Title
APOE, MAPT, and SNCA Genes and Cognitive Performance in Parkinson Disease

Journal
JAMA Neurology, 71(11)

ISSN
2168-6149

Authors
Mata, Ignacio F
Leverenz, James B
Weintraub, Daniel
et al.

Publication Date
2014-11-01

DOI
10.1001/jamaneurol.2014.1455

Peer reviewed

Published in final edited form as:
JAMA Neurol. 2014 November 1; 71(11): 1405–1412. doi:10.1001/jamaneurol.2014.1455.

APOE, *MAPT*, *SNCA*, and Cognitive Performance in Parkinson Disease

Ignacio F. Mata, PhD[1,2], **James B. Leverenz, MD**[1,2,3], **Daniel Weintraub, MD**[4,5,6], **John Q. Trojanowski, MD, PhD**[7,8], **Howard I. Hurtig, MD**[4], **Vivianna M. Van Deerlin, MD, PhD**[7], **Beate Ritz, MD, PhD**[9,10,11], **Rebecca Rausch, PhD**[11], **Shannon L Rhodes, PhD**[9], **Stewart A. Factor, DO**[12], **Cathy Wood-Siverio, MS**[12], **Joseph F. Quinn, MD**[13,14], **Kathryn A. Chung, MD**[13,14], **Amie L. Peterson, MD**[13,14], **Alberto J. Espay, MD**[15], **Fredy J. Revilla, MD**[15,16], **Johnna Devoto, PsyD**[15], **Shu-Ching Hu, MD PhD**[1,2], **Brenna A. Cholerton, PhD**[1,3], **Jia Y. Wan, MS**[17], **Thomas J. Montine, MD, PhD**[18], **Karen L. Edwards, PhD**[17], and **Cyrus P. Zabetian, MD, MS**[1,2,*]

[1]Veterans Affairs Puget Sound Health Care System, Seattle, WA

[2]Department of Neurology, University of Washington School of Medicine, Seattle, WA

[3]Department of Psychiatry and Behavioral Sciences, University of Washington School of Medicine, Seattle, WA

[4]Department of Neurology, University of Pennsylvania, Philadelphia, PA

[5]Department of Psychiatry, University of Pennsylvania, Philadelphia, PA

[6]Philadelphia Veterans Affairs Medical Center, Philadelphia, PA

[7]Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, PA

[8]Institute on Aging, University of Pennsylvania, Philadelphia, PA

[9]Department of Epidemiology, School of Public Health, University of California Los Angeles, Los Angeles, CA

[*]Corresponding Author: VA Puget Sound Health Care System, GRECC S-182, 1660 S. Columbian Way, Seattle, WA 98108. Phone: (206) 277-6167; fax: (206) 764-2569; zabetian@u.washington.edu. .

Author Contributions: Dr. Zabetian had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Mata and Zabetian
Acquisition of data: Mata, Leverenz, Weintraub, Hurtig, Van Deerlin, Ritz, Rausch, Factor, Wood-Siverio, Quinn, Chung, Peterson, Espay, Revilla, Devoto, Hu, Cholerton and Zabetian
Analysis and interpretation of data: All authors
Drafting of the manuscript: Mata and Zabetian
Critical revision of the manuscript for important intellectual content: All authors
Statistical analysis: Mata, Wan and Edwards
Obtained funding: Leverenz, Trojanowski, Ritz, Factor, Quinn, Montine, Edwards and Zabetian
Administrative, technical, or material support: All authors
Supervision: Mata, Leverenz, Weintraub, Trojanowski, Hurtig, Van Deerlin, Ritz, Rausch, Factor, Quinn, Espay, Revilla, Cholerton, Montine, Edwards, and Zabetian

Conflict of interest disclosures: No other disclosures were reported

Additional Contributions: The authors thank all subjects for participating in this work. We also thank Jacqueline Rick and Dora Yearout for technical assistance.

[10]Department of Environmental Health Sciences, School of Public Health, University of California Los Angeles, Los Angeles, CA

[11]Department of Neurology, University of California Los Angeles, Los Angeles, CA

[12]Department of Neurology, Emory University School of Medicine, Atlanta, GA

[13]Portland Veterans Affairs Medical Center, Portland, OR

[14]Department of Neurology, Oregon Health and Science University, Portland, OR

[15]Department of Neurology and Rehabilitation Medicine, University of Cincinnati, Cincinnati, OH

[16]Cincinnati Veterans Affairs Medical Center, Cincinnati, OH

[17]Department of Epidemiology, University of Washington, Seattle, WA, USA

[18]Department of Pathology, University of Washington School of Medicine, Seattle, WA

Abstract

Importance—Cognitive impairment (CI) is a common and disabling problem in Parkinson's disease (PD) that is not well understood and is difficult to treat. Identification of genetic variants that influence the rate of cognitive decline or pattern of early cognitive deficits in PD might provide a clearer understanding of the etiopathogenesis of this important non-motor feature.

Objectives—To determine if common variation in the *APOE*, *MAPT*, and *SNCA* genes is associated with cognitive performance in patients with PD.

Design, Setting and Participants—We studied 1,079 PD patients from six academic centers in the U.S. who underwent assessments of memory (Hopkins Verbal Learning Test-Revised [HVLT-R]), attention/executive function (Letter-Number Sequencing and Trail Making Test), language processing (semantic and phonemic verbal fluency), visuospatial skills (Benton Judgment of Line Orientation) and global cognitive function (Montreal Cognitive Assessment [MoCA]). Subjects were genotyped for *APOE* ε2/ε3/ε4, *MAPT* H1/H2 haplotypes, and *SNCA* rs356219. Linear regression was used to test for association between genotype and baseline cognitive performance adjusting for age, sex, years of education, disease duration, and site. We used a Bonferroni correction to adjust for the nine comparisons that were performed for each gene.

Main Outcomes and Measures—Nine variables derived from seven psychometric tests.

Results—*APOE* ε4 was associated with lower performance on HVLT-R total learning (P=6.7×10^{-6}; corrected P [P_c]=6.0×10^{-5}), delayed recall (P=0.001; P_c=0.009), and recognition discrimination index (P=0.004; P_c=0.04), and semantic verbal fluency (P=0.002; P_c=0.018), Letter-Number sequencing (P=1 × 10^{-5}; P_c=9 × 10^{-5}), and Trails B-A (P=0.002; P_c=0.018). In a subset of 645 non-demented patients, *APOE* ε4 was associated with lower scores on HVLT-R total learning (P=0.005; P_c=0.045) and semantic verbal fluency (P=0.005; P_c=0.045). *MAPT* and *SNCA* variants were not associated with scores on any tests.

