White Matter Degeneration in Atypical Alzheimer Disease

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Purpose: To assess white matter (WM) tract damage in patients with atypical Alzheimer disease (AD), including early-onset AD (EOAD), logopenic variant of primary progressive aphasia (lvPPA), and posterior cortical atrophy (PCA), by using diffusion-tensor magnetic resonance (MR) imaging and to identify similarities and differences across the AD spectrum.

Materials and Methods: This study was approved by the local ethical committees on human studies, and written informed consent from all subjects was obtained prior to enrollment. WM tract damage and cortical atrophy were assessed by using diffusion-tensor MR imaging and voxel-based morphometry, respectively, in 28 patients with EOAD, 12 patients with lvPPA, and 13 patients with PCA relative to age- and sex-matched healthy subjects. Conjunction and interaction analyses were used to define overlapping and syndrome-specific patterns of brain damage.

Results: Patients with EOAD, lvPPA, and PCA shared a common pattern of WM damage that involved the body of the corpus callosum, fornix, and main anterior-posterior pathways (P < .05). They also shared cortical atrophy of the left temporoparietal regions and precuneus (P < .05, family-wise error corrected). Patients with EOAD also had specific damage to the genu and splenium of the corpus callosum and parahippocampal tract bilaterally (P < .05). In all patients with AD, particularly in the two focal forms (lvPPA and PCA), WM damage was more severe and widely distributed than expected on the basis of cortical atrophy.

Conclusion: In atypical AD clinical phenotypes, the distribution of WM damage exceeds cortical atrophy and may reflect the pathologic dissemination through structural connections from atrophic to unaffected cortical regions. WM degeneration may be an early marker of AD pathologic changes in EOAD and focal AD forms.

Online supplemental material is available for this article.
Alzheimer disease (AD) is not a unitary clinical syndrome. Patients with early-onset AD (EOAD; <65 years of age) can present with multidomain cognitive impairment at onset (1,2). This cognitive picture is very different from the typical profile of patients with late-onset AD (≥65 years of age), with progressive memory deficit as the central feature (2,3). In keeping with the multidomain cognitive deficits, EOAD is associated with a widespread pattern of cortical atrophy, centered around the parietal and lateral temporal lobes, with a relative sparing of the medial temporal structures, which are the most severely damaged regions in typical late-onset AD (4–6).

AD can also manifest as atypical, relatively focal clinical syndromes, more frequently associated with EOAD—that is, as posterior cortical atrophy (PCA) (7,8) and logopenic variant of primary progressive aphasia (lvPPA) (9). PCA demonstrates visual and visuospatial impairment with less prominent memory loss (7,8). Over time, patients with PCA can develop visual agnosia, topographical difficulty, optic ataxia, simultaneousagnosia, ocular apraxia (Balint syndrome), alexia, acalculia, right-left confusion, agraphia (Gerstmann syndrome), and, later, more generalized dementia. PCA is associated with main posterior temporal and occipitoparietal brain damage (6) and with an underlying AD disease process (8). Patients with lvPPA present with language deficits characterized by slow rate of speech, with long word-finding pauses. Grammar and articulation are usually preserved in lvPPA, although phonological paraphasias could be present. Repetition and comprehension are impaired for sentences but preserved for single words, and naming is moderately affected (9). In patients with lvPPA, cortical atrophy is usually centered around the left posterior temporoparietal region (6,9), and the most common underlying disease process is AD (10,11).

The factors that drive AD clinicoanatomic heterogeneity are not well understood. One possible mechanism that could explain the involvement of different brain regions in AD variants is the spread of disease via distinct brain networks, such as amyloid β, and tau aggregates may start to accumulate in some vulnerable networks and then propagate transneuronally through white matter (WM) connections, gradually reaching unaffected regions from affected ones (12–14). According to this hypothesis, typical AD seems to target and spread through the default mode network (12,15). What happens in atypical AD, like EOAD and focal variants, is still unclear. Investigators in recent neuroimaging studies have suggested that atypical AD forms may reflect a different pathologic dissemination through specific interconnected neural networks (16,17).

