Background and Purpose—The boundary between vascular dementia and Alzheimer disease (AD) continues to be unclear. Some posit that gradually progressive vascular dementia, as with small vessel disease, is simply vascular disease plus AD. Because AD presents a characteristic pattern on fluorodeoxyglucose positron emission tomography, we sought to determine whether the fluorodeoxyglucose pattern of vascular dementia resembled more AD or the pattern in nondemented patients with severe microvascular brain disease.

Methods—Vascular disease patients were selected on the basis of confluent white matter lesions on both hemispheres. Among them, with a similar degree of vascular disease on MRI, neuropsychological testing separated groups with dementia and without dementia. Patients with AD and healthy controls were also studied. The 4 groups, with 12 subjects each, were matched by age, gender, and educational level. Fluorodeoxyglucose distribution was analyzed using both voxel-based and volume of interest methods.

Results—The AD group had the characteristic pattern of bilaterally decreased metabolism in parieto-temporal association cortex and precuneus. By contrast, patients with vascular disease and dementia had a similar anatomic pattern to that of the vascular patients without dementia, but with greater metabolic abnormalities, particularly in the frontal lobes and deep nuclei.

Conclusions—The anatomy of metabolic abnormalities in vascular disease with dementia suggests that, at least in some cases, dementia with vascular disease may be independent of AD. The metabolic abnormality involves the thalamus, caudate, and frontal lobe, a pattern concordant with the neuropsychological findings of impaired executive function characteristic of vascular dementia. (Stroke. 2010;41:2889-2893.)

Key Words: Alzheimer disease ▪ brain metabolism ▪ vascular dementia ▪ white matter disease

Although in epidemiological series vascular dementia (VaD) follows Alzheimer disease (AD) in incidence and prevalence rates,1,2 the very existence of VaD as a diagnostic entity has been questioned.3 Recent neuropathological studies have highlighted the difficulty in attributing the cognitive impairment characteristic of dementia to either AD changes or vascular injury.3,4 Even more challenging is making a clinical differential diagnosis between VaD and AD.5,6 The presence of vascular changes on MRI or CT, required by NINDS-AIREN diagnostic criteria for VaD, is of limited value, because patients with extensive changes on MRI may not have dementia.7 Some have speculated that progressive VaD, as associated with small vessel disease, is simply vascular disease plus AD.8 By contrast, AD has been postulated to be a vascular disorder.9 Because both disorders increase in prevalence in the 70- to 90-year age group, it is difficult to separate their effects in studies showing an association between cognitive impairment and vascular disease on MRI.10

In contrast to MRI, the pattern of brain metabolism obtained with [18F]-fluorodeoxyglucose (FDG) positron emission tomography (PET) could, in theory, be more specific for either type of dementia, because it is becoming increasingly clear that AD affects a specific functional network.11 Involvement of this network may become evident on functional brain testing before it does on structural
imaging, because impaired function tends to precede atrophy. FDG-PET depicts early in AD a highly characteristic pattern of decreased metabolism in parieto-temporal association cortex and precuneus. Previous studies of FDG-PET in VaD or vascular cognitive impairment have compared the metabolic patterns of patients diagnosed “a priori” as AD or vascular cognitive impairment. Given the difficulty of making an accurate clinical diagnosis of VaD and the methodological issue of avoiding potential circular reasoning in study design, we did not classify the study groups through an a priori definition of vascular dementia. Rather, we compared the metabolic findings in AD with the findings in 2 groups of patients with a similar amount of vascular disease on MRI but different cognitive status: nondemented in one group and demented in the other group. In addition to a region of interest analysis, we performed an analysis of variance with post hoc comparisons of the 3 patient groups to the healthy controls group. Multiple comparison correction was performed by Dunnett test specifically designed for situations in which all groups are to be pitted against one reference group, in this case the healthy controls group. Significance level was set to P<0.05.

MRI Data Acquisition

In the 48 study subjects, high-resolution MRI was obtained on the same 3T Siemens Trio scanner (Siemens Medical Solutions), including T1-weighted structural images acquired using a 3-dimensional magnetization prepared rapid gradient echo sequence, with the following imaging parameters: resolution, 1×1×1.1 mm³; field of view, 240×256 mm²; 160 sagittal slices; repetition time/echo time/inversion recovery delay, 2250/900/2.96 ms; flip angle, 9°; and bandwidth, 230 Hz/pixel. These structural images were used for the segmentation of metabolic PET data, as described.

