**IMPORTANCE** Cognitive impairment is a common and disabling problem in Parkinson 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 nonmotor feature.

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

**DESIGN, SETTING, AND PARTICIPANTS** We studied 1079 PD patients from 6 academic centers in the United States who underwent assessments of memory (Hopkins Verbal Learning Test–Revised [HVLT-R]), attention and executive function (Letter-Number Sequencing Test and Trail Making Test), language processing (semantic and phonemic verbal fluency tests), visuospatial skills (Benton Judgment of Line Orientation test), and global cognitive function (Montreal Cognitive Assessment). Participants underwent genotyping for the APOE ε2/ε3/ε4 alleles, MAPT H1/H2 haplotypes, and SNCA rs356219. We used linear regression to test for association between genotype and baseline cognitive performance with adjustment for age, sex, years of education, disease duration, and site. We used a Bonferroni correction to adjust for the 9 comparisons that were performed for each gene.

**MAIN OUTCOMES AND MEASURES** Nine variables derived from 7 psychometric tests.

**RESULTS** The APOE ε4 allele was associated with lower performance on the HVLT-R Total Recall (P = 6.7 × 10⁻⁶; corrected P [Pc] = 6.0 × 10⁻⁵), Delayed Recall (P = .001; Pc = .009), and Recognition Discrimination Index (P = .004; Pc = .04); a semantic verbal fluency test (P = .002; Pc = .02); the Letter-Number Sequencing Test (P = 1 × 10⁻⁶; Pc = 9 × 10⁻⁵); and Trail Making Test B minus Trail Making Test A (P = .002; Pc = .02). In a subset of 645 patients without dementia, the APOE ε4 allele was associated with lower scores on the HVLT-R Total Recall (P = .005; Pc = .045) and the semantic verbal fluency (P = .005; Pc = .045) measures. Variants of MAPT and SNCA were not associated with scores on any tests.

**CONCLUSIONS AND RELEVANCE** Our data indicate that the APOE ε4 allele is an important predictor of cognitive function in PD across multiple domains. Among PD patients without dementia, the APOE ε4 allele 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 disease than PD.
Cognitive impairment commonly occurs in Parkinson disease (PD) and has a major effect on quality of life, caregiver distress, the need for nursing home placement, and mortality. At the time of diagnosis, 19% to 24% of PD patients have mild cognitive impairment and as many as 80% develop dementia during the course of the disease. The rate of cognitive decline and pattern of early cognitive deficits in PD are highly variable for reasons that are not well understood. Identification of biological markers, including common genetic variants, that account for this heterogeneity could provide important insights into the pathological processes that underlie cognitive impairment in PD.

Few genetic studies have been conducted in this area, and most have focused on the end point of dementia. Available evidence suggests that at least 3 genes, apolipoprotein E (APOE [OMIM 107741]), microtubule-associated protein tau (MAPT [OMIM 157140]), and α-synuclein (SNCA [OMIM 163890]), might play a role in determining susceptibility to cognitive impairment in PD. The APOE ε4 allele is a well-established risk factor for Alzheimer disease (AD) and is also associated with slightly reduced cognition in healthy older adults. The APOE ε4 allele was found to predict earlier onset of dementia or more rapid cognitive decline in patients with PD in some studies but not others. The MAPT H1 haplotype is a well-known risk factor for several neurodegenerative disorders, including PD, progressive supranuclear palsy, and corticobasal degeneration. Two studies found that the MAPT H1 haplotype is a risk factor for dementia in PD, but these findings require further replication. Finally, rare multiplications of the SNCA gene result in PD, often accompanied by early-onset dementia. Common SNCA polymorphisms also convey a risk for PD, but whether these same variants predispose patients with PD to develop cognitive impairment early in their clinical course is not known. In this study we examined the association between common variants in APOE, MAPT, and SNCA and cognitive performance in a large, multicenter sample of patients with PD.