Diffusion-tensor (DT) magnetic resonance (MR) imaging is used to measure the effect of tissue microstructure on the random translational motion of water molecules in biologic tissues, and it is highly sensitive to WM microstructural damage. Despite the growing number of studies that show that severe microstructural abnormalities occur...
along WM tracts in late-onset AD besides the known loss of neurons in the gray matter, to date, a few DT MR imaging studies have demonstrated the WM network involvement in EOAD (4,18), lvPPA (19–21), and PCA (22–24). To our knowledge, no study has been conducted to compare the patterns of WM damage in EOAD, lvPPA, and PCA.

The aim of the present study was to explore the distribution of WM tract damage in EOAD, lvPPA, and PCA by using DT MR imaging and to identify similarities and differences across the AD spectrum, also in relation to the patterns of cortical atrophy. We hypothesized that all forms would show preferential WM damage of the structural connections linking the key nodes of the default mode network, in addition to the involvement of distinct syndrome-specific pathways in each phenotype. We also predicted that in all AD clinical phenotypes, WM damage would not mirror cortical atrophy, thus reflecting the pathologic dissemination from atrophic to unaffected cortical regions.

Materials and Methods

This study was approved by the local ethical committee on human studies, and written informed consent from all subjects was obtained prior to enrollment. Subjects were recruited from September 2011 to March 2014.

Subjects

Patients were recruited at the San Raffaele Scientific Institute. We included patients with a clinical diagnosis of EOAD, lvPPA, or PCA. Clinical diagnoses were based on patients’ history, neurologic examination, and neuropsychological testing. The following diagnostic criteria were applied: the criteria and symptom onset data prior to age 65 years for EOAD as developed by McKhann et al (25), the PCA criteria of McMonagle et al (26) as modified by Alladi et al (27), and the lvPPA criteria of Gorno-Tempini et al (28).

Clinical assessment was performed by experienced neuropsychologists (G.M. and A.M., with 30 years of experience in clinical neurology) who were blinded to MR imaging results. Recent international criteria suggest that including biomarkers in the diagnostic work-up is likely to enhance the pathophysiological specificity of the diagnosis of AD dementia (25,28). For this reason, cerebrospinal fluid (CSF) samples were collected via lumbar puncture in the morning, and amyloid β 1–42, total tau values, and phosphorylated tau values were determined by using the Inno-Bia AlzBio3 kit (Fujirebio, Pomezia, Rome). AD-like CSF biomarkers were considered to be low amyloid β values and high tau values (25). In the case of unavailable CSF biomarkers, we included only patients with typical patterns of hypometabolism and/or perfusion at fluorodeoxyglucose positron emission tomography (PET) or single photon emission computed tomography (SPECT) scanning. Exclusion criteria were a family history suggestive of an autosomal dominant disease; significant medical illnesses or substance abuse that could interfere with cognitive functioning; any other major systemic, psychiatric, or neurologic illnesses; and other causes of focal or diffuse brain damage, including extensive cerebrovascular disorders at routine MR imaging. A total of 57 patients (32 with EOAD, 12 with lvPPA, and 13 with PCA) were screened. Two patients with EOAD were excluded owing to extensive cerebrovascular disorder, and two patients with EOAD were not able to undergo a complete MR imaging examination. CSF samples were available from 21 patients with EOAD, nine patients with lvPPA, and 10 patients with PCA, and AD-like CSF biomarkers were found in all cases. The remaining seven patients with EOAD, three patients with lvPPA, and three patients with PCA showed typical patterns of hypometabolism and/or perfusion on fluorodeoxyglucose PET or SPECT images. Fifty-three patients (28 with EOAD, 12 with lvPPA, and 13 with PCA) were included in the study (Table 1). For each patient variant, a group of age- and sex-matched healthy control subjects was selected (24 control subjects for EOAD, 20 control subjects for lvPPA, and 20 control subjects for PCA) (Table 1). Two healthy control subjects were recruited among patients’ spouses, and the others were recruited by word of mouth. Healthy control subjects underwent a multidimensional assessment, including neuropsychologic assessment and a brief cognitive evaluation with mini-mental state examination. All healthy control subjects had mini-mental state examination scores of at least 28 of 30.