FDG-PET Data Acquisition and Processing

Brain metabolism was measured with [18F]-FDG-PET. Scanning was performed with an ECAT EXACT HR+ unit (Siemens/CTI) 40 minutes after the intravenous injection of 14.4 mCi of [18F]FDG, obtaining 63 simultaneous parallel planes over a 15.2-cm axial field of view. Tomographic resolution was 4.5 mm. After the emission scan, transmission data were obtained using 3 Ge rotating rod sources. The entire intracranial volume, including the cerebellum, was included in the field of view.

For the voxel-based analysis, PET studies were spatially normalized and FDG distribution was compared across groups with statistical parametric mapping software (SPM2, Wellcome Department of Imaging Neuroscience, University College of London) using our customized standard FDG template. Regional activity was normalized to pons uptake and smoothed using a Gaussian filter (full width at half maximum=8 mm). Because the goal was to determine the anatomic networks maximally affected by each disorder, for display purposes (Figure) we used the threshold that best highlighted the brain regions most different between groups. We targeted the threshold to avoid values too low, which resulted in a loss of specificity among brain regions, and values too high, which failed to highlight any regions. The thresholds used are indicated in the legend for the Figure and in Supplemental Table II (available online at http://stroke.ahajournals.org).

Additionally, FDG images of each subject were processed for volume of interest (VOI) analysis and corrected for partial volume effect using the Rousset method implemented in PVLab (pvlab@nru.dk). PET images were coregistered to native-space T1-weighted MRI images using the mutual information method of SPM2. Then, the T1-weighted images were segmented into gray matter, white matter, and cerebrospinal fluid. The segmented gray matter was included in the field of view.

Subjects and Methods

Forty-eight subjects, divided into 4 groups of 12 subjects each, were studied with neuropsychological testing, structural MRI, and FDG-PET. The 4 groups included: (1) patients with AD; (2) patients with vascular disease and dementia; (3) patients with vascular disease but without dementia; and (4) healthy controls. Groups were matched by age, gender, and educational level (Table). The 2 groups with vascular disease included 24 patients whose T2-weighted MRI scans revealed confluent hyperintensities in the periventricular and subcortical white matter (graded as severe or score 3 according to the modified Fazekas scale) These 24 patients were selected from among 1099 patients with “leukoaraiosis” or white matter changes on the official radiological report. From these 1099 patients, 196 met image criteria for inclusion in the study, did not have apparent lesions in the cerebral cortex or hippocampus, and were not using medications that would interfere with FDG-PET testing. Of these 196 patients, with a similar degree of vascular disease on MRI, 123 consented to having clinical and neuropsychological screening (Table) as well as a full neurological evaluation to rule out other neurological disorders. From these 123 patients with vascular disease, we first detected a group of 12 patients with mild to moderate dementia who gave informed consent for the full study. Then, from the same group of 123 patients with vascular disease on MRI, we selected 12 patients without dementia matched to the white matter lesions with dementia group. Two other comparison groups included patients who had MRI scans without or with only mild (Fazekas scale score of 1) leukoaraiosis: 12 patients meeting NINCDS-ADRDA criteria for the diagnosis of probable AD and 12 healthy controls. The study had been approved by the local Ethics Committee following Helsinki guidelines for the study of human subjects. All subjects were fully instructed on the experimental procedures and provided written informed consent, either by themselves or by proxy.

Neuropsychological Testing

The tests performed, listed in the Supplemental Table I (available online at http://stroke.ahajournals.org), were obtained according to standard procedures and were analyzed using SPSS 15 (2008). The performance of the 4 groups was compared using an analysis of variance with post hoc comparisons of the 3 patient groups to the healthy controls group. Multiple comparison correction was performed by Dunnett test specifically designed for situations in which all groups are to be pitted against one reference group, in this case the healthy controls group. Significance level was set to P<0.05.

