

# Effects of White Matter Lesions and Lacunes on Cortical Function

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**Background:** Subcortical ischemic vascular dementia has been ascribed to prominent frontal lobe dysfunction secondary to ischemic lesions in frontothalamic circuits. Whether small-vessel disease in fact predominantly affects the frontal lobes is not well documented.

**Objective:** To investigate the effects of subcortical lesions (lacunes and white matter lesions [WML]) on cortical function, as reflected in glucose metabolism and cognitive function, in elderly individuals.

**Design:** Cross-sectional analyses of case series.

**Setting:** Multicenter, university-based study of subcortical vascular dementia.

**Patients:** Persons with normal cognition, mild cognitive impairment, or dementia and with and without lacunes on magnetic resonance images.

**Main Outcome Measures:** Regional cerebral glucose metabolism, normalized regional metabolic activity, and neuropsychological test scores. Major hypotheses were that volume of lacunes and WML correlate selectively with

hypometabolism of prefrontal cortex and failure of executive cognitive ability.

**Results:** Lacunes correlated with metabolic rates in dorsolateral frontal cortex (DLF); WML substantially reduced metabolic rates throughout cortex, most strongly so in DLF. When regional metabolic activity was normalized to whole brain activity, lacunes remained correlated with DLF activity, whereas the WML effect was no longer found, probably because of its general distribution. Regional cerebral glucose metabolism and normalized activity in DLF also correlated with cortical atrophy. Metabolic activity in DLF correlated with executive function, memory, and global cognitive function, while activity in middle temporal gyrus correlated with memory and global function but not executive function.

**Conclusions:** The metabolic effects of lacunes and WML are most apparent in DLF, but the effects of WML are generalized and frontal hypometabolism correlates with memory and global impairment, cognitive as well as executive function. The effects of subcortical cerebrovascular disease appear to converge on the frontal lobes but are diffuse, complex, and of modest magnitude.

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**C**URRENT CONCEPTUAL MODELS of ischemic vascular dementia (IVD) derive from the concept of multi-infarct dementia<sup>1</sup> and emphasize the role of lacunes and cortical strokes. There is little controversy about the idea that cortical stroke may cause dementia. However, in the absence of frank cortical lesions, the pathogenesis of cognitive failure in cerebrovascular disease (CVD) is less clear.<sup>2</sup> Relationships of diffuse white matter changes and lacunes to cortical dysfunction are not well defined. Case studies have correlated cognitive impairment with the presence<sup>3</sup> or emergence<sup>4</sup> of lacunes, particularly in "strategic" locations<sup>3</sup> such as head of the caudate<sup>5</sup> or thalamus.<sup>6,7</sup>

Defining the role of lacunes is complicated; brain imaging frequently reveals ad-

ditional concomitant abnormalities, including cortical atrophy, hippocampal atrophy, and white matter lesions (WML). Common in older individuals,<sup>8</sup> WML are probably predominantly ischemic in origin<sup>9</sup> and often correlate with executive cognitive impairment<sup>10</sup> and psychomotor slowing. Cortical atrophy is a nonspecific imaging finding associated with normal aging and many degenerative brain illnesses, the most prominent of which is Alzheimer disease (AD). Hippocampal atrophy is marked in AD<sup>11</sup> and may be a marker of the disease.<sup>12</sup> Thus, the effects of lacunes on the aging brain cannot be properly defined without simultaneous examination of the other pathological changes that frequently accompany lacunes.

Cortical dysfunction may be measured with neuropsychological tests. Although the

**Table. Characteristics of the Sample\***

	Cognitively Healthy Subjects	Cognitively Impaired Subjects	Subjects With Dementia
All subjects, No.	31	11	20
Male-female ratio	16:15	7:4	11:9
Age, y	74.2 ± 7.0	70.9 ± 7.9	77.3 ± 8.0
Education, y†	15.2 ± 2.5	13.7 ± 4.5	12.0 ± 3.4
MMSE score† (range)	29.1 ± 1.2 (25-30)	27.5 ± 2.1 (22-30)	19.8 ± 5.3 (7-28)
No. of subjects with glucose metabolic rates	17	6	12
Male-female ratio	9:8	4:2	9:3
Age, y	73.4 ± 7.3	72.1 ± 8.3	77.6 ± 6.0
Education, y†	15.3 ± 2.5	11.5 ± 4.7	11.2 ± 3.0
MMSE score† (range)	29.1 ± 1.1 (26-30)	27.5 ± 2.9 (22-30)	19.7 ± 6.0 (7-27)

Abbreviation: MMSE, Mini-Mental State Examination.