Cognitive Assessment

An extensive neuropsychological assessment was performed by an experienced neuropsychologist who was blinded to MR imaging findings (M. Falantano, with 20 years of experience in clinical neuropsychology). The cognitive protocol has been described previously (18) (Table 2). To make results comparable between different groups of patients, raw cognitive test scores were transformed into Z scores, and the mean Z score for each cognitive domain was calculated (Table 2). Furthermore, patients with lvPPA performed a comprehensive language and speech battery (Table E1 [online]), and patients with PCA underwent an additional evaluation aimed at investigating dorsal and ventral visual symptoms (22) (E.C., with 11 years of experience in clinical neuropsychology). For details, see Appendix E1 (online).

MR Imaging Study

By using a 3.0-T MR imaging unit, three-dimensional T1-weighted fast field-echo and DT MR imaging sequences were performed in all individuals. MR image analysis was performed by a well-trained observer, who was blinded to the individuals’ identity (F.C., with 3 years of experience in neuroimaging). DT MR image analysis was performed by using tract-based spatial statistics implemented in the Functional MR Imaging of the Brain, or FMRIB, software library (FMRIB Analysis Group, Oxford, England), or FSL, and cortical atrophy was assessed by using voxel-based morphometry in Statistical Parametric Mapping 8 (SPM8; www.fil.ion.ucl.ac.uk/
### Table 1

Demographic, Clinical, and CSF Parameters of Patients with EOAD, lvPPA, and PCA and Age-matched Healthy Control Subjects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Healthy Control Subjects vs Patients with EOAD</th>
<th>Healthy Control Subjects vs Patients with lvPPA</th>
<th>Healthy Control Subjects vs Patients with PCA</th>
<th>P Value for Comparisons between Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>24</td>
<td>28</td>
<td>20</td>
<td>...</td>
</tr>
<tr>
<td>Age at MR imaging (y)</td>
<td>59.8 ± 1.9 (57–64)</td>
<td>66.0 ± 3.3 (59–75)</td>
<td>61.1 ± 2.7 (58–67)</td>
<td>.9 for EOAD vs lvPPA</td>
</tr>
<tr>
<td>No. of women</td>
<td>14 (58)</td>
<td>14 (50)</td>
<td>13 (65)</td>
<td>.22 for EOAD vs PCA</td>
</tr>
<tr>
<td>Education (y)</td>
<td>15.3 ± 5.0 (5–24)</td>
<td>14.4 ± 4.0 (8–22)</td>
<td>15.9 ± 4.7 (8–24)</td>
<td>.03 for EOAD vs lvPPA</td>
</tr>
<tr>
<td>Age at onset (y)</td>
<td>56.6 ± 6.7 (48–65)</td>
<td>62.6 ± 8.2 (46–77)</td>
<td>57.9 ± 6.7 (51–76)</td>
<td>.01 for EOAD vs lvPPA, .05 for PCA vs lvPPA</td>
</tr>
<tr>
<td>Disease duration (y from onset to MR imaging)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Clinical Dementia Rating</td>
<td>1.2 ± 0.6 (0.5–3)</td>
<td>0.7 ± 0.4 (0–1)</td>
<td>1.1 ± 0.4 (0.5–2)</td>
<td>.03 for EOAD vs lvPPA</td>
</tr>
<tr>
<td>Sum of Boxes</td>
<td>3.7 ± 2 (0.6–8)</td>
<td>3.2 ± 2.1 (0.6–8)</td>
<td>3.9 ± 2.3 (1–11)</td>
<td>NS</td>
</tr>
<tr>
<td>CSF amyloid β protein (ng/L)</td>
<td>315 ± 121 (98–571)</td>
<td>389 ± 138 (195–627)</td>
<td>329 ± 169 (150–582)</td>
<td>NS</td>
</tr>
<tr>
<td>CSF p-tau (ng/L) (normal value, 0–500)</td>
<td>619 ± 515 (227–2072)</td>
<td>697 ± 83 (313–1064)</td>
<td>510 ± 383 (166–1475)</td>
<td>NS</td>
</tr>
<tr>
<td>CSF p-tau (ng/L) (normal value, 0–61)</td>
<td>99 ± 64 (46–268)</td>
<td>114 ± 33 (64–154)</td>
<td>79 ± 34 (38–148)</td>
<td>.05 for lvPPA vs PCA</td>
</tr>
</tbody>
</table>

Note.—Unless indicated otherwise, values are means ± standard deviations. Numbers in parentheses are the range. NS = not significant.