Conclusions and Relevance—Our data indicate that *APOE* ε4 is an important predictor of cognitive function in PD across multiple domains. Among non-demented PD patients, *APOE* ε4 was only associated with lower performance on word list learning and semantic verbal fluency, a pattern more typical of the cognitive deficits seen in early Alzheimer's disease than PD.

INTRODUCTION

Cognitive impairment (CI) commonly occurs in Parkinson disease (PD) and has a major impact on quality of life, caregiver distress, the need for nursing home placement, and mortality.[1-4] At the time of diagnosis 19-24% of PD patients have mild cognitive impairment (MCI)[5,6] and up to 80% develop dementia (PDD) during the course of the disease.[7,8] The rate of cognitive decline and pattern of early cognitive deficits in PD are highly variable for reasons that are not well understood.[9,10] Identification of biological markers, including common genetic variants, that account for this heterogeneity could provide important insights into the pathological processes that underlie CI in PD.

Few genetic studies have been conducted in this area and most have focused on the endpoint of dementia. Available evidence suggests that at least three genes, *APOE*, *MAPT*, and *SNCA*, might play a role in determining susceptibility to CI in PD. The *APOE* ε4 allele is a well-established risk factor for Alzheimer's disease (AD)[11] and is also associated with slightly reduced cognition in healthy older adults.[12,13] *APOE* ε4 was found to predict earlier onset of dementia or more rapid cognitive decline in patients with PD in some studies[14,15] but not others.[16,17] The *MAPT* H1 haplotype is a well-known risk factor for several neurodegenerative disorders including PD, progressive supranuclear palsy, and corticobasal degeneration.[18,19] Two studies found that the *MAPT* H1 haplotype is a risk factor for dementia in PD[20,21] but these findings require further replication. Finally, rare multiplications of the *SNCA* gene result in PD, often accompanied by early-onset dementia.[22] Common *SNCA* polymorphisms also convey risk for PD[23] but whether these same variants predispose patients with PD to develop CI early in their clinical course is not known.

In this study we examined the association between common variation in *APOE*, *MAPT*, and *SNCA* and cognitive performance in a large, multi-center sample of patients with PD.

METHODS

Subjects

The initial study population was 1,191 patients with PD enrolled in studies at Emory University, the University of Cincinnati, and the Pacific Northwest, University of Pennsylvania, and University of California, Los Angeles (UCLA) Morris K. Udall Centers of Excellence for Parkinson's Disease Research. The Pacific Northwest Udall Center (PANUC) is comprised of two sites, one in Seattle, WA (University of Washington/VA Puget Sound Health Care System) and one in Portland, OR (Oregon Health and Science University/Portland VA Medical Center). All subjects met United Kingdom PD Society Brain Bank clinical diagnostic criteria for PD, except those from UCLA who satisfied clinical diagnostic criteria for PD as described elsewhere.[24] Requirements to meet the latter criteria include: (1) presence of at least two of the following signs: bradykinesia, rigidity, resting tremor, (2) no suggestion of a cause for another parkinsonian syndrome, and (3) no atypical features. Each subject underwent a detailed neuropsychological assessment (performed in the "on" state if medicated) and seven tests that overlapped between sites were chosen as the "core battery" (defined in the following section). Thirty-seven

participants completed less than half of the tests in the core battery and were excluded from the sample. To reduce genetic heterogeneity all participants were genotyped for a panel of ancestry informative markers designed to estimate admixture proportions from four ancestral populations: Europeans, East Asians, Africans, and Amerindians (unpublished results). Seventy-five subjects estimated to have <90% European ancestry were excluded. The final study population was comprised of 1,079 subjects.

Standard protocol approvals, registrations, and patient consents were obtained. All study procedures were approved by the institutional review boards at each participating site.

Neuropsychological assessment

All study participants underwent psychometric testing under the supervision of a neurologist or psychiatrist (University of Pennsylvania), or a neuropsychologist (all other sites) experienced in the assessment of patients with PD. Seven tests that were administered by at least five of the six sites were defined as the core battery: the Montreal Cognitive Assessment (MoCA), Hopkins Verbal Learning Test-Revised (HVLT-R), Letter-Number Sequencing, Trail Making Test (Trails), semantic verbal fluency (animals), phonemic verbal fluency (FAS), and Benton Judgment of Line Orientation (JoLO) (Table 1). Data from subjects enrolled at PANUC-Seattle, PANUC-Portland, the University of Cincinnati, and the University of Pennsylvania Udall Center were reviewed at a diagnostic consensus conference, and subjects were classified as demented or non-demented as previously described.[25,26] The non-demented group included subjects with either no CI or mild CI. Note that scores on tests with less overlap between sites that were not included in the core battery, such as Logical Memory, Boston Naming, Digit Span, and Digit Symbol, were used in determining cognitive diagnosis when available.

Genotyping

Genomic DNA was extracted from peripheral blood using standard methods. All subjects were genotyped for 29 ancestry informative markers and four single nucleotide polymorphisms (SNPs) in the genes of interest: *APOE* rs429358 and rs7412 (which define the ε2, ε3 and ε4 alleles), *MAPT* rs1800547 (which differentiates the H1 and H2 haplotypes), and *SNCA* rs356219. Genotyping was performed using TaqMan assays on the Fluidigm BioMark HD System. The genotyping success rate was 100% for *MAPT* and *SNCA*, and > 99% for *APOE*.

Statistical analysis

We assessed each SNP for Hardy-Weinberg equilibrium (HWE) using an exact test. We selected (*a priori*) nine variables for analysis from the core battery that represent the primary measures most commonly used in a clinical setting for each test: total scores for MoCA, Letter-Number Sequencing, Trails B-A, semantic and phonemic verbal fluency, JoLO, HVLT-R total learning, HVLT-R delayed recall, and HVLT-R recognition discrimination index (calculated as true positive score minus false positive score). The association between genotype and cognitive performance was tested using linear regression under an additive genetic model adjusting for sex, years of education, disease duration, age at testing, and site. Disease duration was calculated as the difference between age at testing and age at

diagnosis. Separately for association tests involving *APOE*, *MAPT*, and *SNCA*, we used a Bonferroni correction to adjust for the nine comparisons that were performed. We used a Pearson χ^2 test to compare categorical subject characteristics across sites and genotypes and to compare genotypes across sites. We used analysis of variance (ANOVA) to compare continuous subject characteristics across sites and genotypes. All analyses were performed using Stata version 10.0 (StataCorp, College Station, TX).

