure and improves the robustness and sensitivity of the overall longitudinal analysis. A previous test-retest study validated that the longitudinal processing provides consistent brain parcellation[24]. All raw images as well as the results of brain parcellation underwent a visual quality control by trained technicians. A partial failure rating for gross parcellation errors in 1 or more specific brain regions occurred in about 15% of the image, but none had a complete parcellation failure. The errors also did not appear to be systematic and MRIs with a partial failure rating were still included in the analyses but only the correctly parcellated brain regions were assessed. The outcome measures of the FreeSurfer workflow were 93 automatically-labeled brain regions, including gyri and subcortical structures, for each subject. MRI data for baseline, year 1 and year 2 visits were utilized for volume and thickness for 34 regions, with left and right hemisphere values averaged.

4. Diffusion tensor imaging (DTI) MRI results were available for a subset of participants who also had structural MRI (N = 151). DTI data from 9 of 160 with MRI had to be excluded

because of poor data quality. DTI measures were mean diffusivity (MD) and fractional anisotropy (FA) for 61 brain regions, with left and right hemisphere values averaged. A cardiac-gated two-dimensional single-shot echo-planar sequence for mapping brain water DTI (TR ranged from 8,400 to 8,800 depending on subjects' heart rate, TE = 88ms, 2 mm isotropic resolution; 72 contiguous slices, twofold acceleration, axial-oblique aligned along the anterior-posterior commissure, with diffusion-weighted gradients along 64 sensitization directions and a b factor of 1000s/mm2) was acquired for each participant. Processing images were first visually inspected for significant image artifacts and then processed using an automated processing script designed for longitudinal data analysis. The initial steps include corrections for head motion, eddy-current effects and susceptibility distortions of DTI[25], followed by the computation of standard scalar parameter maps of the diffusion tensor, such as fractional anisotropy (FA), radial diffusivity (rD), and axial diffusivity (aD). An intra-subject affine registration was performed between the parametric DTI maps and the structural T1- and T2- weighted images at baseline. An inter-subject registration was performed for group analysis using the standard protocol of DARTEL, which involves tissue segmentation of the structural images for DARTEL initialization, a diffeomorphic algorithm for inter-subject image registration, and finally a spatial normalization of the registered images to MNI space[26], allowing the anatomical parcellation of the brain according to the JHU-DTI-MNI (Type I WMPM)[27]. To reduce any group bias in the anatomical parcellation, a group-averaged template was created from all subject images in MNI space, followed by a non-linear registration between the JHU-DTI-MNI atlas and the group-averaged template. The JHU-DTI-MNI atlas is reversely transformed to each subject space, facilitating regions-of-interest (ROIs) extraction from each parametric DTI map at baseline. For group analysis, DTI measures were extracted from 118 ROIs in the entire white matter and subcortical regions, including the basal ganglia and brain stem subregions. The outcome measures of the FreeSurfer workflow were 93 automatically-labeled brain regions, including gyri and subcortical structures, for each subject, based on the Desikan-Killiany brain structure atlas[28].

5. Genotyping was performed with NeuroX, a genotyping platform comprised of standard Illumina exome content (~240,000 variants) and over 24,000 custom content variants focusing on neurologic diseases (~24,000 variants)[29]. Single nucleotide polymorphisms (SNPs) previously associated with cognitive impairment or decline in PD were examined (i.e., apolipoprotein E4 [*ApoE4*], glucocerebrosidase [*GBA*; N3705], leucine-rich repeat kinase 2 [*LRKK2*; G20195], synuclein [rs3910105 and rs356181], microtubule associated protein tau [*MAPT*; rs17649553, which is in linkage dysequilibrium with the H1 haplotype], brain-derived neurotrophic factor val^{66}met [*BDNF* val^{66}met], and Catechol-O-methyltransferase val^{158}met [*COMT* val^{158}met]). rs17649553 is in strong linkage dysequilibrium with an "H1 tagging" SNP (rs242928; D' = 0.991, R2 = 0.203).

Statistical analysis. Longitudinal logistic or linear mixed-effect models were used to find baseline and longitudinal predictors (treated as time-dependent predictors) of cognitive impairment over the 3-year time period. The following covariates were considered for each cognitive outcome: age, sex, race, education level, levodopa equivalent daily dose (LEDD)[30], baseline MDS Unified Parkinson's Disease Rating Scale (MDS-UPDRS) motor score, baseline depression (GDS-15 score $\geq$5), baseline psychosis (MDS-UPDRS 1.2 item score $>$0), and baseline REM sleep behavior disorder (RBDSQ score $\geq$5). To select the most appropriate set of covariates for each outcome, a combination of Akaike information criteria (AIC) fit statistics and univariate p-values were used to perform a backwards selection of covariates to find

the best model fit. AIC fit statistics were also used to determine whether site should be included as a random effect for each outcome. In addition to these selected covariates, models examining MRI volume also adjusted for total intracranial volume (ICV), and models examining MRI DTI measures also adjusted for white matter density in each individual region examined.

After covariates and random effects were selected for each outcome, univariate analyses were run for each biomarker variable to predict cognitive impairment over time. Due to the large number of predictors, a false discovery rate (FDR) approach (FDR = 0.2) was used to select biomarker variables from the univariate analyses for inclusion in multivariable models run with other biomarkers. Then, variables were removed from the multivariable model individually in a backwards selection process until all remaining variables were significant at 0.1 level. To avoid collinearity with biomarkers, the following rules were used when fitting the multivariable models: if contralateral putamen or caudate measures were significant in a univariate manner, they were considered in the multivariable model. If not, but ipsilateral putamen or caudate measures were significant in a univariate manner, they were considered in the multivariable model. Similarly, if any of the individual CSF biomarkers were significant in a univariate manner, they were considered in the multivariable model; CSF ratios were only considered in the multivariable model if neither of the individual biomarkers was significant.

As structural and diffusion tensor MRIs were only available in a subset of patients, two populations were analyzed for each cognitive outcome: (1) the subset of participants with MRI data (these models included MRI plus other biomarker data), and (2) the full population (these models included only other biomarker data). Separate models were run for baseline predictors (all biomarkers) and longitudinal predictors (DAT imaging and structural MRI).

All statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC).

Results

Participant characteristics

Baseline demographic and clinical characteristics for all PD participants (N = 423) are in Table 1. The cohort is approximately two-thirds male, overwhelmingly white, and highly educated. The characteristics for the subset of participants with MRI data (N = 160) was similar to that of the full population. Table 2 lists the number of PD participants with biomarker availability at each time point. Genetic, CSF, and DTI testing was done at baseline, and DAT imaging and MRI thickness and volumes at baseline, year 1 and year 2.