* P values refer to the Mann-Whitney U test or the Fisher exact test (for patient sex only) between each patient group vs age-matched healthy control subjects.

† P values refer to the Mann-Whitney U test or the Fisher exact test (for patient sex only) between patient groups.

‡ Numbers in parentheses are percentages.
Table 2

Neuropsychological Features of Patients with EOAD, lvPPA, and PCA

<table>
<thead>
<tr>
<th>Parameter</th>
<th>EOAD</th>
<th>lvPPA</th>
<th>PCA</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mini–mental state examination (cutoff = 24)</td>
<td>19.8 ± 4.1 (85.7)</td>
<td>22.1 ± 5.7 (54.5)</td>
<td>15.9 ± 5.3 (92.3)</td>
<td>.01 for PCA vs lvPPA</td>
</tr>
<tr>
<td>Digit span forward (cutoff = 3.75)</td>
<td>4.42 ± 0.95 (23.1)</td>
<td>3.80 ± 1.66 (40)</td>
<td>4.38 ± 1.12 (38.5)</td>
<td>...</td>
</tr>
<tr>
<td>Rey list immediate recall (cutoff = 28.53)</td>
<td>22.0 ± 10.08 (71.4)</td>
<td>27.33 ± 15.53 (33.3)</td>
<td>23.00 ± 4.18 (80)</td>
<td>...</td>
</tr>
<tr>
<td>Rey list delayed recall (cutoff = 4.69)</td>
<td>1.29 ± 1.70 (100)</td>
<td>6.67 ± 3.21 (33.3)</td>
<td>2.60 ± 1.82 (80)</td>
<td>...</td>
</tr>
<tr>
<td>Prose memory (cutoff = 8)</td>
<td>2.24 ± 2.23 (95.2)</td>
<td>3.38 ± 2.05 (87.5)</td>
<td>2.28 ± 2.27 (88.9)</td>
<td>...</td>
</tr>
<tr>
<td>Verbal memory domain</td>
<td>−2.0 ± 0.7</td>
<td>−1.8 ± 0.9</td>
<td>−1.8 ± 0.6</td>
<td>NS</td>
</tr>
<tr>
<td>Spatial span (cutoff = 3.75)</td>
<td>2.53 ± 1.18 (82.3)</td>
<td>3.00 ± 1.33 (50)</td>
<td>0.86 ± 1.07 (100)</td>
<td>...</td>
</tr>
<tr>
<td>Rey figure recall (cutoff = 9.47)</td>
<td>1.92 ± 2.46 (96)</td>
<td>8.15 ± 3.76 (50)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Visuospatial memory domain†</td>
<td>−2.4 ± 0.8 (−4.3; −0.8)</td>
<td>−1.7 ± 1.1 (−3.9; 0.7)</td>
<td>−4.9 ± 1.4 (−6.1; −3.4)</td>
<td>&lt;.001 for PCA vs EOAD, &lt;.001 for PCA vs lvPPA</td>
</tr>
<tr>
<td>Rey figure copy (cutoff = 28.88)</td>
<td>10.52 ± 9.31 (95.8)</td>
<td>24.67 ± 5.3 (77.8)</td>
<td>0.44 ± 0.77 (100)</td>
<td>...</td>
</tr>
<tr>
<td>Clock-drawing test (cutoff &lt; 8)</td>