Variables | AD | WML-D | WML-nD | HC
--- | --- | --- | --- | ---
No. of subjects | 12 | 12 | 12 | 12
Gender (female) | 7 | 6 | 6 | 6
Age (years) | 78.2 (4.6) | 79.5 (4.6) | 80.7 (5.2) | 79.2 (3.9)
Cognitive status: nondemented in one group and demented in the other group. In addition to a region of interest analysis, we performed an analysis of variance with post hoc comparisons of the 3 patient groups to the healthy controls group. Multiple comparison correction was performed by Dunnett test specifically designed for situations in which all groups are to be pitted against one reference group, in this case the healthy controls group. Significance level was set to P<0.05.
matter images were spatially normalized into the Montreal Neurological Institute gray matter prior provided by SPM2 and the inverse transformation matrix was used to label the segmented gray matter voxels in the patient’s MRI-PET space according to a template of VOI defined in the Montreal Neurological Institute space. For each VOI, partial volume effect-corrected mean tracer concentrations were calculated and normalized by corresponding cerebellar values. Because PVElab groups the deep brain nuclei into a single region, normalized tracer concentrations for the various deep brain nuclei were obtained using P-MOD software (PMOD Technologies, Zurich, Switzerland). The alignment of the deep nuclei with the appropriate VOI was verified for each subject using native-space MRI. Comparisons between groups were performed by an analysis of variance, with post hoc comparisons corrected by Dunnett method.

Results
Neuropsychological data are summarized in Supplemental Table I. An analysis of variance showed impaired performance in both cognitive and noncognitive domains in subjects with AD and in those with vascular disease and dementia. There were no significant differences between the patients with vascular disease without dementia and the healthy controls. Post hoc contrasts, corrected with Dunnett test and using the healthy controls as the intermediate comparison group, showed that patients with AD had more difficulty with recognition memory than patients with white matter lesions and dementia. Patients with white matter lesions and dementia performed worse than AD in categorial and phonological verbal fluency, Trail Making, and Stroop tests. They also fared worse in the neuropsychiatric inventory.

Regional Metabolism: Voxel-Based Comparison
Compared to healthy controls, the AD group showed the characteristic pattern of bilaterally decreased metabolism in lateral parieto-temporal association cortex and precuneus, in addition to the medial and inferior temporal regions (Figure A, Table II). By contrast, vascular patients with dementia had decreased metabolism in both frontal lobes and right supramarginal gyrus, but not in the precuneus or temporal lobes (Figure B). Vascular patients without dementia had decreased metabolism in regions similar to those of the vascular patients with dementia, but to a lesser degree (Figure C). A comparison between the 2 groups of vascular patients showed that dementia was associated with worse metabolism in the frontal lobe (Figure D).

VOI Comparison
Results for VOI comparisons are listed in Supplemental Table III (available online at http://stroke.ahajournals.org). Compared to healthy controls, AD had decreased metabolism in temporal and parietal lobes, specifically including the precuneus. In contrast, the vascular groups had decreased metabolism in the frontal and parietal lobes, but not in the temporal lobes or in the precuneus. In addition, the vascular group with dementia had decreased metabolism bilaterally in deep nuclei, specifically the caudate nucleus, globus pallidus, and thalamus.

Discussion
Our study confirmed the hypothesis that the metabolic pattern of the group of vascular patients with dementia differed from the pattern in AD and was similar to the pattern in vascular patients without dementia. When comparing the 2 vascular groups, the metabolic abnormality was worse in patients with dementia than in those without dementia. Vascular patients with dementia had bilaterally abnormal metabolism in structures relatively spared in early AD but important for cognition, namely the frontal lobes, caudate nuclei, and thalami. These results buttress the notion that dementia in a random sample of patients with severe microvascular brain disease can result from vascular factors, independently from AD, and
support the existence of cognitive impairment directly related to vascular disease.23

Importantly, the pattern in vascular disease with dementia did not resemble the anatomic distribution of the AD group.