Cognitive outcomes over time

Cognitive assessments were available for up to 423 participants at baseline, 395 at year 1, 376 at year 2, and 239 at year 3 (dropout rate <10%, so the decreasing number of participants over time is largely due to the fact that many participants had not yet reached year 3 of study participation at the time of data download).

Over the 3-year period the mean MoCA score declined by approximately 1 point on average, and the frequency of participants screening positive for cognitive impairment (i.e., MoCA score <26) increased from 22% to 37%, with dementia-level impairment (i.e., MoCA score <21[20]) increasing from 1% to 6% over time, see Table 3. Cognitive impairment increased from 11% to 15% based on detailed neuropsychological test results. Using the site investigator's diagnostic determination, the diagnosis of MCI increased from 9% to 21% and PDD from 0% to 3%.

Table 1. Baseline demographic and clinical characteristics.

Variable	All PD participants (N = 423)	PD participants with MRI data (N = 160)
Age		
Mean years (SD; minimum, maximum)	61.7 (9.7; 33.5, 84.9)	61.0 (9.6; 38.0, 82.3)
Gender		
Male	277 (65.5%)	103 (64.4%)
Female	146 (34.5%)	57 (35.6%)
Education		
<13 years	76 (18.0%)	38 (23.8%)
13–23 years	344 (81.3%)	122 (76.3%)
>23 years	3 (0.7%)	0 (0.0%)
Race		
White	391 (92.4%)	151 (94.4%)
Black/African-American	6 (1.4%)	3 (1.9%)
Asian	8 (1.9%)	3 (1.9%)
Other	18 (4.3%)	3 (1.9%)
Duration of disease (months)		
Mean (SD; minimum, maximum)	6.7 (6.5, 0.4, 35.8)	6.87 (7.0; 0.4, 35.8)
MDS-UPDRS Part III score		
Mean (SD; minimum, maximum)	20.9 (8.9; 4.0, 51.0)	20.9 (9.1; 4.0, 47.0)
GDS score (score ≥5)	59 (13.9%)	25 (15.6%)
MDS-UPDRS psychosis (score ≥1)	13 (3.1%)	6 (3.8%)

https://doi.org/10.1371/journal.pone.0175674.t001

Neurobiological predictors of cognitive impairment

Global cognitive impairment (MoCA). Baseline CSF, DAT imaging, DTI (MD and FA), and MRI (volume and thickness) values, and the eight SNPs examined, did not predict MoCA score <26 over time (data not shown). In the subset of patients with MRI data, baseline decreased entorhinal (p = 0.007) and superior temporal lobe (p = 0.004) volumes were associated with greater decline in MoCA score over time.

Longitudinal DAT imaging did not predict MoCA score <26 over time. In the subset of patients with MRI data, decreased caudal middle frontal (p = 0.096), superior parietal (p = 0.03), and superior temporal (p = 0.08) volumes over time were associated with MoCA score <26 over time. Decreased lateral orbitofrontal (p = 0.05), superior parietal (p = 0.007), and superior temporal (p = 0.07) volumes, and decreased precentral thickness (p = 0.02), over time predicted greater decline in continuous MoCA score over time.

Neuropsychological test-defined cognitive impairment. Baseline CSF, DAT imaging, DTI (MD and FA), and MRI (volume and thickness) values, and the eight SNPs examined, did

Table 2. Biomarker availability at baseline and longitudinally.

Biomarker	Number PD participants			
	Baseline	Year 1	Year 2	Year 3
Genotyping	384	n/a	n/a	n/a
DTI FA and MD	151	n/a	n/a	n/a
MRI volume and thickness	160	148	110	n/a
CSF	412	n/a	n/a	n/a
DAT scan	418	358	296	n/a

https://doi.org/10.1371/journal.pone.0175674.t002

Table 3. Cognitive outcomes over time.

Variable	PD Subjects				Change from Baseline to Year 3 (p value)
	Baseline	Year 1	Year 2	Year 3	
	(N = 423)	(N = 395)	(N = 376)	(N = 239)	
MoCA score					<0.001
N	423	392	371	238	
Mean (SD)	27.13 (2.3)	26.30 (2.8)	26.26 (3.2)	26.02 (3.3)	
(Min, Max)	(17.0, 30.0)	(15.0, 30.0)	(9.0, 30.0)	(13.0, 30.0)	
MoCA score <26					<0.001
N	423	392	371	238	
Yes	93 (22.0%)	135 (34.4%)	121 (32.6%)	89 (37.4%)	
MoCA score <21					0.002
N	423	392	371	236	
Yes	4 (0.9%)	13 (3.3%)	20 (5.4%)	13 (5.5%)	
JLO score					0.02
N	422	394	369	236	
Mean (SD)	12.77 (2.1)	12.33 (2.4)	12.82 (2.3)	12.56 (2.4)	
(Min, Max)	(5.0, 15.0)	(2.0, 15.0)	(0.0, 15.0)	(3.0, 15.0)	
HVLT immediate recall score					0.54
N	422	394	374	238	
Mean (SD)	24.44 (5.0)	23.82 (5.4)	23.71 (5.5)	24.19 (6.1)	
(Min, Max)	(9.0, 36.0)	(4.0, 36.0)	(9.0, 36.0)	(6.0, 36.0)	
HVLT-R delayed recall score					0.06
N	422	394	374	237	
Mean (SD)	8.36 (2.5)	8.10 (2.9)	8.21 (3.0)	8.08 (3.0)	
(Min, Max)	(0.0, 12.0)	(0.0, 12.0)	(0.0, 12.0)	(0.0, 12.0)	
HVLT-R retention score					0.38
N	421	392	374	236	
Mean (SD)	11.18 (1.2)	11.14 (1.4)	11.26 (1.7)	11.08 (1.6)	
(Min, Max)	(0.0, 12.0)	(0.0, 12.0)	(0.0, 12.0)	(0.0, 12.0)	
HVLT-R discrimination recognition score					0.69
N	421	392	374	236	
Mean (SD)	9.63 (2.6)	9.67 (2.5)	10.68 (2.4)	9.69 (2.5)	
(Min, Max)	(-4.0, 12.0)	(-1.0, 12.0)	(-2.0, 12.0)	(-2.0, 12.0)	
LNS score					0.006
N	422	393	374	238	
Mean (SD)	10.59 (2.7)	10.36 (2.7)	10.32 (2.8)	10.15 (3.0)	
(Min, Max)	(2.0, 20.0)	(2.0, 18.0)	(2.0, 19.0)	(1.0, 18.0)	
Semantic fluency total score					0.04
N	422	393	374	238	
Mean (SD)	48.67 (11.6)	48.75 (11.5)	48.98 (13.0)	47.47 (11.3)	
(Min, Max)	(20.0, 103.0)	(18.0, 97.0)	(15.0, 95.0)	(9.0, 86.0)	
SDMT score					<0.001
N	422	394	373	236	
Mean (SD)	41.18 (9.7)	40.78 (10.3)	39.95 (11.1)	39.14 (11.7)	
(Min, Max)	(7.0, 82.0)	(5.0, 70.0)	(2.0, 75.0)	(0.0, 65.0)	
2 scores >1.5 SD below standardized mean					0.05
N	415	386	360	226	
Yes	44 (10.6%)	52 (13.5%)	45 (12.5%)	33 (14.6%)	