<td>2.00 ± 3.24 (94.4)</td>
<td>5.50 ± 3.34 (75.3)</td>
<td>0.13 ± 0.35 (100)</td>
<td>...</td>
</tr>
<tr>
<td>Visuospatial domain†</td>
<td>−5.6 ± 2.4 (−9.3; −0.7)</td>
<td>−2.0 ± 1.7 (−5.7; 0.0)</td>
<td>−7.0 ± 1.0 (−8.4; −5.7)</td>
<td>&lt;.001 for EOAD vs lvPPA, &lt;.001 for PCA vs lvPPA</td>
</tr>
<tr>
<td>Phonemic fluency (cutoff = 17)</td>
<td>16.54 ± 9.50 (53.8)</td>
<td>13.27 ± 7.90 (45.4)</td>
<td>17.69 ± 10.69 (38.5)</td>
<td>...</td>
</tr>
<tr>
<td>Semantic fluency (cutoff = 25)</td>
<td>19.50 ± 9.77 (65.4)</td>
<td>19.64 ± 10.92 (54.5)</td>
<td>16.31 ± 8.02 (76.9)</td>
<td>...</td>
</tr>
<tr>
<td>Fluency domain†</td>
<td>−1.8 ± 0.9 (−3.4; 0.5)</td>
<td>−1.6 ± 1.0 (−3.0; 1.0)</td>
<td>−1.6 ± 0.9 (−2.6; 0.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Raven Colored Progressive Matrices (cutoff = 18)</td>
<td>13.46 ± 7.29 (60.9)</td>
<td>21.75 ± 8.70 (33.3)</td>
<td>3.67 ± 4.59 (100)</td>
<td>...</td>
</tr>
<tr>
<td>Attentive matrices (cutoff = 31)</td>
<td>27.46 ± 11.93 (69.2)</td>
<td>31.20 ± 9.35 (60)</td>
<td>8.29 ± 7.80 (100)</td>
<td>...</td>
</tr>
<tr>
<td>Digit span backward (cutoff = 3.29)</td>
<td>2.67 ± 0.82 (63.3)</td>
<td>2.00 ± 0.0 (100)</td>
<td>2.33 ± 0.58 (66.7)</td>
<td>...</td>
</tr>
<tr>
<td>Trail Making Test (B-A) (cutoff = 186)</td>
<td>282.75 ± 266.62 (37.5)</td>
<td>156.0 ± 60.37 (0)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Executive domain†</td>
<td>−2.9 ± 1.3 (−5.4; −0.4)</td>
<td>−1.5 ± 1.3 (−3.7; 0.6)</td>
<td>−3.7 ± 1.4 (−5.5; −1.3)</td>
<td>.02 for EOAD vs lvPPA, .001 for PCA vs lvPPA</td>
</tr>
<tr>
<td>Right ideomotor apraxia (cutoff = 13)</td>
<td>12.60 ± 5.12 (60)</td>
<td>14.88 ± 6.13 (25)</td>
<td>4.50 ± 3.08 (100)</td>
<td>...</td>
</tr>
<tr>
<td>Left ideomotor apraxia (cutoff = 13)</td>
<td>12.60 ± 5.14 (60)</td>
<td>13.63 ± 5.93 (37.5)</td>
<td>3.93 ± 3.76 (100)</td>
<td>...</td>
</tr>
<tr>
<td>Praxic domain†</td>
<td>−17.3 ± 12.1 (−36.6; 0.3)</td>
<td>−13.4 ± 14.2 (−42.5; 0.3)</td>
<td>−37.4 ± 7.7 (−47.3; −29.4)</td>
<td>.01 for PCA vs EOAD, .003 for PCA vs lvPPA</td>
</tr>
</tbody>
</table>