Both PET analysis methods yielded concordant results: voxel-based comparisons were more specific for the cortical networks, a patchwork on a laminar structure, whereas the VOI analysis was more helpful for the study of deep nuclei, with a more globular configuration. Metabolic differences between AD and VaD have been shown in previous PET studies.14,15,24–26 There are few voxel-based studies, and they show metabolic differences between the 2 types of dementia.14,15 These studies differ from ours in having compared metabolic findings in groups of patients with the a priori diagnosis of vascular dementia15 or vascular mild cognitive impairment.14 This approach was appropriate for these studies but did not fit our purpose, because we sought to ascertain whether the metabolic pattern of AD, reliably associated with AD neuropathology,27 differed from a pattern found in patients with vascular changes and dementia. Thus, for the vascular group we did not use diagnostic criteria for VaD but rather the presence of 2 clearly verifiable phenomena: (1) marked white matter changes on MRI and (2) cognitive impairment severe enough to meet any diagnostic criteria of dementia, including AD. This approach of comparing subjects with and without dementia with vascular brain disease had been used successfully in some region of interest studies,17,28 but the findings had not been analyzed with a voxel-based methodology or compared with AD findings in the same study.

The presence of dementia in the subjects with subcortical vascular disease was associated with a metabolic pattern similar in anatomic distribution, but more abnormal than that in nondemented individuals. Although the 2 groups of vascular patients were drawn from a sample with a similar amount of vascular changes on MRI, vascular disease not easily detectable on MRI could still explain the presence of dementia and metabolic changes. For instance, thalamic lacunes may be underestimated on fluid-attenuated inversion recovery images.29 Microscopic brain infarcts contribute importantly to dementia.30–32 It is likely that such lesions may pass undetected on MRI, perhaps even with careful quantitation of cortical thickness or signal in the cerebral cortex.

Our study does not address the issue of mixed dementia but agrees with previous studies showing the association of frontal hypometabolism and cognitive impairment in patients with white matter changes.33 The high anatomic specificity observed in our study reflects the early stage of the disease in the patients we studied, with a Mini-Mental State Examination score $\approx 20$. This specificity may be lost with advancing disease, when any dementia process affects the brain extensively.

In conclusion, using a systems whole-brain function approach and avoiding aprioristic diagnoses, our study supports the concept that dementia can be associated with vascular brain disease, independent from AD involvement.

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**Disclosure**

None.

**References**


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Brain glucose metabolism in vascular white matter disease with dementia: Differentiation from Alzheimer disease

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3. Department of Radiology, Hospital de Navarra, Pamplona, Spain

Keywords: Vascular dementia, Alzheimer disease, FDG-PET, white matter disease, leukoaraiosis, brain metabolism