RESULTS

There were small but significant differences in all of the clinical and demographic characteristics of the study participants across sites (Table 2). For example, at UCLA, the mean age at testing and mean age at diagnosis were higher, and the mean years of education lower, than for most of the other sites. There was a predominance of males at each site, which was particularly marked at the PANUC Portland site (92.2%).

None of the SNPs deviated significantly from HWE. There were no significant differences in population characteristics across genotypes (eTable 1) or in genotype frequencies across sites (eTable 2).

The *APOE* ε4 allele was associated with lower performance on six of the nine psychometric variables after correction for multiple testing: HVLT-R total learning (corrected *P* [P_c]=6.0×10^{-5}), delayed recall (P_c=0.009), and recognition discrimination index (P_c=0.04), and semantic verbal fluency (P_c=0.018), Letter-Number sequencing ($P_c=9\times10^{-5}$), and Trails B-A (P_c=0.018) (Table 3). Box plots of the data by *APOE* genotype for the six significant variables are presented in the eFigure. However, there was no significant association between either the *MAPT* H1 haplotype or *SNCA* rs356219 and any of the psychometric tests (P>0.05; Table 3). For psychometric variables that deviated from normality when examining histograms and quantile-quantile plots (MoCA, Trails B-A, JoLO, HVLT-R recognition discrimination index), results of the aforementioned association analysis were similar when applying data transformations to better achieve a normal distribution (data not shown).

To allow comparison between the effects of *APOE* and the clinical and demographic covariates included in the regression models, beta coefficients for each of these variables are presented in eTable 3. For example, there was an expected decrease of 1.55 words in mean HVLT-R total learning for each additional copy of the *APOE* ε4 allele. The effect of one *APOE* ε4 allele on HVLT-R total learning was equivalent to the effect of 3.5 (i.e., Beta_{APOE}/ BetaEDUCATION= -1.55/.44) fewer years of education or an increase in age at testing of 6.0 (i.e., Beta_{APOE}/BetaAGE AT TESTING= -1.55/-.26) years given the same values for all other covariates.

In order to assess the effects of *APOE* on cognition in PD prior to the onset of dementia, we then analyzed the ε4 allele in the subset of patients who had received a cognitive diagnosis via consensus diagnosis conference (n = 775). As in the full sample, *APOE* ε4 predicted lower performance in nearly all tests prior to adjustment for multiple comparisons (Table 4). After Bonferroni correction, HVLT-R total learning ($P=2\times10^{-4}$; P_c=0.0018) and semantic

verbal fluency (P=0.002; P_c=0.02) remained significant, and Letter-Number Sequencing (P=0.009; P_c=0.081) and MoCA (P=0.01; P_c=0.09) approached significance. When patients with a diagnosis of dementia (n=130) were removed and the data reanalyzed, the only associations that remained significant were HVLT-R total learning (P=0.005; P_c=0.045) and semantic verbal fluency (P=0.005; P_c=0.045).

DISCUSSION

In a multicenter cohort of patients with PD, the *APOE* ε4 allele predicted lower performance across multiple cognitive domains including memory, attention/executive function, and language processing. In non-demented patients the effect of the ε4 allele was restricted to HVLT-R total learning and semantic verbal fluency. In contrast, the *MAPT* H1 haplotype and *SNCA* rs356219 were not correlated with scores on any of the psychometric tests.

APOE ε4 is a well-known risk factor for AD. In pre-clinical and early AD deficits in episodic memory predominate. However, impairment in semantic fluency, with relative sparing of phonemic fluency, also occurs.[27,28] This observation is attributed to the fact that temporal cortex, one of the first brain regions affected in AD,[29,30] plays a larger role in mediating semantic than phonemic verbal fluency.[31] In contrast, early cognitive deficits in PD usually involve attention and frontal-executive function mediated in part by cortical-striatal dopamine deficiency, though some patients do initially exhibit isolated deficits in other domains.[6,32] We observed that in non-demented PD patients *APOE* ε4 was only associated with poorer performance on word list learning and semantic verbal fluency (Table 4), a pattern more typical of the cognitive deficits seen in early AD than PD. Thus, individuals with PD who carry the ε4 allele might be particularly vulnerable to early semantic memory impairment, and this might in part explain the heterogeneity in cognitive profiles reported in PD patients with MCI.[10,33] In AD, *APOE* ε4 is thought to influence disease risk by accelerating the accumulation of neurotoxicamyloid-β (Aβ) which ultimately leads to neurodegeneration with accompanying “AD neuropathologic changes” (i.e. neuritic plaques and neurofibrillary tangles). Whether the neuropathologic substrate of CI in PD patients who carry *APOE* ε4 consistently involves an increased burden of AD neuropathologic changes is not clear. However, *APOE* genotype was not correlated with measures of AD pathology in a recent PD autopsy series[34] or with brain amyloid burden in PD patients imaged with Pittsburgh compound B.[35] Thus, it is possible that *APOE* might affect cognition in PD through mechanisms unrelated to Aβ processing.