\*Values are expressed as mean ± SD unless otherwise indicated.

†Groups differ significantly,  $P < .01$ .

evidence is mixed, studies tend to show greater executive dysfunction and preservation of memory function in CVD compared with AD.<sup>13-16</sup> An additional measure of cortical function is offered by positron emission tomography (PET) with fluorodeoxyglucose F 18. Numerous studies show that temporoparietal hypometabolism is a reasonably sensitive and specific marker for AD.<sup>17,18</sup> The literature on metabolic patterns in vascular dementia is considerably less consistent.<sup>14,19-24</sup> Some studies of patients with small-vessel disease have shown that reductions in global and regional cerebral glucose metabolism are associated with cognitive impairment.<sup>25,26</sup> Regardless of the exact location of hypometabolism in different dementias, the ability of PET with fluorodeoxyglucose F 18 to define the location and extent of cortical dysfunction offers another approach to understanding the effects of subcortical CVD on cognition.

This study investigated the effects of subcortical cerebrovascular lesions on cortical function by examining the associations between different structural brain abnormalities and measures of cortical function. We studied normal subjects and persons with AD, IVD, or mixed AD/IVD. Persons with cortical lesions were excluded. Lacunes and WML were quantified using volumetric magnetic resonance imaging (MRI), and cortical function was assessed with PET studies of regional cerebral glucose metabolism and with neuropsychological tests. Hippocampal atrophy and cortical atrophy were measured because of their effect on cognition and putative links to AD. We hypothesized that lacunes correlate with hypometabolism of prefrontal cortex, executive dysfunction, and global cognitive impairment, whereas hippocampal atrophy and cortical atrophy correlate with hypometabolism of temporal and parietal cortex, memory failure, and global cognitive impairment.

## METHODS

### SUBJECTS

The sample varied widely along the spectrum of small-vessel CVD and in cognitive function between normal and mild dementia. Exclusion criteria were (1) neurological illness other than AD or CVD, (2) cortical infarction on MRI, (3) significant closed head injury, (4) alcohol abuse within 5 years

of the onset of cognitive loss (or, in normal controls, the last 5 years), and (5) use of neuroleptics or antidepressants other than selective serotonin reuptake inhibitors and regular use of anxiolytics, hypnotics, or antihistamines. The study was conducted in accordance with approved human subjects protection protocols.

Diagnosis was established with a detailed history of cognitive and daily function, medical history, neurological examination, neuropsychological testing, appropriate laboratory tests, and clinical brain imaging. Although clinical diagnosis did not enter into the analyses, it is provided for descriptive purposes: 7 patients with probable AD,<sup>27</sup> 1 patient with possible AD,<sup>27</sup> 5 patients with probable IVD,<sup>28</sup> and 7 patients with mixed dementia. The differentiation between IVD and mixed dementia, which was diagnosed when the clinical team believed that both AD and IVD made equal contributions to the dementia, was difficult and uncertain. Sample characteristics are in the **Table**.

## MEASURES

### Magnetic Resonance Imaging

The MRI protocol has been previously described and included a T1-weighted coronal magnetization prepared rapid gradient echo study with 1.5-mm slices and a double spin-echo axial study.<sup>29</sup> Segmentation to obtain quantitative volumes of lacunes, WML, cortical gray matter (CGM), and hippocampus was accomplished using both the T1-weighted and T2-weighted axial images using methods that have been previously reported.<sup>30</sup> The outline of the hippocampus was manually drawn on the T1 data set, and volumes were generated by a computer algorithm using previously reported methods.<sup>30</sup>

Lacunes, defined as small areas of completed infarction in subcortical regions, were outlined by hand by a trained operator and confirmed and localized by a neuroradiologist according to previously described criteria<sup>25</sup> using proton density, T1- and T2-weighted images. Lacunes were differentiated from dilated perivascular space by signal characteristics, size, and location. Volumes of lacunes in thalamus and caudate were summed to give a measure of strategically located lacunes, and the total volume of lacunes was also calculated.