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- Table S2. Regions with decreased metabolism on the voxel-based SPM analysis
- Table S3. Regions with decreased metabolism on the volume of interest analysis
Table S1. Neuropsychological performance of the four groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>AD</th>
<th>WML-D</th>
<th>WML-nD</th>
<th>HC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cognitive domains</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Memory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAVLT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First five trials</td>
<td>23.1 (7.0)*</td>
<td>23.5 (8.7)*</td>
<td>42.1 (6.3)</td>
<td>38.4 (7.9)</td>
</tr>
<tr>
<td>Immediate recall</td>
<td>2.6 (1.5)*</td>
<td>2.3 (2.5)*</td>
<td>8.7 (2.7)</td>
<td>8.2 (4.1)</td>
</tr>
<tr>
<td>Delayed recall</td>
<td>1.4 (1.9)*</td>
<td>1.7 (2.3)*</td>
<td>7.7 (2.2)</td>
<td>8.1 (4.0)</td>
</tr>
<tr>
<td>Recognition</td>
<td>9.5 (5.0)*</td>
<td>12.4 (2.0)</td>
<td>14.1 (1.9)</td>
<td>13.9 (1.4)</td>
</tr>
<tr>
<td>FCSRT</td>
<td>41.4 (24.7)*</td>
<td>42.4 (18.8)*</td>
<td>76.7 (4.6)</td>
<td>82.8 (4.4)</td>
</tr>
<tr>
<td><strong>Logical Memory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate recall</td>
<td>8.9 (5.3)*</td>
<td>16.9 (12.9)*</td>
<td>32.7 (7.4)</td>
<td>32.5 (10.1)</td>
</tr>
<tr>
<td>Delayed recall</td>
<td>2.1 (2.5)*</td>
<td>5.8 (7.6)*</td>
<td>15.7 (4.1)</td>
<td>18.2 (8.9)</td>
</tr>
<tr>
<td>Recognition</td>
<td>9.4 (6.9)*</td>
<td>13.7 (6.4)*</td>
<td>21.1 (3.0)</td>
<td>20.7 (6.3)</td>
</tr>
<tr>
<td>Rey Complex Figure, recall</td>
<td>3.3 (3.7)*</td>
<td>3.4 (5.4)*</td>
<td>13.1 (5.5)</td>
<td>17.2 (5.5)</td>
</tr>
<tr>
<td><strong>Language</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boston Naming Test</td>
<td>37.3 (12.8)*</td>
<td>35.2 (11.0)*</td>
<td>48.6 (6.3)</td>
<td>51.3 (4.6)</td>
</tr>
<tr>
<td>Verbal Fluency (named in 30 sec)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Animals</td>
<td>11.6 (6.0)</td>
<td>8.7 (4.4)*</td>
<td>17.1 (3.8)</td>
<td>18.2 (3.2)</td>
</tr>
<tr>
<td>- Words starting with letter &quot;P&quot;</td>
<td>12.9 (5.6)</td>
<td>9.2 (5.6)*</td>
<td>14.4 (4.0)</td>
<td>16.6 (5.1)</td>
</tr>
<tr>
<td>Token Test</td>
<td>16.4 (3.3)*</td>
<td>15.7 (2.5)*</td>
<td>19.3 (0.6)</td>
<td>19.5 (0.5)</td>
</tr>
<tr>
<td><strong>Visual spatial function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rey Complex Figure, copy</td>
<td>21.8 (11.2)*</td>
<td>19.7 (10.5)*</td>
<td>30.5 (3.7)</td>
<td>33.6 (2.4)</td>
</tr>
<tr>
<td>Visual Span backwards</td>
<td>3.7 (1.7)*</td>
<td>3.7 (2.4)*</td>
<td>5.1 (2.0)</td>
<td>6.8 (2.1)</td>
</tr>
<tr>
<td><strong>Executive function, attention and speed of processing</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Trail Making Test</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Part A</td>
<td>130.9 (116.3)</td>
<td>142.2 (86.8)*</td>
<td>78.3 (28.2)</td>
<td>66.5 (25.6)</td>
</tr>
<tr>
<td>Part B</td>
<td>275.6 (64.6)*</td>
<td>266.6 (78.3)*</td>
<td>194.5 (88.8)</td>
<td>137.8 (73.5)</td>
</tr>
<tr>
<td>Stroop Test: WC</td>
<td>21.0 (14.3)</td>
<td>21.1 (10.1)*</td>
<td>27.7 (9.0)</td>
<td>32.2 (11.4)</td>
</tr>
<tr>
<td>Mental Control WAIS-R</td>
<td>15.1 (7.2)*</td>
<td>15.6 (5.4)*</td>
<td>19.2 (4.7)</td>
<td>23.4 (6.0)</td>
</tr>
<tr>
<td>Digit Span forward, backwards</td>
<td>10.3 (3.3)*</td>
<td>10.8 (3.2)*</td>
<td>12.4 (2.4)</td>
<td>15.0 (3.6)</td>
</tr>
<tr>
<td>Fluctuation Inventory Scale</td>
<td>0.6 (1.5)</td>
<td>1.0 (2.0)</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td><strong>Other domains</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IADL</td>
<td>20.9 (6.3)*</td>
<td>20.7 (7.7)*</td>
<td>8.2 (0.4)</td>
<td>8.2 (0.6)</td>
</tr>
<tr>
<td>Geriatric Depression Scale</td>
<td>13.1 (7.3)*</td>
<td>14.0 (7.9)*</td>
<td>8.4 (3.7)</td>
<td>3.9 (3.7)</td>
</tr>
<tr>
<td>Neuropsychiatric Inventory</td>
<td>4.7 (3.3)</td>
<td>10.2 (8.1)*</td>
<td>1.1 (1.1)</td>
<td>1.4 (1.8)</td>
</tr>
</tbody>
</table>

Data are presented as means, with standard deviations in parentheses.

AD: Alzheimer's disease
WML-D: patients with white matter changes and dementia
WML-nD: patients with white matter changes but without dementia
HC: healthy controls

Data are missing from four AD patients and two HC.