Previous studies of the effect of *APOE* on CI in PD have yielded mixed results, and the interpretation of these data is complicated by the wide variety of study designs and cognitive measures employed. In an incident cohort of 107 PD patients from the U.K. assessed longitudinally over five years *APOE* ε4 was not associated with risk of dementia or rate of cognitive decline.[16] Similarly, a population-based study of 64 Norwegian PD patients followed for 12 years found no association between the ε4 allele and development of dementia or time to dementia.[17] However, a subsequent longitudinal study of 212 PD patients from the U.S. reported that ε4 carriers displayed a more rapid decline in total score on the Mattis Dementia Rating Scale than non-carriers.[15] A meta-analysis of 17 cross-sectional studies published in 2009 reported a significantly higher *APOE* ε4 frequency in

PDD patients (n = 501) in comparison to non-demented PD patients (n = 1145; odds ratio [OR] = 1.74, 95% confidence interval [CI] 1.36-2.23), though the authors cautioned that small sample sizes, heterogeneity of ORs, and publication bias might have confounded their results.[16] In more recent cross-sectional studies of 879 PD cases from the National Institute of Neurological Disorders and Stroke Neurogenetics repository, [36] and 234 PD patients from South Korea,[37] ε4 carrier status was not associated with Mini-Mental State Examination (MMSE) scores. Finally, in an autopsy-based study in which subjects with substantial concomitant AD neuropathologic changes were excluded, *APOE* ε4 was overrepresented in patients with PDD (n = 81) in comparison to cognitively intact controls (n = 269; OR = 3.1, 95% CI 1.7-5.6).[38] One explanation for these seemingly discordant results is that many prior studies had small sample sizes or used insensitive measures of cognition in PD (e.g. the MMSE[39]), and thus might have lacked adequate power. In contrast, our study included a large sample and used a more extensive psychometric battery to assess cognition. Furthermore, we analyzed cognitive performance using quantitative data which is a more powerful approach than using categorical variables (e.g. demented vs. non-demented).

In evaluating the role of *APOE* ε4 in cognition in diseases other than AD one must consider whether the effects observed differ from the "background" effect of *APOE* in the general population. For example, a meta-analysis of 77 studies consisting of 40,942 cognitively intact individuals (11,108 ε4 carriers and 29,834 ε4 non-carriers) found that *APOE* ε4 had a small but significant negative effect on measures of global cognitive functioning ($P < 0.05$), episodic memory ($P < 0.01$), executive function ($P < 0.05$), and perceptual speed ($P < 0.05$), but not verbal ability (including verbal fluency), primary memory, visuospatial skill, or attention.[13] In comparison, we observed more robust associations for *APOE* ε4 in a much smaller sample, and the effects were present across all cognitive domains tested except visuospatial function (Table 3). These data suggest that the deleterious effect of the ε4 allele seen in our PD cohort is in excess of the background *APOE* effect on cognition.

Relatively few studies have examined the *MAPT* H1 haplotype as a risk factor for CI in PD. The most frequently cited one was conducted in an incident cohort of 122 PD patients followed longitudinally for 5 years. *MAPT* H1 was associated with a more rapid decline in MMSE score ($p = 0.02$) and was a significant risk factor for conversion to dementia (OR = 12.14, 95% CI 1.26-117.36).[21] Though patients in the study underwent detailed neuropsychological assessments, association tests between *MAPT* H1 and change over time in the other cognitive measures were not performed. A cross-sectional PD case-control study from Spain found that *MAPT* H1 was associated with PD in the overall sample, and the effect size was larger in demented patients (n = 48; OR = 3.73, 95% CI 1.64-8.46) than in non-demented patients (n = 154; OR = 1.89, 95% CI 1.03-3.47) in comparison to cognitively intact controls.[20] However, the authors did not directly test for differences in H1 frequency between the demented and non-demented PD groups. A second cross-sectional study in Spain found no difference in H1 frequency between demented (n = 86) and non-demented (n = 138) PD patients.[40] In our much larger cohort we did not observe an association between *MAPT* H1 and baseline performance on any cognitive tests, and none of the variables examined even approached significance (Table 3). Because of the substantial differences in methodologies employed, caution must be used in comparing our findings with those of

previous studies. However, our results suggest that *MAPT* H1 is not associated with cognition in PD.

Our study had several limitations. We were not able to examine longitudinal measures of cognition since these data were not yet available for the majority of the cohort. Thus, we were only able to account for predictors of cognitive function by including demographic characteristics (e.g. years of education and age) in the regression models. Some of the cognitive measures used rely in part on motor function and thus motor symptoms might have interfered with test performance. To lessen these effects we tested subjects in the “on” state. Furthermore, for Trails B we attempted to correct for motor impairment by subtracting the Trails A score. Our participants had a higher than average mean level of education, a known contributor to performance across most cognitive measures. Thus, our sample might not be fully representative of all patients with PD. Though our sample size was large in comparison to previous studies, we might still have lacked adequate power to detect small effects of *MAPT* and *SNCA* variants on cognition.

We have shown that *APOE* is associated with cognitive performance in PD, but whether other modifier genes exist remains to be determined. We have begun work to address this issue using genome-wide techniques which will incorporate longitudinal data as they become available in our PD cohort. The identification of additional genetic determinants for CI in PD will shed new light on the pathophysiology of this disabling non-motor problem and could provide new targets for therapeutic intervention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Dr. Mata is funded by grants from the Department of Veterans Affairs, NIH, and Parkinson’s Disease Foundation.

Dr. Leverenz has served as a consultant for Bayer and Teva Pharmaceuticals and is funded by grants from the American Parkinson Disease Association, Michael J. Fox Foundation, NIH, and Northwest Collaborative Care.

Dr. Weintraub is funded by the National Institutes of Health (NINDS P50 NS053488-02 [Co-PI-Core B; Co-PI-Project 1]), Department of Veterans Affairs (IIR 12-144-2 [Co-PI]), Novartis Pharmaceuticals, and the Michael J. Fox Foundation. He has received honoraria from Teva Pharmaceuticals, Lundbeck Inc., Pfizer, Avanir Pharmaceuticals, Merck & Co., UCB, Bristol-Myers Squibb Company, Novartis Pharmaceuticals, Eli Lilly and Company, Clintrex LLC, Theravance, CHDI Foundation and the Alzheimer’s Disease Cooperative Study. He has also received licensing fees from the University of Pennsylvania for the QUIP and QUIP-RS and legal proceedings from testifying in single court case related to impulse controls disorders in Parkinson’s disease (March, 2013)