(*Continued*)

Table 3. (*Continued*)

Variable	PD Subjects				Change from Baseline to Year 3 (p value)
	Baseline	Year 1	Year 2	Year 3	
	(N = 423)	(N = 395)	(N = 376)	(N = 239)	
Site investigator diagnosis cognitive impairment					0.001
N	106	271	366	235	
Normal	97 (91.5%)	231 (85.2%)	306 (83.6%)	179 (76.2%)	
Mild cognitive impairment	9 (8.5%)	38 (14.0%)	57 (15.6%)	50 (21.3%)	
Dementia	0 (0.0%)	2 (0.7%)	3 (0.8%)	6 (2.6%)	

MoCA = Montreal Cognitive Assessment.

JLO = Benton Judgment of Line Orientation.

HVLT-R = Hopkins Verbal Learning Test-Revised.

LNS = Letter-Number Sequencing.

SDMT-Symbol-Digit Modalities Test.

https://doi.org/10.1371/journal.pone.0175674.t003

not predict test-based cognitive impairment over time (data not shown). Likewise, longitudinal DAT imaging and MRI (volume and thickness) values did not predict test-based cognitive impairment over time (data not shown).

Site investigator diagnosis of cognitive impairment. Table 4 shows lower baseline ipsilateral caudate DAT availability and CSF Aβ 1–42 predicted cognitive impairment after FDR

Table 4. Baseline biomarker predictors of investigator diagnosis of cognitive impairment.

Variable	PD Subjects (N = 403)			
	Univariate p-value	# Subjects Missing	Multivariable Analysis OR (95% CI)	p-value
CSF Biologics				
Alpha-Synuclein	0.87	13	-	-
A-Beta 1–42	<0.001	13	0.995 (0.992, 0.998)	0.001
t-tau	0.87	17	-	-
p-tau	0.56	15	-	-
t-tau/A-Beta 1–42	0.02	17	Not included	NA
p-tau/A-Beta 1–42	0.13	15	-	-
p-tau/t-tau	0.51	19	-	-
Genetics				
ApoE4	0.67	40	-	-
GBA N370S	0.18	37	-	-
LRRK2 G2019S	0.31	36	-	-
MAPT rs17649553	0.11	36	-	-
SNCA rs3910105	0.36	36	-	-
SNCA rs356181	0.96	36	-	-
BDNF val66met	0.09	36	-	-
COMT val158met	0.05	36	-	-
DAT imaging				
Contralateral Caudate	0.09	6	-	-
Ipsilateral Caudate	0.03	6	0.450 (0.237, 0.855)	0.01
Contralateral Putamen	0.48	6	-	-
Ipsilateral Putamen	0.24	6	-	-

https://doi.org/10.1371/journal.pone.0175674.t004

correction and on multivariable analysis. Smaller fusiform, lateral occipital, and lateral orbitofrontal (for MRI volume) and decreased inferior cerebellar peduncle MD (for DTI MD) predicted cognitive impairment in multivariable analyses, see S1 Table.

Table 5 shows lower contralateral caudate DAT availability over time was associated with cognitive impairment in multivariable analyses. In addition, smaller fusiform and superior temporal lobe volumes, and larger caudal anterior cingulate and smaller fusiform thickness, over time were associated with cognitive impairment in multivariate analyses, see S2 Table.

Examining the entire cohort (i.e., excluding MRI variables) and including only patients who were cognitively intact at baseline (N = 394), baseline predictors of incident cognitive impairment (based on site investigator diagnosis) were lower CSF Aβ 1–42, lower ipsilateral caudate DAT availability, *COMT* val158met (val/val genotype), and *BDNF* val66met (val/val genotype), see S3 Table. A longitudinal biomarker predictor of incident cognitive impairment was decreased contralateral putamen DAT availability (p = 0.07).

Discussion

In this multi-modal longitudinal examination of predictors of cognitive impairment in early PD, the biomarkers in general predicting cognitive impairment that remained significant in multivariable models were: (1) dopamine deficiency; (2) brain-wide decreased volume or thickness; (3) white matter tract abnormalities; (4) possible co-morbid AD pathology; and (5) genetic SNPs summarized in S4 Table.

By year three after PD diagnosis, cognitive impairment was diagnosed in 15–37% participants and increased in frequency by 50–200% over this time period depending on the criteria applied, consistent with the relatively high frequency[4, 31] and worsening over time[32] reported in other early PD cohorts.

There were no biological predictors of neuropsychological test-defined impairment; one possible explanation is that the smallest percentage of participants fulfilled this criterion for cognitive impairment over time (15% versus either 24% or 37% for the other criteria). The greatest evidence for biomarkers predicting cognitive decline in this early, relatively cognitively intact population occurred when using the site investigator's annual diagnosis of cognitive impairment.

We found that both caudate and putamen DAT deficits, either at disease onset or worsening over time, predicted cognitive impairment. This confirms previous cross-sectional and longitudinal research in early PD using DAT[33] or other striatal dopamine system imaging ligands[34]. These findings suggest that enhancing dopamine function in early PD might improve cognitive abilities, at least acutely or temporarily[35], and that serial DAT imaging might serve as a cognitive biomarker in PD cognition studies.

Lower CSF Aβ 1–42 levels, suggestive of co-morbid AD Aβ amyloid brain deposition, have been associated with memory impairment in de novo PD patients[31] and as well as future

Table 5. Longitudinal biomarker predictors of investigator diagnosis of cognitive impairment.