* Significantly worse than healthy controls, p < 0.05
Table S2. Regions with decreased metabolism on the voxel-based SPM analysis

<table>
<thead>
<tr>
<th>Contrast</th>
<th>Threshold</th>
<th>Area of Between-Group Difference</th>
<th>Brodmann Area(s)</th>
<th>Side</th>
<th>k</th>
<th>t</th>
<th>Z</th>
<th>P</th>
<th>x, y, z</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD &lt; HC</td>
<td>$T = 4.28$</td>
<td>Lateral parieto-temporal association cortex</td>
<td>39, 40</td>
<td>L</td>
<td>781</td>
<td>5.31</td>
<td>4.63</td>
<td>$p &lt; 0.01^*$</td>
<td>$-48, -60, 30$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lateral parieto-temporal association cortex</td>
<td>39, 40</td>
<td>R</td>
<td>717</td>
<td>4.97</td>
<td>4.39</td>
<td>$p &lt; 0.01^*$</td>
<td>$44, -68, 44$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Precuneus</td>
<td>7</td>
<td>R</td>
<td>452</td>
<td>4.88</td>
<td>4.33</td>
<td>$p &lt; 0.01^*$</td>
<td>$10, -70, 32$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Parahippocampus and inferior temporal gyrus</td>
<td>20, 36</td>
<td>R</td>
<td>81</td>
<td>4.46</td>
<td>4.02</td>
<td>$p &lt; 0.01^*$</td>
<td>$36, -12, -32$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inferior temporal gyrus</td>
<td>37</td>
<td>R</td>
<td>59</td>
<td>4.39</td>
<td>3.97</td>
<td>$p &lt; 0.01^*$</td>
<td>$62, -46, -18$</td>
</tr>
<tr>
<td>WML–D &lt; HC</td>
<td>$T = 3.29$</td>
<td>Frontal pole</td>
<td>10</td>
<td>R</td>
<td>54</td>
<td>4.78</td>
<td>4.26</td>
<td>$p &lt; 0.001^+$</td>
<td>$12, 70, 6$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inferior frontal gyrus</td>
<td>44</td>
<td>R</td>
<td>124</td>
<td>4.47</td>
<td>4.03</td>
<td>$p &lt; 0.001^+$</td>
<td>$58, 10, 26$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Superior frontal gyrus</td>
<td>9</td>
<td>L</td>
<td>81</td>
<td>4.46</td>
<td>4.02</td>
<td>$p &lt; 0.001^+$</td>
<td>$-14, 42, 54$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Superior frontal gyrus</td>
<td>6</td>
<td>L</td>
<td>50</td>
<td>4.28</td>
<td>3.88</td>
<td>$p &lt; 0.001^+$</td>
<td>$-18, -2, 76$</td>
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<tr>
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<td>Frontal pole and superior frontal gyrus</td>
<td>9</td>
<td>L</td>
<td>76</td>
<td>4.18</td>
<td>3.80</td>
<td>$p &lt; 0.001^+$</td>
<td>$-8, 58, 36$</td>
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<tr>
<td></td>
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<td>Precentral and middle frontal gyri</td>
<td>4, 6</td>
<td>R</td>
<td>105</td>
<td>4.07</td>
<td>3.72</td>
<td>$p &lt; 0.001^+$</td>
<td>$56, 6, 44$</td>
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<td>Heschl’s gyrus and parietal opercular cortex</td>
<td>41, 42</td>
<td>R</td>
<td>315</td>
<td>4.03</td>
<td>3.69</td>
<td>$p &lt; 0.001^+$</td>
<td>$44, -24, 14$</td>
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<tr>
<td></td>
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<td>Frontal pole</td>
<td>9</td>
<td>R</td>