Dr. Trojanowski has received funding for travel and honoraria from Takeda Pharmaceutical Company Ltd.; has received speaker honoraria from Pfizer Inc.; serves as an Associate Editor of Alzheimer’s & Dementia; may accrue revenue on patents re: Modified avidin-biotin technique, Method of stabilizing microtubules to treat Alzheimer’s disease, Method of detecting abnormally phosphorylated tau, Method of screening for Alzheimer’s disease or disease associated with the accumulation of paired helical filaments, Compositions and methods for producing and using homogeneous neuronal cell transplants, Rat comprising straight filaments in its brain, Compositions and methods for producing and using homogeneous neuronal cell transplants to treat neurodegenerative disorders and brain and spinal cord injuries, Diagnostic methods for Alzheimer’s disease by detection of multiple MRNAs, Methods and compositions for determining lipid peroxidation levels in oxidant stress syndromes and diseases, Compositions and methods for producing and using homogenous neuronal cell transplants, Method of identifying, diagnosing and treating alpha-synuclein positive neurodegenerative disorders, Mutation-specific functional impairments in distinct tau isoforms of hereditary frontotemporal dementia and parkinsonism linked to

chromosome-17: genotype predicts phenotype, Microtubule stabilizing therapies for neurodegenerative disorders, and Treatment of Alzheimer's and related diseases with an antibody; and receives research support from the NIH (NIA P01 AG 09215-20 [PI], NIA P30 AG 10124-18 [PI], NIA PO1 AG 17586-10 [Project 4 Leader], NIA 1PO1 AG-19724-07 [Core C Leader], NIA 1 U01 AG 024904-05 [Co-PI Biomarker Core Laboratory], NINDS P50 NS053488-02 [PI], NIA UO1 AG029213-01 [Co-I]; RC2NS069368 [PI], RC1AG035427 [PI], and NIA P30AG036468 [PI]), and from the Marian S. Ware Alzheimer Program.

Dr. Hurtig is funded by three grants: 1P50 NS053488 (John Trojanowski PI); 1P50NS071675 (David Eidelberg PI); USAMRAA 8100002 DOD (Richard Doty PI). He is also the movement disorders section editor for UpToDate, an online evidence-based resource for clinical decision making, and receives royalties for his work.

Dr. Van Deerlin receives research support from the NIH (NIA P30 AG 10124 [Co-PI], NIA PO1 AG 17586 [Core Leader], NINDS P50 NS053488 [Co-PI], and NIA P30AG032953 [Co-PI].

Dr. Ritz received funding from NIH grants R01-ES010544, U54-ES012078, P01-ES016732, and P50-NS038367, Department of Defense grant PC051037 and initial funding from a pilot grant by the American Parkinson Disease Association.

Dr. Rausch received support from NIH P50 NS038367.

Dr. Rhodes was funded by NIH grants R01 ES010544, U54 ES012078, P01 ES016732, and P50 NS038367.

Dr. Factor has received Honoraria from Scientiae for CME program, University of Florida speaker program, Current Neurology and Neuroscience section editor, Merz, Chelsea Therapeutics, ADAMAS and grants from Ceregene, TEVA, Ipsen, Allergan, Medtronics, Michael J. Fox Foundation and the NIH. He has also received royalties from Demos and Blackwell Futura for textbooks

Dr. Quinn is funded by grants from the Department of Veterans Affairs and the NIH (UH2TR000903-02, U10NS077350-01, P30 AG008017, P50 NS062684).

Dr. Chung is funded by a grant from the Department of Veterans Affairs.

Dr. Peterson is funded by a grant from the Department of Veterans Affairs.

Dr. Espay is supported by the K23 career development award (NIMH, 1K23MH092735); has received grant support from CleveMed/Great Lakes Neurotechnologies, and Michael J Fox Foundation; personal compensation as a consultant/scientific advisory board member for Solvay (now Abbvie), Chelsea Therapeutics, TEVA, Impax, Merz, Pfizer, Solstice Neurosciences, Eli Lilly, and USWorldMeds; royalties from Lippincott Williams & Wilkins and Cambridge; and honoraria from Novartis, UCB, TEVA, the American Academy of Neurology, and the Movement Disorders Society. He serves as Associate Editor of Movement Disorders and Frontiers in Movement Disorders and on the editorial board of The European Neurological Journal.

Dr. Revilla has received funding for travel and honoraria from Lundbeck Speaker's Bureau.

Dr. Devoto is supported by the Michael J. Fox Foundation.

Dr. Hu is funded by NIH grants R01 NS065070, R01 ES017462 and R21 NS070202.

Ms. Wan is funded by grants from the NIH.

Dr. Montine is funded by grants from the NIH and receives personal compensation in the form of honoraria from invited scientific presentations to universities and professional societies not exceeding $5,000 per year.

Dr. Edwards is funded by grants from the NIH.

Dr. Zabetian is funded by grants from the American Parkinson Disease Association, Department of Veterans Affairs, NIH, Northwest Collaborative Care, and Parkinson's Disease Foundation.

Funding/Support: This work was supported by grants from the Department of Veterans Affairs (1I01BX000531), National Institutes of Health (P50 NS062684, P50 NS053488, P50 NS038367, R01 NS065070), and the Consolidated Anti-Aging Foundation.

Role of the Sponsors: The funding agencies had no input in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