Variable	PD Subjects (N = 365)			
	Univariate p-value	# Subjects Missing	Multivariable Analysis OR (95% CI)	p-value
DAT imaging				
Contralateral Caudate	0.05	2	0.484 (0.237, 0.989)	0.05
Ipsilateral Caudate	0.03	2	Not included	NA
Contralateral Putamen	0.22	2	-	-
Ipsilateral Putamen	0.16	2	-	-

https://doi.org/10.1371/journal.pone.0175674.t005

cognitive decline[36, 37]. AD pathology is associated with increasing age in PD, but here an association was shown between cognitive impairment and baseline Aβ 1–42 levels, when the mean age of patients was only 62 years, suggesting that AD-related changes in PD can occur at a relatively young age and long prior to the development of dementia, as reported for MCI in the general population[38] and in preliminary PD neuropathological studies[39].

Multiple, widely spread brain regions of decreased volume, and to a lesser extent thickness, predicted cognitive impairment, and for some brain regions cognitive impairment was predicted by ongoing atrophy, including frontal, parietal, temporal and occipital lobe regions. These findings overlap with previous findings of temporal-parietal and frontal atrophy and thinning with MCI in early PD [40]. It is possible that the cortical atrophy observed in vivo using structural MRI is associated with cortical PD- or AD-related neuropathological changes, which would be consistent with neuropathology studies showing that both cortical LBD pathology and co-morbid Aβ amyloid plaque deposits are associated with cognitive impairment in PD[41].

Specific brain regions (associated cognitive function) implicated included the lateral occipital (object recognition and spatial vision), lateral orbitofrontal (executive abilities), and entorhinal (memory) cortices, subserving cognitive abilities that can be impaired early in the course of PD. The latter finding is consistent with recent research that medial temporal lobe atrophy is associated with cognitive impairment and decline in non-demented PD patients [42].

Neither increased MD nor decreased FA predicted cognitive impairment. Previous research in de novo PD reported an association between increased MD in frontal and parietal white matter tracts and specific cognitive tests[43]. Cohort and study design differences may in part explain these discrepant findings, but the analyses performed here were more stringent than those utilized in previous research.

Two SNPs associated with cognitive decline, the *COMT* val158met SNP and *BDNF* val66-met. There is a complex association between the *COMT* val158met SNP and cognition in PD, influenced by both disease severity and use of dopaminergic medication[44]. In our analyses, the high activity *COMT* val158met genotype was associated with cognitive impairment. Regarding *BDNF*, its product is important for survival and differentiation of dopaminergic neurons in the basal ganglia. A recent study found that the *BDNF* val-allele carriers had great decline in executive abilities over time, consistent with our findings [45].

Unlike some previous studies, we did not show an association between *ApoE4* or *MAPT* status and cognitive impairment. For *ApoE4*, it is important to note that most previous studies have focused on PD patients with dementia[46], and the PPMI sample is relatively young and cognitively intact. For *MAPT*, the H1 haplotype has been associated with cognitive decline or dementia in some[47] but not all[11] PD studies. Longer duration of follow up of this cohort will unveil if genetic risks are important in later-onset or more advanced cognitive dysfunction.

Strengths of the study are inclusion of multiple and international sites; the relatively large sample size; inclusion of multiple biomarkers, including some obtained serially; enrollment of participants starting at symptom onset; annual cognitive and clinical assessments; use of four definitions of cognitive impairment; and a stringent, multi-step statistical analysis plan. Limitations include: highly educated and overwhelmingly white cohort limiting generalizability; variable sample sizes for the different biomarkers, with less than half the patients having research quality MRI scans for inclusion; although CSF is collected serially in PPMI, currently only baseline values are available; the cognitive battery utilized in PPMI is limited and the site investigator's diagnosis of cognitive impairment was available for the entire cohort only starting at year two; other biomarkers associated with early cognitive decline in PD (e.g., measures

of cholinergic integrity and FDG-PET) are not included in PPMI; and lack of comparison with the healthy controls enrolled in PPMI to assess the disease specificity of our findings.

Cognitive decline in early PD is independently predicted by multiple biomarker changes, including nigrostriatal dopamine system deficits, wide-ranging atrophy consistent with cortical neurodegenerative disease, evidence for co-morbid AD pathology, and genetic factors. This provides confirmation for heterogeneity in the neural substrate of the early cognitive deficits in PD, and highlights the need to incorporate multiple biomarkers when risk factors for cognitive decline. Validation and extension of these findings will help in the design of clinical trials for cognitive impairment in PD, including those testing possible disease-modifying therapies from disease onset, and also be a step toward personalized medicine.

Supporting information

S1 Table. Baseline biomarker predictors of investigator diagnosis of cognitive impairment in participants with MRI data.
(DOCX)

S2 Table. Longitudinal biomarker predictors of investigator diagnosis of cognitive impairment in participants with MRI data.
(DOCX)

S3 Table. Baseline biomarker predictors of incident cognitive impairment.
(DOCX)

S4 Table. Summary table of significant biomarker predictors of cognitive impairment.
(DOCX)

Acknowledgments

Data used in the preparation of this article were obtained from the Parkinson's Progression Markers Initiative (PPMI) database (www.ppmi-info.org/data). For up-to-date information on the study, visit www.ppmi-info.org.

¶ Parkinson's Progressions Markers Initiative (PPMI) Authors List

Steering Committee and Study Cores

Kenneth Marek, MD (Principal Investigator, Institute for Neurodegenerative Disorders, New Haven, CT); Danna Jennings, MD (Site Investigator, Olfactory Core, PI; Institute for Neurodegenerative Disorders, New Haven, CT); Shirley Lasch, MBA(Institute for Neurodegenerative Disorders, New Haven, CT); Caroline Tanner, MD, PhD (Site Investigator, University of California, San Francisco, CA);Tanya Simuni, MD (Site Investigator, Northwestern University, Chicago, IL); Christopher Coffey, PhD (Statistics Core, PI; University of Iowa, Iowa City, IA); Karl Kieburtz, MD, MPH (Clinical Core, PI; Clinical Trials Coordination Center, University of Rochester, Rochester, NY); Renee Wilson, MA (Clinical Trials Coordination Center, University of Rochester, Rochester, NY); Werner Poewe, MD (Site Investigator, Innsbruck Medical University, Innsbruck, Austria); Tatiana Foroud, PhD (Genetics Coordination Core, BioRepository PI; Indiana University, Indianapolis, IN); Daniel Weintraub, M.D (Cognitive and Behavioral, University of Pennsylvania, Philadelphia, PA); John Trojanowski, MD, PhD(University of Pennsylvania, Philadelphia, PA); Les Shaw, PhD (University of Pennsylvania, Philadelphia, PA); Todd Sherer, PhD (The Michael J. Fox Foundation for Parkinson's Research, New York, NY); Sohini Chowdhury (The Michael J. Fox Foundation for Parkinson's

Research, New York, NY); Mark Frasier, PhD (The Michael J. Fox Foundation for Parkinson's Research, New York, NY); Catherine Kopil, PhD (The Michael J. Fox Foundation for Parkinson's Research, New York, NY); Vanessa Arnedo (The Michael J. Fox Foundation for Parkinson's Research, New York, NY).

