White matter hyperintensities (WMHs) represent a pathologic process that occurs with increasing prevalence in aging. They appear in brain magnetic resonance (MR) imaging as areas of high signal intensity in subcortical or periventricular white matter and provide a good signal for vascular disease. Evidence indicates that WMHs are associated with various markers of vascular disease and other age-related morbidity and dementia. It has been hypothesized that WMHs may be directly related to Alzheimer disease (AD). However, current data suggest that WMHs are not associated with typical markers of AD. Nevertheless, WMHs may increase the risk of AD through a separate pathway that does not involve markers typically associated with AD neurodegeneration.

Existing data suggest that WMHs may operate partly through disruption of frontosubcortical circuits. Moreover, WMHs and other forms of vascular pathology (eg, lacunar infarcts) have been shown to be associated with reduced glucose metabolism seen using positron emission tomography with fluorodeoxyglucose F18 (FDG-PET) and changes in functioning associated with frontal brain regions (eg, executive function) but not those areas that are known to be associated with AD neurodegeneration (ie, temporoparietal metabolism).
We hypothesized that WMHs would be associated with reduced frontal metabolism and that cerebrospinal fluid β-amyloid (CSF-Aβ), a measure of AD, would be associated with lower temporoparietal metabolism in the same patients. It is possible that WMHs may co-occur with AD, evidenced by reduced metabolism in different brain regions, to increase the risk of AD in patients with mild cognitive impairment (MCI).

Methods

Participants

Participants were enrolled in the Alzheimer’s Disease Neuroimaging Initiative (ADNI). ADNI is a multicenter project supported by the National Institutes of Health, private pharmaceutical companies, and nonprofit organizations for the purpose of developing and using biomarkers for monitoring progression in MCI and AD. Briefly, enrolled patients were aged 55 to 90 years, including control subjects, patients with MCI, and patients with AD. Of these, only those patients with MCI were examined in the present study. ADNI exclusion criteria included a history of structural brain lesions or head trauma, a score of 4 or higher on the Hachinski Ischemic Scale, significant neurological disease other than incipient AD, and the use of psychotropic medications that could affect memory. Findings on MR imaging that served as exclusionary criteria included major hemispheric infarction or structural abnormalities that severely distort brain anatomy, such as a tumor or prior resective surgery. Further details about exclusion criteria and study protocols (eg, MR imaging review) applied in ADNI are given elsewhere. Study updates are available at http://www.adni-info.org. The study was approved by institutional review boards of all participating institutions. All patients or their representatives gave written informed consent for the study procedures before participation.

At baseline, all patients underwent a clinical evaluation and MR imaging. Patients with MCI were selected for the present study and included those with FDG-PET imaging. In addition, CSF samples were collected for half the patients at baseline and for a subset of those at the 12-month follow-up examination. Therefore, the number of patients available for analysis differed depending on the set of biomarkers examined.

Evaluations were repeated for these patients during 3 years, at 6, 12, 18, 24, and 36 months. In total, 203 patients with baseline data that included FDG-PET and MR imaging were available for analysis, with decreasing numbers at different follow-up stages (Table 1), for a total of 844 observations. Of 203 patients in the study, 101 had CSF sample data.

WMH Measure

Structural MR images (1.5 T) were acquired at multiple ADNI sites based on a standardized protocol. Images were spin-echo T1 weighted, T2 weighted, and proton density weighted, and a validated fully automated WMH detection method was applied. The method aligned imaging data to a template image for older patients. White matter hyperintensities were identified on a per-voxel basis. The method is based on image intensities and knowledge of prior probabilities of WMH occurrence at each brain location. For each individual, a resultant map of WMH voxels across the brain (excluding WMHs occurring in the occipital lobe) was summarized by an estimate of total WMH volume, and the percentage of total brain volume was calculated. Each patient’s WMH data were examined and edited for potential outliers, where any values exceeding 3 SDs of the mean of the remaining values were excluded (ie, 2.8% of original data).