References

1. Levy G, Tang MX, Louis ED, et al. The association of incident dementia with mortality in PD. Neurology. Dec 10; 2002 59(11):1708–1713. [PubMed: 12473757]
2. Aarsland D, Larsen JP, Tandberg E, Laake K. Predictors of nursing home placement in Parkinson's disease: a population-based, prospective study. J Am Geriatr Soc. Aug; 2000 48(8):938–942. [PubMed: 10968298]
3. Aarsland D, Larsen JP, Karlsen K, Lim NG, Tandberg E. Mental symptoms in Parkinson's disease are important contributors to caregiver distress. Int J Geriatr Psychiatry. Oct; 1999 14(10):866–874. [PubMed: 10521886]
4. Klepac N, Trkulja V, Relja M, Babic T. Is quality of life in non-demented Parkinson's disease patients related to cognitive performance? A clinic-based cross-sectional study. Eur J Neurol. Feb; 2008 15(2):128–133. [PubMed: 18217883]
5. Aarsland D, Bronnick K, Larsen JP, Tysnes OB, Alves G. Norwegian ParkWest Study G. Cognitive impairment in incident, untreated Parkinson disease: the Norwegian ParkWest study. Neurology. Mar 31; 2009 72(13):1121–1126. [PubMed: 19020293]
6. Muslimovic D, Post B, Speelman JD, Schmand B. Cognitive profile of patients with newly diagnosed Parkinson disease. Neurology. Oct 25; 2005 65(8):1239–1245. [PubMed: 16247051]
7. Aarsland D, Andersen K, Larsen JP, Lolk A, Kragh-Sorensen P. Prevalence and characteristics of dementia in Parkinson disease: an 8-year prospective study. Arch Neurol. Mar; 2003 60(3):387–392. [PubMed: 12633150]
8. Hely MA, Reid WG, Adena MA, Halliday GM, Morris JG. The Sydney multicenter study of Parkinson's disease: the inevitability of dementia at 20 years. Mov Disord. Apr 30; 2008 23(6):837–844. [PubMed: 18307261]
9. Aarsland D, Andersen K, Larsen JP, et al. The rate of cognitive decline in Parkinson disease. Arch Neurol. Dec; 2004 61(12):1906–1911. [PubMed: 15596611]
10. Janvin CC, Larsen JP, Aarsland D, Hugdahl K. Subtypes of mild cognitive impairment in Parkinson's disease: progression to dementia. Mov Disord. Sep; 2006 21(9):1343–1349. [PubMed: 16721732]
11. Farrer LA, Cupples LA, Haines JL, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. Jama. Oct 22-29; 1997 278(16):1349–1356. [PubMed: 9343467]
12. Small BJ, Rosnick CB, Fratiglioni L, Backman L. Apolipoprotein E and cognitive performance: a meta-analysis. Psychol Aging. Dec; 2004 19(4):592–600. [PubMed: 15584785]
13. Wisdom NM, Callahan JL, Hawkins KA. The effects of apolipoprotein E on non-impaired cognitive functioning: a meta-analysis. Neurobiology of aging. Jan; 2011 32(1):63–74. [PubMed: 19285755]
14. Pankratz N, Byder L, Halter C, et al. Presence of an APOE4 allele results in significantly earlier onset of Parkinson's disease and a higher risk with dementia. Mov Disord. Jan; 2006 21(1):45–49. [PubMed: 16116614]
15. Morley JF, Xie SX, Hurtig HI, et al. Genetic influences on cognitive decline in Parkinson's disease. Mov Disord. Apr; 2012 27(4):512–518. [PubMed: 22344634]
16. Williams-Gray CH, Goris A, Saiki M, et al. Apolipoprotein E genotype as a risk factor for susceptibility to and dementia in Parkinson's disease. J Neurol. Mar; 2009 256(3):493–498. [PubMed: 19308307]
17. Kurz MW, Dekomien G, Nilsen OB, Larsen JP, Aarsland D, Alves G. APOE alleles in Parkinson disease and their relationship to cognitive decline: a population-based, longitudinal study. J Geriatr Psychiatry Neurol. Sep; 2009 22(3):166–170. [PubMed: 19321880]
18. Pittman AM, Fung HC, de Silva R. Untangling the tau gene association with neurodegenerative disorders. Hum Mol Genet. Oct 15; 2006 15(Suppl 2):R188–195. [PubMed: 16987883]
19. Zabetian CP, Hutter CM, Factor SA, et al. Association analysis of MAPT H1 haplotype and subhaplotypes in Parkinson's disease. Ann Neurol. May 18; 2007 62(2):137–144. [PubMed: 17514749]

20. Seto-Salvia N, Clarimon J, Pagonabarraga J, et al. Dementia risk in Parkinson disease: disentangling the role of MAPT haplotypes. Arch Neurol. Mar; 2011 68(3):359–364. [PubMed: 21403021]
21. Williams-Gray CH, Evans JR, Goris A, et al. The distinct cognitive syndromes of Parkinson's disease: 5 year follow-up of the CamPaIGN cohort. Brain. Nov; 2009 132(Pt 11):2958–2969. [PubMed: 19812213]
22. Fuchs J, Nilsson C, Kachergus J, et al. Phenotypic variation in a large Swedish pedigree due to SNCA duplication and triplication. Neurology. Mar 20; 2007 68(12):916–922. [PubMed: 17251522]
23. Pihlstrom L, Toft M. Genetic variability in SNCA and Parkinson's disease. Neurogenetics. Nov; 2011 12(4):283–293. [PubMed: 21800132]
24. Kang GA, Bronstein JM, Masterman DL, Redelings M, Crum JA, Ritz B. Clinical characteristics in early Parkinson's disease in a central California population-based study. Mov Disord. Sep; 2005 20(9):1133–1142. [PubMed: 15954133]
25. Chahine LM, Qiang J, Ashbridge E, et al. Clinical and biochemical differences in patients having Parkinson disease with vs without GBA mutations. JAMA Neurol. Jul; 2013 70(7):852–858. [PubMed: 23699752]
26. Cholerton BA, Zabetian CP, Quinn JF, et al. Pacific Northwest Udall Center of excellence clinical consortium: study design and baseline cohort characteristics. J Parkinsons Dis. 2013; 3(2):205–214. [PubMed: 23938350]
27. Cottingham ME, Hawkins KA. Verbal fluency deficits co-occur with memory deficits in geriatric patients at risk for dementia: Implications for the concept of mild cognitive impairment. Behav Neurol. 2010; 22(3-4):73–79. [PubMed: 20595739]
28. Murphy KJ, Rich JB, Troyer AK. Verbal fluency patterns in amnestic mild cognitive impairment are characteristic of Alzheimer's type dementia. J Int Neuropsychol Soc. Jul; 2006 12(4):570–574. [PubMed: 16981610]
29. Twamley EW, Ropacki SA, Bondi MW. Neuropsychological and neuroimaging changes in preclinical Alzheimer's disease. J Int Neuropsychol Soc. Sep; 2006 12(5):707–735. [PubMed: 16961952]
30. Markesbery WR, Schmitt FA, Kryscio RJ, Davis DG, Smith CD, Wekstein DR. Neuropathologic substrate of mild cognitive impairment. Arch Neurol. Jan; 2006 63(1):38–46. [PubMed: 16401735]
31. Baldo JV, Schwartz S, Wilkins D, Dronkers NF. Role of frontal versus temporal cortex in verbal fluency as revealed by voxel-based lesion symptom mapping. J Int Neuropsychol Soc. Nov; 2006 12(6):896–900. [PubMed: 17064451]
32. Watson GS, Leverenz JB. Profile of cognitive impairment in Parkinson's disease. Brain Pathol. May; 2010 20(3):640–645. [PubMed: 20522089]
33. Goldman JG, Weis H, Stebbins G, Bernard B, Goetz CG. Clinical differences among mild cognitive impairment subtypes in Parkinson's disease. Mov Disord. Aug; 2012 27(9):1129–1136. [PubMed: 22778009]
34. Irwin DJ, White MT, Toledo JB, et al. Neuropathologic substrates of Parkinson disease dementia. Ann Neurol. Oct; 2012 72(4):587–598. [PubMed: 23037886]
35. Gomperts SN, Locascio JJ, Rentz D, et al. Amyloid is linked to cognitive decline in patients with Parkinson disease without dementia. Neurology. Jan 1; 2013 80(1):85–91. [PubMed: 23243071]
36. Federoff M, Jimenez-Rolando B, Nalls MA, Singleton AB. A large study reveals no association between APOE and Parkinson's disease. Neurobiol Dis. May; 2012 46(2):389–392. [PubMed: 22349451]
37. Ryu HG, Kwon OD. Apolipoprotein E epsilon 4 allele is not associated with age at onset or MMSE of Parkinson's disease in a Korean study. Parkinsonism Relat Disord. Nov; 2010 16(9): 615–617. [PubMed: 20674461]
38. Tsuang D, Leverenz JB, Lopez OL, et al. APOE epsilon4 increases risk for dementia in pure synucleinopathies. JAMA Neurol. Feb; 2013 70(2):223–228. [PubMed: 23407718]