Methods

Subjects

The initial study population consisted of 1191 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) consists of 2 sites, one in Seattle (University of Washington/Veterans Affairs Puget Sound Health Care System) and the other in Portland (Oregon Health and Science University/Portland Veterans Affairs Medical Center). All participants met UK PD Society Brain Bank clinical diagnostic criteria for PD, except those from UCLA who satisfied clinical diagnostic criteria for PD as described elsewhere. Requirements to meet the latter criteria include (1) presence of at least 2 of the following signs: bradykinesia, rigidity, or resting tremor; (2) no suggestion of a cause for another parkinsonian syndrome; and (3) no atypical features. Each participant underwent a detailed neuropsychological assessment (performed in the “on” state if receiving medication), and 7 tests that overlapped between sites were chosen as the core battery (defined in the following section). Thirty-seven participants completed fewer than half of the tests in the core battery and were excluded from the sample. To reduce genetic heterogeneity, all participants underwent genotyping for a panel of ancestry-informative markers designed to estimate admixture proportions from the following 4 ancestral populations: European, East Asian, African, and Amerindian (I.F.M., unpublished data, January 2013). Seventy-five individuals estimated to have less than 90% European ancestry were excluded. The final study population consisted of 1079 participants.

Standard protocol approvals, registrations, and written informed patient consent 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 a psychiatrist (University of Pennsylvania) or a neuropsychologist (all other sites) experienced in the assessment of patients with PD. The following 7 tests that were administered by at least 5 of the 6 sites were defined as the core battery: the Montreal Cognitive Assessment (MoCA), Hopkins Verbal Learning Test–Revised (HVLT-R), Trail Making Test (TMT), a semantic (number of animals generated) and a phonemic verbal fluency test, and Benton Judgment of Line Orientation test (JoLO) (Table 1). Data from participants 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 participants were classified as having or not having dementia as previously described. The group without dementia included participants with mild or no cognitive impairment. Scores on tests with less overlap between sites that were not included in the core battery, such as the Logical Memory Test, Boston Naming Test, and Digit Span and Digit Symbol tests, were used in determining cognitive diagnosis when available.

Genotyping

Genomic DNA was extracted from peripheral blood samples using standard methods. All participants underwent genotyping for 29 ancestry-informative markers and 4 single-nucleotide polymorphisms in the 3 genes of interest, including 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 commercially available assays (TaqMan assays [Life Technologies] on the BioMark HD System [Fluidigm Corporation]). The genotyping success rate was 100% for MAPT and SNCA and greater than 99% for APOE.

Statistical Analysis

We assessed each single-nucleotide polymorphism for Hardy-Weinberg equilibrium using an exact test. We selected (a priori)
Results

We found 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 were lower than for all of the other sites. We found a predominance of male participants at each site, which was particularly marked at the PANUC Portland site (92.2%).

None of the single-nucleotide polymorphisms deviated significantly from Hardy-Weinberg equilibrium. We found no significant differences in population characteristics across genotypes (eTable 1 in the Supplement) or in genotype frequencies across sites (eTable 2 in the Supplement). The APOE ε4 allele was associated with lower performance on the following 6 of the 9 psychometric variables after correction for multiple testing: HVLT-R Total Recall (corrected \( P \approx 6.0 \times 10^{-3} \)), Delayed Recall (\( P \approx .009 \)), and Recognition Discrimination Index (\( P \approx .04 \)); semantic verbal fluency (\( P \approx .02 \)); Letter-Number Sequencing (\( P \approx 9 \times 10^{-3} \)); and TMT B minus TMT A (\( P \approx .02 \)) (Table 3). Box plots of the data by APOE genotype for the 6 significant variables are presented in the eFigure in the Supplement. However, we found no significant association between the MAPT H1 haplotype or SNCA rs356219 and any of the psychometric test results (\( P \approx .05 \)) (Table 3). For psychometric variables that deviated from normality when examining histograms and quantile-quantile plots (MoCA, TMT B – TMT A, JoLO, and 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 pre-

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### Table 1. Description of Cognitive Tests and Observed Performance by Domain