Clinical Coordination Core: Cynthia Casaceli, MBA (Clinical Trials Coordination Center, University of Rochester, Rochester, NY).

Imaging Core: John Seibyl, MD (Principal Investigator; Institute for Neurodegenerative Disorders, New Haven, CT); Nichole Deagle (Institute for Neurodegenerative Disorders, New Haven, CT); Duygu Tosun-Turgut (University of California, San Francisco, CA), Norbert Schuff, PhD (University of California, San Francisco, CA).

Statistics Core: Christopher Coffey, PhD (University of Iowa, Iowa City, IA); Chelsea Caspell (University of Iowa, Iowa City, IA); Liz Uribe (University of Iowa, Iowa City, IA); Eric Foster [(University of Iowa, Iowa City, IA); Katherine Gloer PhD (University of Iowa, Iowa City, IA); Jon Yankey MS (University of Iowa, Iowa City, IA).

Bioinformatics Core: Arthur Toga, PhD (Principal Investigator, Laboratory of Neuroimaging (LONI), University of Southern California), Karen Crawford, MLIS (Laboratory of Neuroimaging (LONI), University of Southern California) Grace Liang MD (Laboratory of Neuroimaging (LONI), University of Southern California)

BioRepository: Danielle Elise Smith (Indiana University, Indianapolis, IN); Paola Casalin (BioRep, Milan, Italy); Giulia Malferrari (BioRep, Milan, Italy).

Bioanalytics Core: Brit Mollenhauer, MD (Principal Investigator/ Site Investigator; Paracelsus-Elena Klinik, Kassel, Germany), Douglas Galasko, MD(Co-Principal/ Site Investigator; University of California, San Diego, CA)

Genetics Core: Andrew Singleton, PhD (Principal Investigator; National Institute on Aging, NIH, Bethesda, MD)

Genetics Coordination Core: Cheryl Halter (Indiana University, Indianapolis, IN); Laura Heathers (Indiana University, Indianapolis, IN).

Site Investigators

David Russell, MD, PhD (Institute for Neurodegenerative Disorders, New Haven, CT); Stewart Factor, DO (Emory University of Medicine, Atlanta, GA); Penelope Hogarth, MD (Oregon Health and Science University, Portland, OR); David Standaert, MD, PhD (University of Alabama at Birmingham, Birmingham, AL); Robert Hauser, MD, MBA (University of South Florida, Tampa, FL); Joseph Jankovic, MD (Baylor College of Medicine, Houston, TX); Matthew Stern, MD (University of Pennsylvania, Philadelphia, PA); Lama Chahine, MD (University of Pennsylvania, Philadelphia, PA); Shu-Ching HU, MD PhD (University of Washington, Seattle, WA); Marie Saint-Hilaire MD (Boston University, Boston, MA); Samuel Frank, MD (Boston University, Boston, MA); Claudia Trenkwalder, MD (Paracelsus-Elena Klinik, Kassel, Germany); Wolfgang Oertel MD (Philipps University Marburg, Germany); Irene Richard, MD (University of Rochester, Rochester, NY); Klaus Seppi, MD (Innsbruck Medical University, Innsbruck, Austria); Eva Reiter, MD (Innsbruck Medical University, Innsbruck, Austria); Holly Shill, MD (Banner Research Institute, Sun City, AZ); Hubert Fernandez, MD (Cleveland Clinic, Cleveland, OH); Anwar Ahmed, MD (Cleveland Clinic, Cleveland, OH); Daniela Berg, MD (University of Tuebingen, Tuebingen, German); Isabel Wurster MD (University of Tuebingen, Tuebingen, German); Zoltan Mari, MD (Johns Hopkins University, Baltimore, MD); David Brooks, MD (Imperial College of London, London, UK); Nicola Pavese, MD (Imperial College of London, London, UK); Yen Tai, MD (Imperial College of London, London, UK); Paolo Barone, MD, PhD (University of Salerno, Salerno, Italy); Stuart Isaacson, MD

(Parkinson's Disease and Movement Disorders Center, Boca Raton, FL); Alberto Espay, MD, MSc (University of Cincinnati, Cincinnati, OH); Dominic Rowe, MD, PhD (Macquarie University, Sydney Australia); Melanie Brandabur MD (The Parkinson's Institute, Sunnyvale, CA); James Tetrud MD (The Parkinson's Institute, Sunnyvale, CA); Karen Marder Columbia Medical, New York, NY); Jean-Christophe Corvol (Pitié-Salpêtrière Hospital, Paris France); Jose Felix Martí Masso (University of Donostia-Service of Neurology Hospital, San Sebastian, Spain); Eduardo Tolosa (University of Barcelona-Hospital Clinic of Barcelona, Barcelona, Spain); Jan O. Aasly (Norwegian University of Science and Technology, Trondheim, Norway); Nir Giladi (Tel Aviv Sourasky Medical Center, Tel Aviv, Isreal); Leonidas Stefanis (Foundation for Biomedical research of the Academy of Athens, Athens, Greece).