FDG-PET Measure

The FDG-PET scans were acquired at sites nationwide using a standardized protocol in which all images were transformed to a uniform voxel size and 8-mm full width at half maximum resolution (http://adni.loni.ucla.edu/methods/pet-analysis/pet-acquisition/). The FDG-PET scans were then spatially normalized to a PET template in Montreal Neurological Institute space using SPM5. Additional details of PET image processing are provided elsewhere.

Five regions of interest (ROIs) were identified through a literature search of regions most frequently cited in differentiating patients with AD and healthy control subjects. These ROIs included bilateral angular gyri, bilateral inferior temporal cortices, and the posterior cingulate–precuneus region. The mean FDG-PET counts were extracted from each ROI and divided by a pons-vermis reference region. An average of these pons-vermis–referenced ROI mean counts was used to create a single temporoparietal FDG-PET composite measure.

Additional frontal ROIs were included using automated anatomic label–defined bilateral middle frontal and bilateral inferior frontal gyri in Montreal Neurological Institute space. A composite measure of frontal metabolism for each patient was created by averaging FDG-PET means across these regions.

Table 1. Alzheimer’s Disease Neuroimaging Initiative Participants Having MCI With Magnetic Resonance Imaging and FDG-PET at Baseline and the Follow-up Evaluation

<table>
<thead>
<tr>
<th>Evaluation, mo</th>
<th>Converters (n = 74)</th>
<th>Nonconverters (n = 129)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Full Sample</td>
<td>CSF-Aβ Subsample</td>
</tr>
<tr>
<td>Baseline</td>
<td>74</td>
<td>43</td>
</tr>
<tr>
<td>6</td>
<td>72</td>
<td>42</td>
</tr>
<tr>
<td>12</td>
<td>70</td>
<td>41</td>
</tr>
<tr>
<td>18</td>
<td>60</td>
<td>35</td>
</tr>
<tr>
<td>24</td>
<td>50</td>
<td>29</td>
</tr>
<tr>
<td>36</td>
<td>10</td>
<td>7</td>
</tr>
</tbody>
</table>

Abbreviations: CSF-Aβ, cerebrospinal fluid β-amyloid; FDG-PET, positron emission tomography with fluorodeoxyglucose F18; MCI, mild cognitive impairment.
CSF-\(\beta\)- Measure

Details of CSF collection and processing are given elsewhere. In the present study, CSF-\(\beta\) was used as an indirect, quantitative measure of amyloid pathology.

Other Measurements

Other covariates, including age, sex, and educational status, were used to describe the study sample. Alzheimer disease conversion status at follow-up visits was determined based on standard diagnosis. Other AD markers for describing the sample included hippocampal volume and apolipoprotein E4 allele (ApoE4) status. Details about the measurement of hippocampal volume and determination of ApoE4 genotype are available in previous studies.

Statistical Analysis

Analyses were conducted separately for MCI patients who converted to AD and for patients who did not convert during the 3-year study. The analysis was aimed at quantifying the association of WMHs and FDG-PET measured in different brain regions. A repeated-measures design was used to account for the multiple time points when patients were evaluated during the study, with generalized estimating equations to account for within-patient correlation. This design allowed for quantification of WMHs with respect to brain metabolism that was not based on a single time point but accounted for WMH progression and its successive effect on metabolism over time. Linear regression models were used to examine the associations of interest. The outcome variable in the regression models was represented by FDG-PET, measured in both the frontal and temporoparietal regions. The independent variables of the models included age, WMHs, and an interaction of WMHs and an indicator variable to denote the brain region measured with FDG-PET in the outcome (ie, 0 for temporoparietal and 1 for frontal). Therefore, the regression coefficients from the models represented the associations of WMHs with temporoparietal and frontal metabolism (relative to temporoparietal). These regressions were repeated to examine the association of CSF-\(\beta\) with the same FDG-PET measures.