<table>
<thead>
<tr>
<th>Cognitive Domain</th>
<th>Test</th>
<th>Test Description</th>
<th>Observed Score Mean (SD)</th>
<th>Range of Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global cognition</td>
<td>MoCA&lt;sup&gt;24,29&lt;/sup&gt;</td>
<td>Brief assessment of global cognitive abilities, including orientation, attention, memory, language, abstract reasoning, and visuospatial items (in points)</td>
<td>24.2 (3.9)</td>
<td>6 to 30</td>
</tr>
<tr>
<td></td>
<td>HVLT-R Total Recall&lt;sup&gt;27&lt;/sup&gt;</td>
<td>Participant is asked to recall a12-item word list across 3 learning trials</td>
<td>21.5 (6.1)</td>
<td>0 to 35</td>
</tr>
<tr>
<td></td>
<td>HVLT-R Delayed Recall&lt;sup&gt;27&lt;/sup&gt;</td>
<td>Participant is asked to recall previously learned words following an approximate 20-min delay</td>
<td>6.8 (3.6)</td>
<td>0 to 12</td>
</tr>
<tr>
<td></td>
<td>HVLT-R Recognition Discrimination Index&lt;sup&gt;27&lt;/sup&gt;</td>
<td>After delayed recall, participant is asked to determine which words were on the original list; calculated as No. of true-positive minus No. of false-positive responses</td>
<td>9.4 (2.4)</td>
<td>-2 to 12</td>
</tr>
<tr>
<td></td>
<td>Letter-Number Sequencing Test&lt;sup&gt;5,6&lt;/sup&gt;</td>
<td>No. of words generated that begin with the letters F, A, and S in separate 1-min trials</td>
<td>17.5 (6.0)</td>
<td>0 to 37</td>
</tr>
<tr>
<td></td>
<td>Phonemic verbal fluency test&lt;sup&gt;30&lt;/sup&gt;</td>
<td>No. of words generated that begin with the letters F, A, and S in separate 1-min trials</td>
<td>36.8 (14.0)</td>
<td>3 to 91</td>
</tr>
<tr>
<td></td>
<td>TMTB – TMT A&lt;sup&gt;29&lt;/sup&gt;</td>
<td>TMT A score is subtracted from TMT B score to minimize the effects of motor disability</td>
<td>92.7 (69.2)</td>
<td>0 to 272</td>
</tr>
<tr>
<td></td>
<td>HVLT-R Delayed Recall&lt;sup&gt;27&lt;/sup&gt;</td>
<td>Participant is asked to recall previously learned words following an approximate 20-min delay</td>
<td>46.9 (28.2)</td>
<td>13 to 150</td>
</tr>
<tr>
<td></td>
<td>HVLT-R Total Recall&lt;sup&gt;27&lt;/sup&gt;</td>
<td>Participant is asked to recall a12-item word list across 3 learning trials</td>
<td>92.7 (69.2)</td>
<td>&lt;300</td>
</tr>
<tr>
<td></td>
<td>HVLT-R Recognition Discrimination Index&lt;sup&gt;27&lt;/sup&gt;</td>
<td>After delayed recall, participant is asked to determine which words were on the original list; calculated as No. of true-positive minus No. of false-positive responses</td>
<td>92.7 (69.2)</td>
<td>&lt;300</td>
</tr>
<tr>
<td></td>
<td>JoLO&lt;sup&gt;13,21&lt;/sup&gt;</td>
<td>A visual-perceptual task in which the participant is asked to match pairs of angled lines to a display array of lines</td>
<td>22.9 (5.5)</td>
<td>0 to 30</td>
</tr>
</tbody>
</table>

Abbreviations: HVLT-R, Hopkins Verbal Learning Test—Revised; JoLO, Benton Judgment of Line Orientation test; LNS, Letter-Number Sequencing Test; MoCA, Montreal Cognitive Assessment; NL, no limit; TMT, Trail Making Test.

<sup>a</sup> A lower score indicates poorer performance on all tests except TMT A, B, and B minus A, where a higher score indicates poorer performance.

<sup>b</sup> Indicates scores observed in the full sample (n = 1079).

<sup>c</sup> Not administered at University of California, Los Angeles.

<sup>d</sup> Not administered at Emory University, Atlanta, Georgia.