Coordinators

Debra Smejdir (Institute for Neurodegenerative Disorders, New Haven, CT); Julia PelaggI (Institute for Neurodegenerative Disorders, New Haven, CT); Linda Rees, MPH(Institute for Neurodegenerative Disorders, New Haven, CT); Barbara Sommerfeld, RN, MSN (Emory University of Medicine, Atlanta, GA); Cathy Wood-Siverio, MS (Emory University of Medicine, Atlanta, GA); Alicia Portillo (Oregon Health and Science University, Portland, OR); Art Lenahan (Oregon Health and Science University, Portland, OR); Karen Williams (Northwestern University, Chicago, IL); Stephanie Guthrie, MSN (University of Alabama at Birmingham, Birmingham, AL); Ashlee Rawlins (University of Alabama at Birmingham, Birmingham, AL); Sherry Harlan (University of South Florida, Tampa, FL); Christine Hunter, RN (Baylor College of Medicine, Houston, TX); Baochan Tran (University of Pennsylvania, Philadelphia, PA); Abigail Darin (University of Pennsylvania, Philadelphia, PA); Carly Linder (University of Pennsylvania, Philadelphia, PA); Gretchen Todd (University of Washington, Seattle, WA); Cathi-Ann Thomas, RN, MS (Boston University, Boston, MA); Raymond James, RN (Boston University, Boston, MA); Cheryl Deeley, MSN (University of Rochester, Rochester, NY); Courtney Bishop BS (University of Rochester, Rochester, NY); Fabienne Sprenger, MD (Innsbruck Medical University, Innsbruck, Austria); Diana Willeke (Paracelsus-Elena Klinik, Kassel, Germany); Sanja Obradov (Banner Research Institute, Sun City, AZ); Jennifer Mule (Cleveland Clinic, Cleveland, OH); Nancy Monahan (Cleveland Clinic, Cleveland, OH); Katharina Gauss (University of Tuebingen, Tuebingen, German); Kathleen Comyns (University of California, San Francisco, CA); Deborah Fontaine, BSN, MS, RN, GNP, MS (University of California, San Diego, CA); Christina Gigliotti (University of California, San Diego, CA); Erica Stacey (Johns Hopkins University, Baltimore, MD); Becky Dunlop (Johns Hopkins University, Baltimore, MD); Bina Shah, BSc (Imperial College of London, London, UK); Susan Ainscough (University of Salerno, Salerno, Italy); Angela James (University of Cincinnati, Cincinnati, OH); Rebecca Silverstein (Parkinson's Disease and Movement Disorders Center, Boca Raton, FL); Kristy Espay (University of Cincinnati, Cincinnati, OH); Madelaine Ranola (Macquarie University, Sydney Australia); Helen M. Santana (Columbia Medical, New York, NY); Nelly Ngono (Pitié-Salpêtrière Hospital, Paris France); Elisabet Rezola (University of Donostia-Service of Neurology Hospital, San Sebastian, Spain); Delores Vilas Rolan (University of Barcelona-Hospital Clinic of Barcelona, Barcelona, Spain); Bjorg Waro (Norwegian University of Science and Technology, Trondheim, Norway); Anat Mirlman (Tel Aviv Sourasky Medical Center, Tel Aviv, Isreal); Maria Stamelou (Foundation for Biomedical research of the Academy of Athens, Athens, Greece).

ISAB (Industry Scientific Advisory Board)

Maurizio Facheris, MD (Abbvie); Andrew Siderowf, MD, MSCE (Avid Radiopharmaceuticals); Mark A. Mintun, MD (Avid Radiopharmaceuticals); Jesse Cedarbaum, MD (Biogen

Idec); Peggy Taylor, ScD (BioLegend); Holly Soares, PhD (Bristol-Myers Squibb Company); Irfan Qureshi, PhD (Bristol-Myers Squibb Company); Michael Ahlijanian, PhD (Bristol-Myers Squibb Company); Lawrence Slieker, PhD (Eli Lilly and Company); Colin Watson, PhD (GE Healthcare); Etienne Montagut, MBA (GE Healthcare); Zulfiqar Haider Sheikh (GE Healthcare); Marcel van der Brug, PhD (Genentech); Remi Forrat (Genyzme Sanofi); Pablo Sardi, PhD (Genyzme Sanofi); Tanya Fischer, MD, PhD (Genyzme Sanofi); Alastair D. Reith, PhD (GlaxoSmithKline Pharmaceuticals R&D); Jan Egebjerg, PhD (H. Lundbeck A/S); Lone Frydelund Larsen (H. Lundbeck A/S); Nathalie Breysse, PhD (H. Lundbeck A/S); Paul E.G. Kristijansen, MD, PhD (H. Lundbeck A/S); Barbara Saba, MD (Institut de Recherches Internationales Servier); Vera Kiyasova, MD, PhD (Institut de Recherches Internationales Servier); Chris Min, MD, PhD (Merck); Thomas McAvoy, PhD (Merck); Robert Umek, PhD (Meso Scale Discovery); Eva Jajos-Korcsok, PhD (Pfizer Inc); Thomas Comery, PhD (Pfizer Inc); Susan De Santi, PhD (Piramal); Christian Czech, PhD (Roche); Frank Boess, PhD (Roche); Jeffrey Sevigny, MD (Roche); Thomas Kremer, PhD (Roche); Igor Grachev, MD, PhD (Teva); Kaplana Merchant, PhD (TransThera Consulting); Andreja Avbersek, MD (UCB Pharma S.A); Pierandrea Muglia, MD (UCB Pharma S.A); Alexandra Stewart, MBA (Weston Brain Institute); Rene Prashad, PhD (Weston Brain Institute).

Author Contributions

Data curation: LAS.

Formal analysis: EDF J-HK A. Singleton MN YZ I-WW DT-T CC-G.

Methodology: TS CC DB LAS.

Project administration: DW SL CC JQT A. Singleton DT-T TS.

Supervision: SL.

Writing – original draft: CC-G TS DT-T I-WW YZ MN A. Singleton J-HK JQT A. Siderowf CC SL DA DB LMC AJE EDF KAH IL IR DW LAS.

Writing – review & editing: CC-G TS DT-T I-WW YZ MN A. Singleton J-HK JQT A. Siderowf CC SL DA DB LMC AJE EDF KAH IL IR DW.

References

1. Aarsland D, Bronnick K, Williams-Gray C, Weintraub D, Marder K, Kulisevsky J, et al. Mild cognitive impairment in Parkinson's disease: A multicenter pooled analysis. Neurology. 2010; 75:1062–9. https://doi.org/10.1212/WNL.0b013e3181f39d0e PMID: 20855849
2. Aarsland D, Andersen K, Larsen J, Lolk A, Kragh-Sørensen P. Prevalence and characteristics of dementia in Parkinson disease: an 8-year prospective study. Archives of Neurology. 2003; 60:387–92. PMID: 12633150
3. Pigott K, Rick J, Xie S, Hurtig H, Chen-Plotkin A, Duda J, et al. Longitudinal study of normal cognition in Parkinson disease. Neurology. 2015; 85(15):1276–82. PubMed Central PMCID: PMCPMC4617168. https://doi.org/10.1212/WNL.0000000000002001 PMID: 26362285
4. Aarsland D, Bronnick K, Larsen J, Tysnes O, Alves G, Group FtPS. Cognitive impairment in incident, untreated Parkinson disease: The Norwegian ParkWest Study. Neurology. 2009; 72:1121–6. https://doi.org/10.1212/01.wnl.0000338632.00552.cb PMID: 19020293
5. Weintraub D, Burn D. Parkinson's disease: the quintessential neuropsychiatric disorder. Movement Disorders. 2011; 26:1022–31. https://doi.org/10.1002/mds.23664 PMID: 21626547
6. Hurtig H, Trojanowski J, Galvin J, al. e. Alpha-synuclein cortical Lewy bodies correlate with dementia in Parkinson's disease. Neurology. 2000; 54(10):1916–21. PMID: 10822429