39. Hoops S, Nazem S, Siderowf AD, et al. Validity of the MoCA and MMSE in the detection of MCI and dementia in Parkinson disease. Neurology. Nov 24; 2009 73(21):1738–1745. [PubMed: 19933974]

40. Ezquerra M, Campdelacreu J, Gaig C, et al. Lack of association of APOE and tau polymorphisms with dementia in Parkinson's disease. Neurosci Lett. Dec 19; 2008 448(1):20–23. [PubMed: 18930114]

Table 1

Cognitive Tests: Description and Observed Performance by Domain

Cognitive domain	Test	Test Description[a]	Observed Mean ± SD (units)[b]	Observed Range[b]	Possible Range
Global Cognition	MoCA[c]	Brief assessment of global cognitive abilities, including orientation, attention, memory, language, abstract reasoning, and visuospatial items	24.2 ± 3.9 (points)	6 - 30	0 - 30
Learning/ Memory	HVLT-R Total	Participant is asked to recall a12-item word list across 3 learning trials	21.5 ± 6.1 (words)	0 - 35	0 - 36
	HVLT-R Delay	Participant is asked to recall previously learned words following a ~20 minute delay	6.8 ± 3.6 (words)	0 - 12	0 - 12
	HVLT-R Discrim	Following delayed recall, participant is asked to determine which words were on the original list. Recognition Discrimination Index is the number of true positive minus the number of false positive responses	9.4 ± 2.4 (words)	(−2) - 12	(−12) - 12
Verbal Fluency	Semantic	Number of animals generated in one minute	17.5 ± 6.0 (words)	0 - 37	0 - NL
	Phonemic	Number of words generated that begin with the letters F, A, and S in separate one minute trials	36.8 ± 14.0 (words)	3 - 91	0 – NL
Working Memory/ Executive Function	LNS[d]	A measure of auditory working memory in which the participant hears a combination of numbers and letters and is asked to repeat the numbers in ascending order followed by the letters in alphabetical order	8.5 ± 3.0 (items)	0 - 18	0 - 21
	Trails A[e]	Trails A is a test of simple graphomotor speed in which the participant is asked to sequence consecutive numbers; maximum time allowed, 150 seconds	46.9 ± 28.2 (seconds)	13 - 150	≤ 150
	Trails B[e]	Trails B is a test of graphomotor divided attention in which the participant is asked to sequence alternating numbers and letters; maximum time allowed, 300 seconds	139.8 ± 85.4 (seconds)	28 - 300	≤ 300
	Trails B – A[e]	Trails A is subtracted from Trails B to minimize the effects of motor disability	92.7 ± 69.2 (seconds)	0 - 272	< 300
Visuospatial	JoLO[c]	A visual-perceptual task in which the participant is asked to match pairs of angled lines to a display array of lines	22.9 ± 5.5 (items)	0 - 30	0 - 30

Abbreviations: Delay, Delayed Recall; Discrim, Recognition Discrimination Index; HVLT-R, Hopkins Verbal Learning Test-Revised; JoLO, Benton Judgment of Line Orientation; LNS, Letter-Number Sequencing; MoCA, Montreal Cognitive Assessment; NL, no limit; SD, standard deviation; Total, Total Learning.

[a] A lower score indicates poorer performance on all tests except Trails A, B, and B-A, where a higher score indicates poorer performance.

[b] Mean and range observed in the full sample (n = 1,079)

[c] Not administered at University of California, Los Angeles

[d] Not administered at Emory University

[e] Not administered at University of Pennsylvania

Table 2

Characteristics of the Study Population

Site	N	Male, n (%)	Age, y			Disease Duration	Years of Education	Demented n (%)
			At Testing mean ± SD	At Diagnosis mean ± SD	At Disease Onset mean ± SD			
Emory University	142	93 (65.5)	65.2 ± 9.1	59.4 ± 9.9	57.6 ± 10.0	5.8 ± 4.1	15.9 ± 2.6	NA
PANUC (Portland)	103	95 (92.2)	68.7 ± 7.8	61.2 ± 10.4	58.9 ± 10.8	7.5 ± 5.9	15.9 ± 3.3	20 (19.4)
PANUC (Seattle)	416	271 (65.1)	67.9 ± 9.3	60.6 ± 11.0	58.5 ± 11.3	7.3 ± 6.4	16.1 ± 2.7	83 (19.9)
UCLA	162	94 (58.0)	72.5 ± 9.5	67.1 ± 9.8	NC	5.5 ± 2.5	14.6 ± 3.3	NA
U. of Cincinnati	37	26 (70.3)	64.6 ± 7.8	60.4 ± 8.7	57.4 ± 8.7	3.6 ± 3.1	15.5 ± 2.8	4 (10.8)
U. of Pennsylvania	219	154 (70.3)	70.8± 7.5	64.1 ± 8.7	62.8 ± 8.8	6.7 ± 5.2	15.9 ± 2.4	23 (10.5)
Total	1079	733 (67.9)	68.8 ± 9.1	62.2 ± 8.7	59.4 ± 10.6	6.6 ± 5.4	15.8 ± 2.8	130 (16.8)
p [a]		4.2×10^{-7}	1.6×10^{-14}	1.4×10^{-12}	2.6×10^{-6}	2.6×10^{-5}	3.7×10^{-7}	0.014