Although the distribution of WMHs was characteristically skewed, its relationship with FDG-PET in the different brain regions was linear (data not shown). Therefore, the variable was not transformed for the analysis. However, to avoid potential end point effects that high WMH values could have on regression estimates, WMHs were restricted to less than 2% of total brain volume, where approximately 8% of observations had WMHs of 2% or greater. Patients whose data consisted entirely of WMHs of 2% or greater (1 converter and 2 nonconverters) were excluded from the analysis.

Analyses were performed using statistical software (SAS software version 9.1.3; SAS Institute, Inc.). R software (version 2.4.1; http://cran.r-project.org/bin/windows/base/old/2.4.1/) was also used.

Results

Baseline distributions of study variables were compared for patients with MCI who converted and who did not convert to AD in the 3-year study (Table 2). Distributions differed significantly between groups and in expected directions for markers typically associated with AD, including CSF-\(\beta\), ApoE4 status, hippocampal volume, and FDG-PET (temporoparietal region). Distributions for other variables did not differ significantly between groups, nor did the groups differ in terms of WMH distribution at baseline.

Table 3 gives estimates of the associations of WMHs with FDG-PET in different brain regions in converters and nonconverters. In converters, a 1% increase in WMH volume relative to total brain volume was associated with a reduction in frontal glucose metabolism (model 1 coefficient, \(-0.048; P \leq 0.001\) compared with no reduction in temporoparietal metabolism (model 1 coefficient, \(0.01; P = .28\). When the analysis was restricted to those with available CSF-\(\beta\) data, similar results were observed for relationships between WMHs and glucose metabolism, with almost identical coefficients (model 2). By contrast, greater CSF-\(\beta\) (per 10-\(\mu\)g/mL increase) in these same patients (Table 4) was associated with increased temporoparietal

Table 2. Baseline Characteristics of 203 Alzheimer’s Disease Neuroimaging Initiative Participants Having MCI With Magnetic Resonance Imaging and FDG-PET

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Combined (N = 203)</th>
<th>Converters (n = 74)</th>
<th>Nonconverters (n = 129)</th>
<th>(P) Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>75.5 (7.2)</td>
<td>75.2 (6.9)</td>
<td>75.6 (7.4)</td>
<td>.71</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>67.5</td>
<td>65.2</td>
<td>67.0</td>
<td>.22</td>
</tr>
<tr>
<td>Education, mean (SD), y</td>
<td>15.8 (2.9)</td>
<td>16.0 (2.6)</td>
<td>15.7 (3.0)</td>
<td>.47</td>
</tr>
<tr>
<td>Follow-up period, mean (SD), y</td>
<td>1.6 (0.7)</td>
<td>1.9 (0.6)</td>
<td>1.5 (0.8)</td>
<td>.001</td>
</tr>
<tr>
<td>FDG-PET, mean (SD)**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frontal region</td>
<td>1.1 (0.1)</td>
<td>1.1 (0.1)</td>
<td>1.1 (0.1)</td>
<td>.99</td>
</tr>
<tr>
<td>Temporoparietal region</td>
<td>1.2 (0.1)</td>
<td>1.1 (0.1)</td>
<td>1.2 (0.1)</td>
<td>.001</td>
</tr>
<tr>
<td>Hippocampal volume, mean (SD), mm³</td>
<td>3290 (520)</td>
<td>3134 (532)</td>
<td>3382 (492)</td>
<td>.001</td>
</tr>
<tr>
<td>CSF-(\beta), mean (SD), pg/dL</td>
<td>159.3 (51.5)</td>
<td>146.5 (43.6)</td>
<td>168.8 (55.2)</td>
<td>.005</td>
</tr>
<tr>
<td>ApoE4 status, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Allele</td>
<td>40.4</td>
<td>47.3</td>
<td>36.4</td>
<td>.005</td>
</tr>
<tr>
<td>2 Alleles</td>
<td>12.8</td>
<td>20.3</td>
<td>8.5</td>
<td></td>
</tr>
<tr>
<td>WMHs, % of total brain volume*</td>
<td>0.12, 0.28, 0.62</td>
<td>0.13, 0.26, 0.55</td>
<td>0.10, 0.30, 0.64</td>
<td>.60</td>
</tr>
</tbody>
</table>

**CSF-\(\beta\) measured at baseline.

†Based on 101 participants with CSF-\(\beta\) measured at baseline.