Note.—Unless indicated otherwise, values are means ± standard deviations, with the percentage of patients with abnormal test scores compared with the normative data of reference in parentheses. NS = not significant.

* Mini–mental state examination and Z scores were compared between groups by using the analysis of variance model, followed by pairwise comparisons with Bonferroni correction.

† Numbers in parentheses are ranges.

By using S0 release 9.1 software (SAS Institute, Cary, NC), normal distribution assumption was checked by means of Q-Q plot and glm procedures. The resulting statistical maps were thresholded at a P value less than .05, family-wise error corrected for multiple comparisons at the cluster level by using the threshold-free cluster enhancement option (30).

Table 2 shows the results of the statistical analysis. The results were compared between groups using the analysis of variance model, followed by pairwise comparisons with Bonferroni correction. The statistical analysis was conducted by M.C., with 6 years of experience in biostatistics.

WM damage.—DT MR imaging voxelwise statistical analysis was performed to compare mean diffusivity, fractional anisotropy (FA), axial diffusivity, and radial diffusivity between groups by using a permutation-based inference tool for nonparametric statistical thresholding (‘randomise,’ part of FSL) (29). The number of permutations was set at 5000 (29). Analyses were adjusted for individual age. The resulting statistical maps were thresholded at a P value less than .05, family-wise error corrected for multiple comparisons at the cluster level by using the threshold-free cluster enhancement option (30).

Two WM atlases within FSL (http://fsl.fmrib.ox.ac.uk/fsl/data/atlas-descriptions.html), the Johns Hopkins University WM tractography atlas (http://fsl.fmrib.ox.ac.uk/fsl/data/atlas-descriptions.html), and the ICBM DTI WM labels atlas (http://www.loni.usc.edu/ICBM/Downloads/Downloads_DTI_81.shtml) were used to guide the identification of WM tracts of interest: the body, genu, and splenium of the corpus callosum; fornix; cingulum; parahippocampal tract; external capsule; anterior inferior fronto-occipital fasciculus and uncinate fasciculus; posterior part of the inferior fronto-occipital fasciculus and inferior longitudinal fasciculus; superior longitudinal fasciculus; and medial parietal WM. WM tracts of interest were overlaid onto the mean FA image of each individual and masked with the WM skeleton. For each subject, mean FA and mean diffusivity values were derived for each WM tract bilaterally. By using SAS release 9.1 software (SAS Institute, Cary, NC), normal distribution assumption was checked by means of Q-Q plot and glm procedures. The resulting statistical maps were thresholded at a P value less than .05, family-wise error corrected for multiple comparisons at the cluster level by using the threshold-free cluster enhancement option (30).

By using S0 release 9.1 software (SAS Institute, Cary, NC), normal distribution assumption was checked by means of Q-Q plot and glm procedures. The resulting statistical maps were thresholded at a P value less than .05, family-wise error corrected for multiple comparisons at the cluster level by using the threshold-free cluster enhancement option (30).
Shapiro-Wilk and Kolmogorov-Smirnov tests. FA and mean diffusivity values were compared between groups by using analysis of covariance models, followed by pairwise comparisons (SAS release 9.1; SAS Institute). A conjunction analysis was performed to identify the overlapping components of the WM damage among AD syndromes, and interaction analyses were conducted to define the patterns of WM damage specific to each AD variant (SAS release 9.1; SAS Institute). To account for the two different DT MR imaging sequences, we used a linear mixed-effects model with random intercepts for sequence covariates. All analyses were adjusted for age. The analyses were repeated by also adjusting for years of education.

Cortical atrophy.—In SPM8, linear contrasts were performed to identify patterns of cortical atrophy in patients with each syndrome versus age-matched healthy control subjects. A conjunction analysis was conducted to identify regions of common atrophy across the AD variants. To investigate regions of atrophy specific to each AD syndrome compared with the others, the relevant linear contrast (eg, less in patients with PCA than in healthy control subjects) was inclusively masked with the appropriate contrast between that syndrome and the other two (eg, less in patients with PCA than in patients with EOAD and lvPPA), as described previously (6). All analyses were adjusted for total intracranial volume and age, and results were tested at a P value less than .05, family-wise error corrected for multiple comparisons. The analyses were repeated by also adjusting for years of education.

Results

Cognitive Findings

Patients with EOAD showed severe and multidomain cognitive impairment with prominent involvement of the verbal and visuospatial memory, visuospatial abilities, and executive functions (Table 2). In addition to the typical language deficit profile (Table E1 [online]), most patients with lvPPA also presented with verbal memory and visuospatial impairment. PCA showed prominent deficits of visuospatial abilities, visuospatial memory, and praxis. Patients with lvPPA were the least cognitively impaired group, compared with the others (Table 2). Patients with PCA performed worse than those with lvPPA and EOAD in praxis and visuospatial memory domains and performed lower than those with lvPPA in visuospatial and executive tasks (Table 2). Patients with EOAD scored lower on visuospatial and executive tests relative to patients with lvPPA (Table 2).