<td>105</td>
<td>3.94</td>
<td>3.62</td>
<td>$p &lt; 0.001^+$</td>
<td>$36, 52, 28$</td>
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<tr>
<td></td>
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<td>Angular gyrus</td>
<td>39</td>
<td>R</td>
<td>150</td>
<td>3.72</td>
<td>3.45</td>
<td>$p &lt; 0.001^+$</td>
<td>$50, -50, 50$</td>
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<tr>
<td></td>
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<td>Frontal pole</td>
<td>10</td>
<td>L</td>
<td>76</td>
<td>3.66</td>
<td>3.40</td>
<td>$p &lt; 0.001^+$</td>
<td>$-38, 48, 24$</td>
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<tr>
<td></td>
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<td>Paracingulate gyrus</td>
<td>32</td>
<td>L</td>
<td>57</td>
<td>3.49</td>
<td>3.25</td>
<td>$p &lt; 0.001^+$</td>
<td>$-12, 30, 28$</td>
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<tr>
<td>WML–nD &lt; HC</td>
<td>$T = 3.29$</td>
<td>Dorsal temporal pole</td>
<td>38</td>
<td>R</td>
<td>165</td>
<td>4.60</td>
<td>4.12</td>
<td>$p &lt; 0.001^+$</td>
<td>$56, 10, -6$</td>
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<tr>
<td></td>
<td></td>
<td>Precentral gyrus</td>
<td>4</td>
<td>R</td>
<td>42</td>
<td>4.59</td>
<td>4.12</td>
<td>$p &lt; 0.001^+$</td>
<td>$44, -22, 68$</td>
</tr>
<tr>
<td></td>
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<td>Inferior frontal gyrus</td>
<td>6</td>
<td>R</td>
<td>54</td>
<td>3.87</td>
<td>3.57</td>
<td>$p &lt; 0.001^+$</td>
<td>$38, 4, 30$</td>
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<tr>
<td>WML-D &lt; WML-nD</td>
<td>T = 2.42</td>
<td>Location</td>
<td>Side</td>
<td>Cluster Size</td>
<td>Z Value</td>
<td>T Value</td>
<td>p Value</td>
<td>Location</td>
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<td>Middle frontal gyrus</td>
<td>6, 8</td>
<td>R</td>
<td>192</td>
<td>3.01</td>
<td>2.85</td>
<td>p = 0.02†</td>
<td>52, 8, 44</td>
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<tr>
<td>Supramarginal gyrus</td>
<td>19</td>
<td>R</td>
<td>209</td>
<td>2.97</td>
<td>2.81</td>
<td>p = 0.02†</td>
<td>34, -58, 42</td>
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<tr>
<td>Frontal pole and orbito-frontal cortex</td>
<td>11</td>
<td>R</td>
<td>72</td>
<td>2.94</td>
<td>2.79</td>
<td>p = 003†</td>
<td>40, 42, -20</td>
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<tr>
<td>Frontal pole and superior frontal gyrus</td>
<td>9</td>
<td>L</td>
<td>68</td>
<td>2.77</td>
<td>2.64</td>
<td>p = 0.04†</td>
<td>-12, 44, 52</td>
<td></td>
<td></td>
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<tr>
<td>Superior frontal gyrus</td>
<td>6</td>
<td>R</td>
<td>47</td>
<td>2.74</td>
<td>2.62</td>
<td>p = 0.04†</td>
<td>32, -10, 72</td>
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<tr>
<td>Middle frontal gyrus</td>
<td>46</td>
<td>L</td>
<td>84</td>
<td>2.52</td>
<td>2.42</td>
<td>p = 0.08†</td>
<td>-42, 8, 52</td>
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<td></td>
</tr>
</tbody>
</table>