*Given the skewness of this variable, the distribution is reported as 25th, 50th, and 75th percentiles.

**Based on the cerebral metabolic rate of glucose consumption.

*Statistical test to compare converters and nonconverters are based on \(t\) test for continuous data, \(\chi²\) test for categorical data, and Wilcoxon rank sum test for WMHs.

Table 2 gives estimates of the associations of WMHs with FDG-PET in different brain regions in converters and nonconverters. In converters, a 1% increase in WMH volume relative to total brain volume was associated with a reduction in frontal glucose metabolism (model 1 coefficient, \(-0.048; P \leq 0.001\) compared with no reduction in temporoparietal metabolism (model 1 coefficient, \(0.01; P = .28\). When the analysis was restricted to those with available CSF-\(\beta\) data, similar results were observed for relationships between WMHs and glucose metabolism, with almost identical coefficients (model 2). By contrast, greater CSF-\(\beta\) (per 10-\(\mu\)g/mL increase) in these same patients (Table 4) was associated with increased temporoparietal
metabolism (model 1 coefficient, 0.005; P = .03). Higher CSF-Aβ was not associated with greater frontal metabolism (model 1 coefficient, 0.002; P = .54).

Results for nonconverters had a pattern similar to that of converters with respect to relationships between WMHs and frontal hypometabolism and between CSF-Aβ and both frontal and temporoparietal hypometabolism. However, although more WMHs were negatively associated with frontal metabolism, more WMHs were positively associated with glucose metabolism in the temporoparietal regions in both the larger study group (model 3 coefficient, 0.051; P = .001) and the CSF-Aβ restricted group (model 4 coefficient, 0.023; P = .14) (Table 3). Although the association was not significant in the restricted group (i.e., model 4), it was found to be larger and significant (0.036; 95% CI, 0.006-0.066) after the exclusion of an individual with comparatively low CSF-Aβ (<50 pg/mL), low temporoparietal metabolism (<0.80), and high WMHs (1.3% of total brain volume).

Fitted data from the models estimates in Table 3 and Table 4 are shown in Figure 1 for converters and in Figure 2 for nonconverters. These plots show patterns of the associations between WMHs and regional glucose metabolism that are opposite to those for CSF-Aβ. For example, in converters (Figure 1A and B) the slopes for frontal glucose metabolism reveal a steep decline in frontal metabolism as WMHs increase but no change in temporoparietal metabolism. In contrast, Figure 1C shows an increase in temporoparietal metabolism with increasing CSF-Aβ but little change in frontal glucose metabolism. These relationships are similar in nonconverters except that increasing WMHs are associated also with increases in glucose metabolism in temporoparietal cortex (Figure 2A and B).

Table 3. Association of Regional Glucose Metabolism and WMHs in Participants Having MCI, With Conversion Status During the 3-Year Follow-up Period

<table>
<thead>
<tr>
<th>Variable</th>
<th>Converters</th>
<th>Nonconverters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>1.113 (1.092 to 1.134)</td>
<td>1.176 (1.156 to 1.196)</td>
</tr>
<tr>
<td>Age</td>
<td>-0.004 (-0.006 to -0.002)</td>
<td>0.002 (-0.004 (-0.007 to -0.001)</td>
</tr>
<tr>
<td>Temporoparietal region</td>
<td>0.010 (-0.010 to 0.030)</td>
<td>0.28 (0.027 to 0.076)</td>
</tr>
<tr>
<td>Frontal region</td>
<td>-0.048 (-0.067 to -0.029)</td>
<td>-0.043 (-0.061 to -0.025)</td>
</tr>
</tbody>
</table>