Table E1 (online) shows the language test scores obtained in patients with lvPPA and highlights deficits in sentence repetition, naming, and syntactic comprehension, whereas object knowledge and single-word comprehension were relatively spared. Almost all patients with PCA showed ventral symptoms, such as visual agnosia (92%), prosopagnosia (69%), or alexia (85%). Among ventral symptoms, simultagnosia was detected in 15% of patients. A minority of patients with PCA also showed dorsal signs, such as optic ataxia (38%), oculomotor apraxia (31%), and neglect (23%). Simultagnosia (often resulting from both ventral and dorsal stream impairment) was detected in 15% of patients. Gerstmann syndrome signs were common in the PCA group, including left-right disorientation (31% of patients), dysgraphia (77%), calculation difficulties (54%), and finger agnosia (85%).

WM Damage

Patients with each syndrome versus matched healthy control subjects.—Patients with EOAD compared with control subjects showed a distributed and symmetrical pattern of FA decrease and mean diffusivity, axial diffusivity, and radial diffusivity increases in the corpus callosum, cingulum, fornix, parahippocampal tract, and dorsal frontoparietal pathways, including the superior longitudinal fasciculus (P < .05, family-wise error corrected; Figs 1, 2; Figs E1, E2 [online]). Patients with EOAD relative to healthy control subjects showed DT MR imaging alterations in the brainstem, involving the cerebral peduncles and middle and inferior cerebellar peduncles bilaterally (P < .05, family-wise error corrected; Figs E1, E2 [online]).

The analyses were repeated with control subjects, patients with lvPPA showed a left lateralized FA decrease in the corpus callosum, cingulum, fornix, parahippocampal tract, and dorsal frontoparietal pathways, including the superior longitudinal fasciculus (P < .05, family-wise error corrected; Fig 1). The pattern of increased mean diffusivity, axial diffusivity, and radial diffusivity was more distributed and extended to the left external and internal capsules and the same regions of the right hemisphere (P < .05, family-wise error corrected; Fig 2; Figs E1, E2 [online]).

Compared with control subjects, patients with PCA compared with control subjects showed a distributed and symmetrical pattern of FA decrease, as well as axial diffusivity and radial diffusivity increases in the corpus callosum, parahippocampal tracts, and posterior part of the cingulum, superior longitudinal fasciculus, inferior longitudinal fasciculus, and inferior fronto-occipital fasciculus (P < .05, family-wise error corrected; Fig 1; Figs E1, E2 [online]). The pattern of increased mean diffusivity extended to the frontal regions, although a decreasing gradient from posterior to anterior was present (P < .05, family-wise error corrected; Fig 2).

Overlapping and specific patterns of WM damage across the AD variants.—Figures 1 and 2 show the overlapping patterns of FA decrease and mean diffusivity increase among AD variants in the left corpus callosum, frontoparietal, and parietotemporal connections. Tables E2 and E3 (online) show the mean FA and mean diffusivity values of the main WM tracts in patients and control subjects. The conjunction
analysis demonstrated that patients with EOAD, lvPPA, and PCA shared DT MR imaging abnormalities of the body of the corpus callosum, fornix, right cingulum, left superior longitudinal fasciculus, and external capsule bilaterally ($P < .05$). In addition to this common pattern, the interaction analysis showed that patients with EOAD experienced additional damage to the genu and splenium of the corpus callosum and parahippocampal tract bilaterally ($P < .05$; Tables E2 and E3 [online]). There were no additional regions of damage specific to patients with lvPPA or PCA relative to the other two groups. All the results described herein did not change when years of education were added as covariates in the statistical design.

**Cortical Atrophy**

Voxel-based morphometry results of patient groups relative to healthy control subjects are shown in Figure E3 (online) ($P < .05$, family-wise error corrected). The severity and regional distribution of cortical atrophy in each AD variant were consistent with those reported previously (4–6,18). Briefly, patients with EOAD showed a widespread pattern of gray matter atrophy, involving mainly the medial and lateral parietal, temporal, and occipital lobes, extending bilaterally to the frontal regions. Patients with lvPPA showed a focal, left-lateralized atrophy of the temporoparietal junction and hippocampus. In PCA, cortical atrophy was localized in the bilateral occipital lobes; temporal regions, including the hippocampus; and medial and lateral parietal cortices, with smaller regions of atrophy in the frontal cortex bilaterally.