<sup>e</sup> Not administered at University of Pennsylvania, Philadelphia.
In a multicenter cohort of patients with PD, the APOE ε4 allele predicted lower performance across multiple cognitive do-
mains, including memory, attention and executive function, and language processing. In patients without dementia, the effect of the ε4 allele was restricted to HVLT-R Total Recall and semantic verbal fluency scores. In contrast, the MAPT H1 haplotype and SNCA rs356219 were not correlated with scores on any of the psychometric tests.

The APOE ε4 allele is a well-known risk factor for AD. In preclinical and early AD, deficits in episodic memory predominate. However, impairment in semantic verbal fluency, with relative sparing of phonemic fluency, also occurs.37,38 This observation is attributed to the fact that the temporal cortex, one of the first brain regions affected in AD,39,40 plays a larger role in mediating semantic than phonemic verbal fluency.41 In contrast, early cognitive deficits in PD usually involve attention and frontal-executive function mediated in part by corticostriatal dopamine deficiency, although some patients initially exhibit isolated deficits in other domains.5,42 We observed that in PD patients without dementia, the APOE ε4 allele 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, which might in part explain the heterogeneity in cognitive profiles reported in PD patients with mild cognitive impairment.10,43 In AD, the APOE ε4 allele is thought to influence disease risk by accelerating the accumulation of neurotoxic β-amyloid, which ultimately leads to neurodegeneration with accompanying AD neuropathological changes (ie, neuritic plaques and neurofibrillary tangles). Whether the neuropathological substrate of cognitive impairment in PD patients who carry the APOE ε4 allele consistently involves an increased burden of AD neuropathological changes is not clear. However, the APOE genotype was not correlated with measures of AD neuropathological changes in a recent PD autopsy series44 or with brain amyloid burden in PD patients who underwent imaging with Pittsburgh compound B.45 Thus, APOE might affect cognition in PD through mechanisms unrelated to β-amyloid processing.

Previous studies of the effect of APOE on cognitive impairment in PD have yielded mixed results, and the interpretation of these data is complicated by the wide variety of study designs and cognitive measures used. In an incident cohort of 107 PD patients from the United Kingdom undergoing longitudinal assessment for 5 years, the APOE ε4 allele was not associated with the risk for dementia or the rate of cognitive decline.46 Similarly, a population-based study of 64 Norwegian PD patients followed up for 12 years47 found no association between the ε4 allele and development of dementia or time to dementia. However, a subsequent longitudinal study of 212 PD patients from the United States48 reported that ε4 carriers displayed a more rapid decline in total score on the Mattis Dementia Rating Scale than noncarriers. A meta-analysis of 17 cross-sectional studies published in 200946 reported a significantly higher frequency of the APOE ε4 allele in PD patients with dementia (n = 501) compared with those without (n = 1145; odds ratio [OR], 1.74 [95% CI, 1.36-2.23]), although the authors cautioned that small sample sizes, heterogeneity of ORs, and publication bias might have confounded their results. In more recent cross-sectional studies of 879 PD cases from the National Institute of Neurological Disorders and Stroke Neurogenetics repository46 and 234 PD patients from South Korea,47 ε4 carrier status was not associated with Mini-Mental State Examination scores. Finally, in an autopsy-based study in which participants with substantial concomitant AD neuropathological changes were excluded,46 the APOE ε4 allele was overrepresented in PD patients with dementia (n = 81) compared with cognitively intact control subjects (n = 269; OR, 3.1 [95% CI, 1.7-5.6]). One explanation for these seemingly discordant results is that many prior studies had small sample sizes or used insensitive measures of cognition.