Table 4. Association of Regional Glucose Metabolism and CSF-Aβ in Participants Having MCI, With Conversion Status During the 3-Year Follow-up Period

<table>
<thead>
<tr>
<th>CSF-Aβ Subsample</th>
<th>Converters</th>
<th>Nonconverters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>1.124 (1.098 to 1.145)</td>
<td>1.172 (1.137 to 1.206)</td>
</tr>
<tr>
<td>Age</td>
<td>-0.003 (-0.006 to 0.000)</td>
<td>0.003 (-0.008 to 0.002)</td>
</tr>
<tr>
<td>Temporoparietal region</td>
<td>0.001 (-0.025 to 0.027)</td>
<td>0.023 (-0.015 to 0.060)</td>
</tr>
<tr>
<td>Frontal region</td>
<td>-0.044 (-0.066 to -0.022)</td>
<td>-0.053 (-0.076 to -0.030)</td>
</tr>
</tbody>
</table>

Abbreviations: CSF-Aβ, cerebrospinal fluid β-amyloid; FDG-PET, positron emission tomography with fluorodeoxyglucose F18; MCI, mild cognitive impairment; WMHs, white matter hyperintensities.

To avoid endpoint effects, records with WMHs of 2% or greater were excluded from the analysis, which included 3 participants (1 converter and 2 nonconverters) whose records consisted entirely of WMHs of 2% or greater.

* Associated change in temporoparietal glucose metabolism measured by FDG-PET (see the FDG-PET Measure subsection of the Methods section for details) per 1% increase in WMHs relative to total brain volume.

* Associated change in frontal glucose metabolism measured by FDG-PET (see the FDG-PET Measure subsection of the Methods section for details) per 1% increase in WMHs relative to total brain volume.
Discussion

Our primary findings indicate a dissociation in the pattern of relationships between different presumptive pathologic substrates of dementia and regional glucose metabolism: greater WMHs are associated with decreased frontal metabolism, while greater CSF-Ab is associated with increased temporoparietal metabolism (ie, lower CSF-Ab is associated with temporoparietal hypometabolism). These results support the hypothesis that WMHs, as a measure of vascular pathology and vascular burden, are associated with frontal lobe dysfunction rather than dysfunction in those brain regions more closely linked to AD neurodegeneration. A likely marker of AD, CSF-Ab, was more closely associated with differences in temporoparietal metabolism than frontal levels. This dissociative pattern adds to evidence that these respective pathologic conditions, when they co-occur, are operating simultaneously through metabolic alterations in different brain regions and potentially represent independent pathways to AD progression in MCI.

The observed associations of WMHs, CSF-Ab, and regional metabolism did not vary substantially between nonconverters and converters. However, this finding is not surprising given that WMHs have been shown to be associated with reduced frontal metabolism and with cognitive markers related to frontal brain regions regardless of disease status (eg, patients without AD and cognitive impairment in otherwise healthy individuals).3-5,30 Also, the consistency of the associations between CSF-Ab and regional metabolism regardless of conversion status may reflect that CSF-Ab represents a stronger marker of AD in the initial stages of the disease as opposed to a marker of AD progression.28,31-33 In other words, CSF-Ab levels, which change less over time during the disease, may be associated with similar levels of synaptic dysfunction in MCI regardless of the final outcome in such patients.32
Another noteworthy result was the positive association between temporoparietal metabolism and greater WMHs that was observed for nonconverters. One explanation for this finding could be that individuals with nonconverting MCI and more WMHs may have higher levels of temporoparietal metabolism, which enables them to remain stable. Studies have found increased levels of executive dysfunction, one of the cognitive risks associated with WMHs, in patients with AD, suggesting that WMHs may have a role in conversion. We did not observe this positive association between greater WMHs and temporoparietal metabolism for converters. In fact, temporoparietal metabolism was significantly reduced in converters compared with nonconverters, as were other markers of AD (eg, hippocampal volume). Therefore, the likelihood of conversion may be related to the interplay between these brain systems, with individuals having high WMHs and low frontal metabolism being more likely to convert in the setting of temporoparietal hypometabolism due to AD but less likely to convert when this AD biomarker is absent.