Overlapping and specific patterns of gray matter atrophy in AD variants were in line with our previous report (6) (Fig 3). Patients with EOAD, lvPPA, and PCA shared left-sided areas of cortical atrophy, including the precuneus, inferior parietal regions, and lateral temporal cortex ($P < .05$, family-wise error corrected). Cortical atrophy specific to EOAD included the right hippocampus, parahippocampal cortex, and precuneus ($P < .05$, family-wise error corrected). The lvPPA-specific cortical atrophy occurred in the left middle temporal gyrus ($P <$
.05, family-wise error corrected). Cortical atrophy specific to PCA included the inferior and middle occipital gyri, fusiform and lingual gyri bilaterally, left calcarine cortex, and small regions in the right lateral temporal and parietal cortices (P < .05, family-wise error corrected). All the results described herein did not change when years of education were added as covariates in the statistical design.

### Discussion

EOAD, lvPPA, and PCA offer an ideal framework for exploring AD pathologic changes in terms of altered brain cortical and WM networks. In this study, we used DT MR imaging to compare the patterns of WM tract damage in these patients. We also explored the distribution of cortical atrophy by using voxel-based morphometry. We found that all patients shared a common pattern of WM damage involving the corpus callosum and the main anterior-posterior pathways. When we looked at the commonly altered cortical regions, we found that the three groups shared a pattern of atrophy, including the left temporoparietal regions and precuneus, in agreement with previous studies (6,31). More importantly, we demonstrated that the microstructural WM damage is more severe and more widely distributed than expected on the basis of cortical atrophy in all clinical phenotypes studied.

The cognitive profile of each group of patients highly reflects the distribution of cortical atrophy and the patterns of WM tract damage. In EOAD, brain damage was severe and diffuse, in keeping with the multidomain cognitive dysfunction. Compared with lvPPA and PCA and consistent with the anterior brain damage, patients with EOAD were more impaired in executive tasks consistently with their anterior brain damage and had greater memory deficits in agreement with their more severe involvement of the medial temporal and parietal cortices, splenium of the corpus callosum, and parahippocampal tracts. Patients with PCA, who are characterized by poor performance in visuospatial tests,
showed a severe and diffuse pattern of cortical atrophy, but this was more centered around bilateral occipitoparietal regions. We also found that fibers connecting the occipital cortices with temporal and frontal regions, particularly on the right side, were those with more severe DT MR imaging abnormalities in patients with PCA. Patients with lvPPA showed highly asymmetric brain damage on the left side of the brain to posterior temporal and parietal regions and superior longitudinal fasciculus and inferior fronto-occipital fasciculus and uncinate involvement, in agreement with their typical language deficits.

The most important finding of the present study is that WM damage was more severe and more widely distributed than expected on the basis of cortical atrophy and the cognitive profiles, particularly in the atypical AD forms in which cortical atrophy remains localized and the clinical symptoms relatively focal. Together with the few previous studies in which WM damage was assessed in separate series of EOAD (4,18), PCA (22–24), and lvPPA (19–21), our findings indicate that DT MR imaging may be able to demonstrate subtle abnormalities along WM pathways that link atrophic regions with still unaffected gray matter regions. More importantly, we found that DT MR imaging has the potential to allow assessment of the extensive disorganization of brain networks in focal AD, even before overt cognitive deficits become apparent.

To date, the causes of WM degeneration in AD are still unknown. In mild cognitive impairment and healthy subjects, WM damage can be detected even before the development of cortical atrophy and overt dementia (32,33). Converging data support the notion that WM damage has a central role in how the disease strikes and progresses. A series of recent studies has provided evidence for prion-like mechanisms of pathologic transmission of amyloid β and tau aggregates in AD from neuron to neuron along WM connections (14). We recently proposed (34) that microglia activation in the presence of amyloid β in excess produces neurotoxic and oligodendrotoxic oligomers that, through WM tract damage, spread disease to neighboring and connected areas.

Within this framework, the WM damage we observed in patients with EOAD, lvPPA, and PCA may be interpreted as a result of the disease spreading through structural connections. The discrepancy we found between cortical atrophy and WM damage, together with the anatomic distribution of our findings, may suggest that the disease has targeted specific peripheral networks.
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