### Table 4. Association of APOE With Psychometric Test Scores in All Patients With a Cognitive Diagnosis and in Those Without Dementia*

<table>
<thead>
<tr>
<th>Test</th>
<th>All Patients With a Cognitive Diagnosis (n = 775)</th>
<th>Patients Without Dementia (n = 645)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β Coefficient (95% CI) P Value</td>
<td>P Value</td>
</tr>
<tr>
<td>Semantic verbal fluency test</td>
<td>-1.31 (-2.11 to -0.52) .001</td>
<td>.009</td>
</tr>
<tr>
<td>Phonemic verbal fluency test</td>
<td>-1.56 (-3.59 to 0.47) .13</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>HVLT-R Total Recall</td>
<td>-1.57 (-2.82 to -0.85) 2 x 10^-4 .002</td>
<td>.021</td>
</tr>
<tr>
<td>HVLT-R Delayed Recall</td>
<td>-0.59 (-1.10 to 0.08) .02</td>
<td>.21</td>
</tr>
<tr>
<td>HVLT-R Recognition Discrimination Index</td>
<td>-0.44 (-0.81 to -0.07) .02</td>
<td>.17</td>
</tr>
<tr>
<td>JoLO</td>
<td>-0.39 (-1.18 to 0.39) .33</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>LNS</td>
<td>-0.56 (-0.98 to -0.14) .009</td>
<td>.081</td>
</tr>
<tr>
<td>TMT B − TMT A</td>
<td>9.68 (-1.28 to 20.63) .08</td>
<td>.75</td>
</tr>
<tr>
<td>MoCA</td>
<td>-0.71 (-1.25 to -0.17) .01</td>
<td>.09</td>
</tr>
</tbody>
</table>

Abbreviations: HVLT-R, Hopkins Verbal Learning Test–Revised; JoLO, Benton Judgment of Line Orientation test; LNS, Letter-Number Sequencing Test; MoCA, Montreal Cognitive Assessment; P<sub>c</sub>, Bonferroni-corrected P value for 9 comparisons; TMT, Trail Making Test.

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

<sup>indicates number who completed each psychometric test.</sup>

<sup>c</sup> 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.
in PD (eg, the Mini-Mental State Examination\textsuperscript{49}) 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 (eg, with vs without dementia).

In evaluating the role of the APOE ε4 allele 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 noncarriers)\textsuperscript{33} found that the APOE ε4 allele had a small but significant negative effect on measures of global cognitive functioning ($P < .05$), episodic memory ($P < .01$), executive function ($P < .05$), and perceptual speed ($P < .05$) but not verbal ability (including verbal fluency), primary memory, visuospatial skill, or attention. In comparison, we observed more robust associations for the APOE ε4 allele 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 cognitive impairment in PD. The most frequently cited study\textsuperscript{46} was conducted in an incident cohort of 122 PD patients followed up longitudinally for 5 years. The MAPT H1 haplotype was associated with a more rapid decline in Mini-Mental State Examination score ($P = .02$) and was a significant risk factor for conversion to dementia (OR, 12.14 [95% CI, 1.26-117.36]). Although patients in the study underwent detailed neuropsychological assessments, association tests between the H1 haplotype and change over time in the other cognitive measures were not performed. A cross-sectional PD case-control study from Spain\textsuperscript{39} found that the MAPT H1 haplotype was associated with PD in the overall sample, and the effect size was larger in patients with dementia ($n = 48$; OR, 3.73 [95% CI, 1.64-8.46]) than in those without ($n = 154$; OR, 1.89 [95% CI, 1.03-3.47]) compared with cognitively intact controls. However, the authors did not test for differences in H1 frequency directly between the demented and nondemented PD groups. A second cross-sectional study\textsuperscript{50} in Spain found no difference in H1 frequency between PD patients with ($n = 86$) and without ($n = 138$) dementia. In our much larger cohort we did not observe an association between the MAPT H1 haplotype and baseline performance on any cognitive tests, and none of the variables examined even approached significance (Table 3). Because of the substantial differences in methods used, one must exercise caution when comparing our findings with those of previous studies. However, our results suggest that the MAPT H1 haplotype is not associated with cognition in PD.

Our study had several limitations. We were not able to examine longitudinal measures of cognition because these data were not yet available for most of the cohort. Thus, we were only able to account for predictors of cognitive function by including demographic characteristics (eg, 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 our patients underwent testing while in the “on” state. Furthermore, for TMT B we attempted to correct for motor impairment by subtracting the TMT 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 PD patients. Although our sample size was large compared with those of previous studies, we still might have lacked adequate power to detect small effects of MAPT and SNCA variants on cognition.