Table showing the anatomical locations where in statistical parametric mapping (SPM) analysis there were differences between comparison groups ("Contrast") at the given height T value threshold ("Threshold").

Minimal cluster size was set at 40 voxels.

Independent clusters found are listed and characterized as location of the entire cluster ("Area" and "Side"), cluster size (k), as well as statistics (t, Z, and P) and location (x,y,z) of the maximum voxel.

AD: Alzheimer’s disease

WML-D: patients with white matter changes and dementia

WML-nD: patients with white matter changes but without dementia

HC: healthy controls

*False Discovery Rate (FDR) corrected
† Uncorrected p value
**Table S3.** Regional metabolism. Mean and standard deviation in volumes of interest.

<table>
<thead>
<tr>
<th>ROI</th>
<th>AD</th>
<th>WML-D</th>
<th>WML-nD</th>
<th>HC</th>
</tr>
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<tbody>
<tr>
<td><strong>PVElab</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R Temporal Lobe</td>
<td>0.98 (0.13)*</td>
<td>1.03 (0.10)</td>
<td>1.04 (0.05)</td>
<td>1.10 (0.09)</td>
</tr>
<tr>
<td>L Temporal Lobe</td>
<td>1.00 (0.10)*</td>
<td>1.05 (0.08)</td>
<td>1.05 (0.07)</td>
<td>1.11 (0.08)</td>
</tr>
<tr>
<td>R Parietal Lobe</td>
<td>1.23 (0.25)*</td>
<td>1.12 (0.23)*</td>
<td>1.21 (0.21)*</td>
<td>1.51 (0.21)</td>
</tr>
<tr>
<td>L Parietal Lobe</td>
<td>1.22 (0.20)*</td>
<td>1.20 (0.19)*</td>
<td>1.26 (0.24)*</td>
<td>1.54 (0.19)</td>
</tr>
<tr>
<td>R Frontal Lobe</td>
<td>1.37 (0.16)</td>
<td>1.32 (0.16)*</td>
<td>1.32 (0.12)*</td>
<td>1.48 (0.14)</td>
</tr>
<tr>
<td>L Frontal Lobe</td>
<td>1.38 (0.16)</td>
<td>1.35 (0.18)*</td>
<td>1.35 (0.11)*</td>
<td>1.51 (0.14)</td>
</tr>
<tr>
<td>Anterior Cingulate</td>
<td>0.98 (0.09)</td>
<td>0.95 (0.15)†</td>
<td>1.01 (0.11)</td>
<td>1.05 (0.07)</td>
</tr>
<tr>
<td>Precuneus</td>
<td>1.22 (0.11)†</td>
<td>1.30 (0.29)</td>
<td>1.33 (0.15)</td>
<td>1.39 (0.11)</td>
</tr>
<tr>
<td>Deep Gray Matter</td>
<td>1.12 (0.10)</td>
<td>1.03 (0.12)*</td>
<td>1.09 (0.04)</td>
<td>1.15 (0.11)</td>
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<tr>
<td><strong>PMOD</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>R Caudate</td>
<td>1.00 (0.10)*</td>
<td>0.96 (0.14)*</td>
<td>1.04 (0.09)</td>
<td>1.10 (0.06)</td>
</tr>
<tr>
<td>L Caudate</td>
<td>0.83 (0.12)</td>
<td>0.75 (0.11)*</td>
<td>0.83 (0.12)</td>
<td>0.91 (0.09)</td>
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<tr>
<td>R Pallidum</td>
<td>1.34 (0.08)</td>
<td>1.24 (0.13)*</td>
<td>1.33 (0.06)</td>
<td>1.36 (0.13)</td>
</tr>
<tr>
<td>L Pallidum</td>
<td>1.07 (0.07)</td>
<td>1.01 (0.08)*</td>
<td>1.06 (0.04)</td>
<td>1.09 (0.08)</td>
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<tr>
<td>R Putamen</td>
<td>1.39 (0.08)</td>
<td>1.28 (0.14)*</td>
<td>1.36 (0.05)</td>
<td>1.40 (0.12)</td>
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<tr>
<td>R Thalamus</td>
<td>0.16 (0.07)*</td>
<td>1.14 (0.08)*</td>
<td>1.19 (0.07)</td>
<td>1.26 (0.07)</td>
</tr>
<tr>
<td>L Thalamus</td>
<td>1.12 (0.11)</td>
<td>1.05 (0.09)*</td>
<td>1.10 (0.08)*</td>
<td>1.20 (0.07)</td>
</tr>
</tbody>
</table>

* Significantly worse than healthy controls, p < 0.05
† Trend for impairment compared to healthy controls, p < 0.07

**AD:** Alzheimer’s disease

**WML-D:** patients with white matter changes and dementia

**WML-nD:** patients with white matter changes but without dementia

**HC:** healthy controls

Figures lack units of measurement because the values are ratios of the metabolism in the given volume of interest divided by the metabolism in the reference region (cerebellum) and therefore, dimensionless.

PVElab provides a more accurate estimate for cortical regions; PMOD separates deep nuclei (see text). Only the regions showing significant differences among groups are listed.