Abbreviations: NA, not applicable; NC, not collected; PANUC, Pacific Northwest Udall Center; UCLA, University of California, Los Angeles; SD, standard deviation

[a] Overall test of differences across sites using X^2 test (male and demented) or ANOVA (age at testing, age at diagnosis, age at onset, disease duration, and years of education)

Table 3

Association of *APOE*, *MAPT*, and *SNCA* with Cognitive Performance in the Full Parkinson Disease Cohort[a]

Test	N[b]	*APOE ε4*			*MAPT*			*SNCA*		
		β (95%CI)[c]	*P*	P_c	β (95%CI)[c]	*P*	P_c	β (95%CI)[c]	*P*	P_c
Semantic Fluency	1071	−1.09 (−1.77 to −0.40)	0.002	0.018	0.14 (−0.47 to 0.75)	0.65	1	0.40 (−0.06 to 0.86)	0.09	0.81
Phonemic Fluency	1042	−1.34 (−2.99 to 0.31)	0.11	1	0.66 (−0.80 to 2.12)	0.38	1	0.54 (−0.58 to 1.65)	0.35	1
HVLT-R Total	1041	−1.55 (−2.23 to −0.88)	6.7×10^{-6}	6.0×10^{-5}	−0.27 (−0.87 to 0.34)	0.39	1	0.44 (−0.02 to −0.9)	0.06	0.55
HVLT-R Delay	1040	−0.72 (−1.14 to −0.31)	0.001	0.009	−0.12 (−0.49 to 0.25)	0.53	1	0.2 (−0.08 to 0.49)	0.16	1
HVLT-R Discrim	1028	−0.43 (−0.72 to −0.14)	0.004	0.04	−0.09 (−0.35 to 0.17)	0.49	1	0.19 (−0.01 to 0.38)	0.06	0.51
JoLO	901	−0.33 (−1.05 to 0.38)	0.36	1	0.13 (−0.52 to 0.78)	0.69	1	0.23 (−0.26 to 0.72)	0.36	1
LNS	890	−0.77 (−1.15 to −0.38)	1.0×10^{-5}	9.0×10^{-5}	0.17 (−0.18 to 0.52)	0.34	1	0.06 (−0.20 to 0.32)	0.65	1
Trails B-A	845	14.41 (5.5 to 23.32)	0.002	0.018	−0.13 (−8.07 to 7.81)	0.97	1	−5.07 (−11.13 to 0.99)	0.1	1
MoCA	873	−0.66 (−1.14 to −0.17)	0.008	0.07	−0.20 (−0.63 to 0.23)	0.37	1	0 (−0.33 to 0.33)	0.97	1

Abbreviations: Delay, Delayed Recall; Discrim, Recognition Discrimination Index; JoLO, Benton Judgment of Line Orientation; HVLT-R, Hopkins Verbal Learning Test-Revised; LNS, Letter-Number Sequencing; MoCA, Montreal Cognitive Assessment; *P*, uncorrected *P*-value; P_C, Bonferroni-corrected *P*-value for 9 comparisons; Total, Total Learning.

[a] All analyses are adjusted by sex, years of education, disease duration, age at testing, and site.

[b] Number of subjects who completed each psychometric test.

[c] Beta coefficient indicates the expected change in mean psychometric test score per allele of the corresponding gene (*APOE* ε4, *MAPT* H2, or *SNCA* rs356219 "G") given the same values for all adjustment covariates.

Table 4

Association of *APOE* with Psychometric Test Scores in all Patients with a Cognitive Diagnosis and in those without Dementia[a]

Test	All Patients with a Cognitive Diagnosis (N=775)				Non-demented Patients (N=645)			
	N[b]	β (95%CI)[c]	*P*	P_c	N[b]	β (95%CI)[c]	*P*	P_c
Semantic Fluency	769	−1.31 (−2.11 to −0.52)	0.001	0.009	645	−1.16 (−1.96 to −0.35)	0.005	0.045
Phonemic Fluency	741	−1.56 (−3.59 to 0.47)	0.13	1	621	−1.03 (−3.21 to 1.15)	0.35	1
HVLT-R Total	738	−1.57 (−2.28 to −0.76)	2×10^{-4}	0.0018	624	−1.17 (−1.99 to −0.35)	0.005	0.045
HVLT-R Delay	736	−0.59 (−1.10 to −0.08)	0.023	0.21	621	−0.39 (−0.93 to 0.16)	0.16	1
HVLT-R Discrim	725	−0.44 (−0.81 to −0.07)	0.019	0.17	613	−0.16 (−0.52 to 0.20)	0.40	1
JoLO	759	−0.39 (−1.18 to 0.39)	0.33	1	635	−0.12 (−0.91to 0.16)	0.76	1
LNS	723	−0.56 (−0.98 to −0.14)	0.009	0.081	618	−0.38 (−0.80 to 0.03)	0.07	0.63
Trails B-A	546	9.68 (−1.28 to 20.63)	0.083	0.75	444	3.46 (−6.71 to 13.63)	0.51	1
MoCA	732	−0.71 (−1.25 to −0.17)	0.01	0.09	616	−0.53 (−1.03 to −0.04)	0.034	0.31

Abbreviations: Delay, Delayed Recall; Discrim, Recognition Discrimination Index; JoLO, Benton Judgment of Line Orientation; HVLT-R, Hopkins Verbal Learning Test-Revised; LNS, Letter-Number Sequencing; MoCA, Montreal Cognitive Assessment; *P*, uncorrected *P*-value; P_C, Bonferroni-corrected *P*-value for 9 comparisons; Total, Total Learning.

[a] All analyses are adjusted by sex, years of education, disease duration, age at testing and site.

[b] Number of subjects who completed each psychometric test.

[c] Beta coefficient indicates the expected change in mean psychometric test score per allele of the corresponding gene (*APOE* ε4, *MAPT* H2, or *SNCA* rs356219 “G”) given the same values for all adjustment covariates.