7. Jellinger K, Seppi K, Wenning G, Poewe W. Impact of coexistent Alzheimer pathology on the natural history of Parkinson's disease. Journal of Neural Transmission. 2002; 109:329–39. https://doi.org/10.1007/s007020200027 PMID: 11956955
8. Bohnen N, Albin R. Cholinergic denervation occurs early in Parkinson's disease. Neurology. 2010; 73:256–7.
9. Kaasinen V, Rinne J. Functional imaging studies of dopamine system and cognition in normal aging and Parkinson's disease. Neuroscience and Biobehavioral Reviews. 2002; 26:785–93. PMID: 12470690
10. Zweig R, Cardillo J, Cohen M, Giere S, Hedreen J. The locus ceruleus and dementia in Parkinson's disease. Neurology. 1993; 43:986. PMID: 8492957
11. Morley J, Xie S, Hurtig H, Stern M, Colcher A, Horn S, et al. Genetic influences on cognitive decline in Parkinson's disease. Movement Disorders. 2012; 27:512–8. https://doi.org/10.1002/mds.24946 PMID: 22344634
12. Foltynie T, Lewis S, Goldberg T, Blackwell A, Kolachana B, Weinberger D, et al. The BDNF Val^{66}Met polymorphism has a gender specific influence on planning ability in Parkinson's disease. Journal of Neurology. 2005; 252:833–8. https://doi.org/10.1007/s00415-005-0756-5 PMID: 15772739
13. Williams-Gray C, Hampshire A, Barker R, Owen A. Attentional control in Parkinson's disease is dependent on COMT val^{158}met genotype. Brain. 2008; 131:397–408. https://doi.org/10.1093/brain/awm313 PMID: 18178571
14. Williams-Gray C, Evans J, Goris A, Foltynie T, Ban M, Robbins T, et al. The distinct cognitive syndromes of Parkinson's disease: 5 year follow-up of the CamPaIGN cohort. Brain. 2009; 132:2958–69. https://doi.org/10.1093/brain/awp245 PMID: 19812213
15. Burton E, McKeith I, Burn D, Williams E, O'Brien J. Cerebral atrophy in Parkinson's disease with and without dementia: A comparison with Alzheimer's disease, dementia with Lewy bodies and controls. Brain. 2004; 127:791–800. https://doi.org/10.1093/brain/awh088 PMID: 14749292
16. Gattellaro G, Minati L, Grisoli M, Mariani C, Carella F, Osio M, et al. White matter involvement in idiopathic Parkinson disease: a diffusion tensor imaging study. American Journal of Neuroradiology. 2009; 30:1222–6. https://doi.org/10.3174/ajnr.A1556 PMID: 19342541
17. Marek K, Jennings D, Lasch S, Siderowf A, Tanner C, Simuni T, et al. The Parkinson Progression Marker Initiative (PPMI). Progress in Neurobiology. 2011; 95:629–35. https://doi.org/10.1016/j.pneurobio.2011.09.005 PMID: 21930184
18. Weintraub D, Simuni T, Caspell-Garcia C, Coffey C, Lasch S, Siderowf A, et al. Cognitive performance and neuropsychiatric symptoms in early, untreated Parkinson's disease. Movement Disorders. 2015; 30(7):919–27. PubMed Central PMCID: PMCPMC4855523. https://doi.org/10.1002/mds.26170 PMID: 25737166
19. Litvan I, Goldman J, Troster A, Schmand B, Weintraub D, Petersen R, et al. Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force Guidelines. Movement Disorders. 2012; 27(3):349–56. PubMed Central PMCID: PMCPMC3641655. https://doi.org/10.1002/mds.24893 PMID: 22275317
20. Dalrymple-Alford J, MacAskill M, Nakas C, Livingston L, Graham C, Crucian G, et al. The MoCA: well-suited screen for cognitive impairment in Parkinson disease. Neurology. 2010; 75:1717–25. https://doi.org/10.1212/WNL.0b013e3181fc29c9 PMID: 21060094
21. Emre M, Aarsland D, Brown R, Burn D, Duyckaerts C, Mizuno Y, et al. Clinical diagnostic criteria for dementia associated with Parkinson's disease. Movement Disorders. 2007; 22:1689–707. https://doi.org/10.1002/mds.21507 PMID: 17542011
22. Kang JH, Mollenhauer B, Coffey CS, Toledo JB, Weintraub D, Galasko DR, et al. CSF biomarkers associated with disease heterogeneity in early Parkinson's disease: the Parkinson's Progression Markers Initiative study. Acta Neuropathol. 2016; 131(6):935–49. PubMed Central PMCID: PMCPMC5031365. https://doi.org/10.1007/s00401-016-1552-2 PMID: 27021906
23. Fischl B. FreeSurfer. Neuroimage. 2012; 62(2):774–81. PubMed Central PMCID: PMCPMC3685476. https://doi.org/10.1016/j.neuroimage.2012.01.021 PMID: 22248573
24. Reuter M, Schmansky NJ, Rosas HD, Fischl B. Within-subject template estimation for unbiased longitudinal image analysis. Neuroimage. 2012; 61(4):1402–18. PubMed Central PMCID: PMCPMC3389460. https://doi.org/10.1016/j.neuroimage.2012.02.084 PMID: 22430496
25. Schuff N, Wu IW, Buckley S, Foster ED, Coffey CS, Gitelman DR, et al. Diffusion imaging of nigral alterations in early Parkinson's disease with dopaminergic deficits. Mov Disord. 2015; 30(14):1885–92. https://doi.org/10.1002/mds.26325 PMID: 26260437
26. Evans A, Collins D, Mills S, Brown E, Kelly R, Peters T, editors. 3D Statistical Neuroanatomical Models from 305 MRI Volumes. Nuclear Science Symposium & Medical Imaging Conference; 1993 1993.