Conclusions

We have shown that APOE is an important predictor of cognitive function in PD across multiple domains. Among PD patients without dementia, the APOE ε4 allele was only associated with lower performance on word list learning and semantic verbal fluency, a pattern more characteristic of the cognitive deficits seen in early AD than PD. In contrast, the MAPT H1 haplotype and SNCA rs356219 were not associated with scores on any psychometric tests. Whether other genes exist that modify cognitive performance in PD remains to be determined. We have begun work to address this issue using genome-wide techniques that will incorporate longitudinal data as they become available in our PD cohort. The identification of additional genetic determinants for cognitive impairment in PD will shed new light on the pathophysiology of this disabling nonmotor problem and could provide new targets for therapeutic intervention.
Cognitive Performance in Parkinson Disease

Study concept and design: Mata, Zabetian.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Mata, Montine, Edwards, Zabetian.

Critical revision of the manuscript for important intellectual content: All authors.


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Study supervision: Mata, Leverenz, Weintroub, Trojanowski, Hurtig, Van Deelen, Ritz, Rausch, Factor, Quinn, Espay, Revilla, Cholerton, Montine, Edwards, Zabetian.

Conflict of Interest Disclosures: Dr Mata has received grants from the Department of Veterans Affairs, National Institutes of Health (NIH), and Parkinson’s Disease Foundation. Dr Leverenz has served as a consultant for Boehringer-Ingelheim, Ciligroup, Navidea Biopharmaceuticals, Piramal Healthcare, Bayer, and Teva Pharmaceuticals and received grants from the American Parkinson Disease Association, Michael J. Fox Foundation, NIH, Northwest Collaborative Care, and the Jane and Lee Seidman Fund. Dr Weintroub has received funding from the NIH (from the National Institute of Neurological and Communicative Diseases and Stroke [NINDS]), Department of Veterans Affairs, Novartis Pharmaceuticals, and Michael J. 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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 for the modified avidin-biotin technique; a method of stabilizing microtubules to treat Alzheimer disease (AD), a method of screening for AD or disease associated with the accumulation of paired helical filaments, compositions and methods for producing and using homogenous neuronal cell transplants with straight filaments in its brain, compositions and methods for producing and using homogenous neuronal cell transplants to treat neurodegenerative disorders and brain and spinal cord injuries, diagnostic methods for AD by detection of antibodies against the RNAAs, 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, a method of identifying, diagnosing, and treating α-synuclein-positive neurodegenerative disorders, mutation-specific functional impairments in distinct tau isoforms of hereditary frontotemporal dementia and parkinsonism linked to chromosome-17 genotype predicting phenotype, microtubule-stabilizing therapies for neurodegenerative disorders, and has received royalties with an antibody, and receives research support from the NIH (from the National Institute on Aging and from the NINDS) and from the Marian S. Ware Alzheimer Program. Dr Hurtig has received grants from the Department of Defense; is the movement disorders section chief at Upstate, an online evidence-based resource for clinical decision making; and receives royalties for his work. Dr Van Deelen receives research support from the NIH (from the NIA and from the NINDS). Dr Ritz received funding from the NIH, the Department of Defense, and initial funding by a pilot grant from the American Parkinson Disease Association. Dr Rausch received support from the NIH. Dr Rhodes was supported by grants from the NIH. Dr Factor has received honoraria from Scientia for the CME program, University of Florida speaker program, Merz, Chelsea Therapeutics, and ADAMAS and grants from Ceregene, TEVA, Ipsen, Allergan, Medtronic, Michael J. Fox Foundation, and the NIH; is a section editor for Current Neurology and Neuroscience; and has received royalties from Demos and Blackwell Futura for textbooks. 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Additional Contributions: Jacqueline Rick, PhD, Department of Neurology, University of Pennsylvania, Philadelphia, and Dora Yearout, BS, Geriatric Research, Education, and Clinical Center, Veterans Affairs Puget Sound Health Care System, Seattle, Washington, and Department of Neurology, University of Washington School of Medicine, Seattle, provided technical assistance. We thank all participants in this study.

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