Previous studies have found that other forms of vascular pathology, including WMHs, are associated with reduced metabolism in the frontal lobes and with reduced frontal-mediated cognitive function (eg, executive dysfunction). ADNI patients were prescreened and were excluded based on evidence of strategic hemispheric infarcts and self-reported clinical cerebrovascular disease. However, it is possible that patients with different underlying subclinical cerebrovascular disease (eg, silent infarcts) were not excluded entirely. Also, patients were not excluded based simply on the presence of WMHs and may have also subsequently developed WMHs or other cerebrovascular disease (eg, cortical and subcortical lesions) after enrollment in the study. Therefore, it is possible that both WMHs and other vascular pathologic conditions associated with WMHs might in part explain the present findings.

This study did not control for certain factors that may have partly contributed to the findings. Models were not adjusted for depression or medication use, both of which could be independently associated with metabolism in the different brain regions. However, adjustment for these variables (eg, depression) could have led to overadjustment of the models because depression may mediate the effects of WMHs on cognition and potentially brain metabolism. Moreover, we did not adjust for other vascular risk factors (eg, hypertension) given that previous investigations have either shown that the effects of WMHs occur independent of these risk factors or better explain the relationship of vascular disease and metabolic and cognitive end points. Nevertheless, it is possible that the exclusion of these variables may have resulted in biased estimates from residual confounding.

We investigated the follow-up difference that was observed for nonconverters and converters with respect to the findings. Nonconverters who were lost to follow-up contact may have converted before the end of the study period (ie, 3 years), which could partly explain the similar associations observed for the 2 groups. We restricted the analysis to those patients with at least 2 years of follow-up data (data not shown). Although the sample was reduced as a result, the estimates of the associations were comparable with those based on the full sample.

Despite its potential limitations, this study contributes substantially to the existing literature with regard to the associations between AD and vascular pathologic substrates and brain metabolism. This is one of the first studies to examine these associations in a large sample of the same patients. Availability of different measures in the same patients, which included a quantified measurement of WMHs, allowed for multimarker comparisons, while fewer comparisons were possible in previous studies. Moreover, the associations observed for WMHs and FDG-PET, measured for different brain regions, were based on data sampled over time. In other words, the study findings may more accurately reflect the underlying relationships of these associations based on changes occurring with progressive white matter disease and its metabolic effects over time. Compared with estimates based on WMHs from a single time point (eg, baseline assessment only), the estimates from this study may better represent biologic changes concomitant with brain aging and age-related brain disease.

In summary, our findings are consistent with the hypothesis that markers of AD and vascular pathology operate simultaneously to affect metabolism in different brain regions. The observed patterns of dissociation of different pathologic features and metabolism measured in different brain regions suggest the plausibility of 2 different pathways contributing to AD risk in patients with MCI and serve as motivation for further research examining risk factors for longitudinal outcomes.
Prevalence of cerebral white matter lesions in the frontal-subcortical syndrome of aging.


REFERENCES

Prevalence of cerebral white matter lesions in the frontal-subcortical syndrome of aging.


Additional Information: Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://www.loni.ucla.edu/ADNI). As such, the investigators within ADNI contributed to the design and implementation of ADNI or provided data but did not participate in the analysis or writing of this article.

Additional Contributions: Natalie L. Marchant, PhD, provided helpful discussion about the study.


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