27. Oishi K, Faria A, Jiang H, Li X, Akhter K, Zhang J, et al. Atlas-based whole brain white matter analysis using large deformation diffeomorphic metric mapping: application to normal elderly and Alzheimer's disease participants. Neuroimage. 2009; 46(2):486–99. PubMed Central PMCID: PMCPMC2885858. PMID: 19385016

28. Desikan RS, Segonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage. 2006; 31(3):968–80. https://doi.org/10.1016/j.neuroimage.2006.01.021 PMID: 16530430

29. Nalls M, Keller M, Hernandez D, Chen L, Stone D, Singleton AB, Investigators obotPsPMIP. Baseline genetic associations in the Parkinson's Progression Markers Initiative (PPMI). Movement Disorders. 2016; 31:79–85. https://doi.org/10.1002/mds.26374 PMID: 26268663

30. Tomlinson C, Stowe R, Patel S, Rick C, Gray R, Clarke C. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Movement Disorders. 2010; 25:2649–53. https://doi.org/10.1002/mds.23429 PMID: 21069833

31. Yarnall A, Breen D, Duncan G, Khoo T, Coleman S, Firbank M, et al. Characterizing mild cognitive impairment in incident Parkinson disease: The ICICLE-PD Study. Neurology. 2014; 82:308–16. https://doi.org/10.1212/WNL.0000000000000066 PMID: 24363137

32. Williams-Gray C, Foltynie T, Brayne C, Robbins T, Barker R. Evolution of cognitive dysfunction in an incident Parkinson's disease cohort. Brain. 2007; 130:1787–98. https://doi.org/10.1093/brain/awm111 PMID: 17535834

33. Ravina B, Marek K, Eberly S, Oakes D, Kurlan R, Ascherio A, et al. Dopamine transporter imaging is associated with long-term outcomes in Parkinson's disease. Movement Disorders. 2012; 27:1392–7. https://doi.org/10.1002/mds.25157 PMID: 22976926

34. Bohnen NI, Albin R, Muller M, Petrou M, Kotagal V, Koeppe R, et al. Frequency of cholinergic and caudate nucleus dopaminergic deficits across the predemented cognitive spectrum of Parkinson disease and evidence of interaction effects. JAMA Neurology. 2015; 72:194–200. https://doi.org/10.1001/jamaneurol.2014.2757 PMID: 25506674

35. Poletti M, Bonuccelli U. Acute and chronic cognitive effects of levodopa and dopamine agonists on patients with Parkinson's disease: a review. Therapeutic advances in psychopharmacology. 2013; 3(2):101–13. https://doi.org/10.1177/2045125312470130 PMID: 24167681

36. Siderowf A, Xie S, Hurtig H, Weintraub D, Duda J, Chen-Plotkin A, et al. CSF amyloid *B* 1–42 predicts cognitive decline in Parkinson's disease. Neurology. 2010; 75:1055–61. https://doi.org/10.1212/WNL.0b013e3181f39a78 PMID: 20720189

37. Alves G, Lange J, Blennow K, Zetterberg H, Andreasson U, Forland M, et al. CSF A-Beta$_{42}$ predicts early-onset dementia in Parkinson disease. Neurology. 2014; 82(1784):1790.

38. Buchhave P, Minthon L, Zetterberg H, Wallin AK, Blennow K, Hansson O. Cerebrospinal fluid levels of B-amyloid 1–42, but not of tau, are fully changed already 5 to 10 years before the onset of Alzheimer dementia. Arch Gen Psychiatry. 2012; 69:98–106. https://doi.org/10.1001/archgenpsychiatry.2011.155 PMID: 22213792

39. Adler C, Caviness J, Sabbagh M, Shill H, Connor D, Sue L, et al. Heterogeneous neuropathological findings in Parkinson's disease with mild cognitive impairment. Acta Neuropathologica. 2010; 120:827–8. https://doi.org/10.1007/s00401-010-0744-4 PMID: 20838798

40. Uribe C, Segura B, Baggio HC, Abos A, Marti MJ, Valldeoriola F, et al. Patterns of cortical thinning in nondemented Parkinson's disease patients. Mov Disord. 2016; 31(5):699–708. PubMed Central PMCID: PMCPMC5061099. https://doi.org/10.1002/mds.26590 PMID: 27094093

41. Compta Y, Parkkinen L, O'Sullivan S, Vandrovcova J, Holton J, Collins C, et al. Lewy- and Alzheimer-type pathologies in Parkinson's disease dementia: which is more important? Brain. 2011; 134:1493–505. https://doi.org/10.1093/brain/awr031 PMID: 21596773

42. Weintraub D, Dietz N, Duda J, Wolk D, Doshi J, Xies S, et al. Alzheimer's disease pattern of brain atrophy predicts cognitive decline in Parkinson's disease. Brain. 2012; 135:170–80. https://doi.org/10.1093/brain/awr277 PMID: 22108576

43. Duncan G, Firbank M, Yarnall A, Khoo T, Brooks D, Barker R, et al. Gray and white matter imagine: a biomarker for cognitive impairment in early Parkinson's disease? Movement Disorders. 2016; 31:103–10. https://doi.org/10.1002/mds.26312 PMID: 26202802

44. Foltynie T, Goldberg T, Lewis S, Blackwell A, Kolachana B, Weinberger D, et al. Planning ability in Parkinson's disease is influenced by the COMT Val^{158}Met polymorphism. Movement Disorders. 2004; 19:885–91. https://doi.org/10.1002/mds.20118 PMID: 15300652

45. van der Kolk NM, Speelman AD, van Nimwegen M, Kessels RP, IntHout J, Hakobjan M, et al. BDNF polymorphism associates with decline in set shifting in Parkinson's disease. Neurobiol Aging. 2015; 36(3):1605 e1–6.

46. Tsuang D, Leverenz J, Lopez O, Hamilton R, Bennett D, Schneider J, et al. *APOE* E4 increases risk for dementia in pure synulceinopathies. JAMA Neurology. 2013; 70:223–8. PubMed Central PMCID: PMCPMC3580799. https://doi.org/10.1001/jamaneurol.2013.600 PMID: 23407718

47. Seto-Salvia N, Clarimon J, Pagonabarraga J, Pascual-Sedano B, Campolongo A, Combarros O, et al. Dementia risk in Parkinson disease: Disentangling the role of MAPT haplotypes. Archives of Neurology. 2011; 68:359–64. https://doi.org/10.1001/archneurol.2011.17 PMID: 21403021