### Positron Emission Tomography

Studies were performed on a CTI/Siemens (Knoxville, Tenn) ECAT EXACT HR PET scanner [74] using the glucose metabolic tracer

fluorodeoxyglucose F 18 within 3 months of clinical evaluation and MRI. A subset of subjects had quantitative studies using a radial artery catheter to collect a blood input function. Positron emission tomographic scanning commenced approximately 40 minutes after tracer injection with 40 minutes of emission data acquisition followed by a 20-minute transmission scan. During the period of tracer uptake, the subject undertook a verbal continuous recognition memory task.<sup>25</sup>

Positron emission tomography data were analyzed in 2 forms: (1) atrophy-corrected metabolic rates and (2) atrophy-corrected count ratios, with volume of interest (VOI) counts normalized to whole brain counts. Whole brain was chosen as the denominator because some subjects had infarcts in pons or cerebellum, which had the potential to substantially affect metabolic activity measures in these structures, thus adding noise to the ratio data. Regions were outlined by a skilled operator using procedures described in detail elsewhere.<sup>31</sup> We used a series of 2-dimensional regions of interest drawn on magnetic resonance data that were subsequently tiled together to form a VOI that was projected back to the original PET data to calculate activity within the 3-dimensional region. The VOI count values were adjusted for the effects of partial volume caused by cerebral atrophy using the segmented MRI data set as prior information in the manner developed by Meltzer et al.<sup>32</sup>

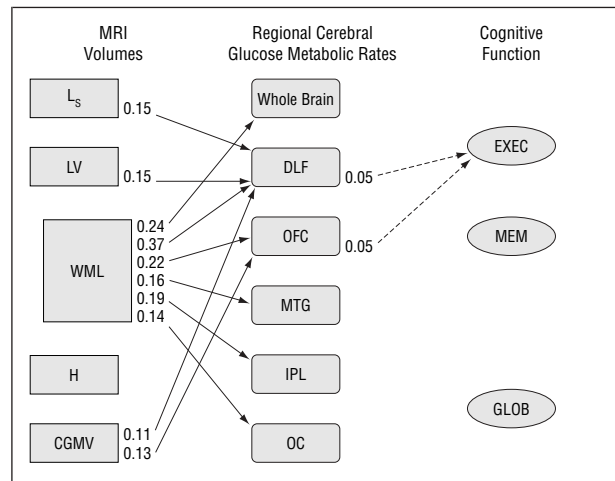
All VOIs were drawn on the 3-dimensional T1-weighted data acquired as described earlier, by either of 2 operators blind to patient classification, using rules to define VOI boundaries. Interoperator reliability of region drawing in our laboratory is high, with differences in regional cerebral glucose metabolism (rCMRglc) in regions drawn by different operators averaging less than 5%.<sup>31</sup> The VOIs were dorsolateral frontal cortex (DLF), orbitofrontal cortex (OFC), middle temporal gyrus (MTG), inferior parietal lobe (IPL), occipital cortex (OC), and hippocampus. Whole brain counts were determined by drawing a VOI that encompassed both cerebral hemispheres, the posterior fossa, and subcortical structures and then applying calculations outlined earlier, including atrophy correction.

### Cognitive Function

Cognitive function was measured with scales of Verbal Memory (MEM), Executive Function (EXEC), and Global Cognition (GLOB), each composed of items from standard neuropsychological tests that were selected using item-response theory methods on data from more than 400 subjects.<sup>33</sup> These psychometrically matched scales have linear measurement properties and have no significant floor or ceiling effects across a 4–standard deviation range. The MEM scale is heavily weighted with delayed recall items from a verbal list learning task; the EXEC scale is weighted with mental control (sequence reversal), working memory, and verbal fluency items; and the GLOB scale includes verbal list learning acquisition, verbal fluency, and attention scores.

### STATISTICAL ANALYSES

Comparisons between groups are offered for the purpose of describing the sample, but group status was not a variable of interest. Rather, the hypotheses were tested using the continuous measures of cognitive status, brain function, and MRI abnormalities described earlier. Two sets of analyses were performed, first using the sample for which metabolic rates had been obtained, followed by analysis of the whole sample using activity count ratios. Hypotheses were tested using a regression approach to examine associations between MRI, metabolic, and cognitive function.

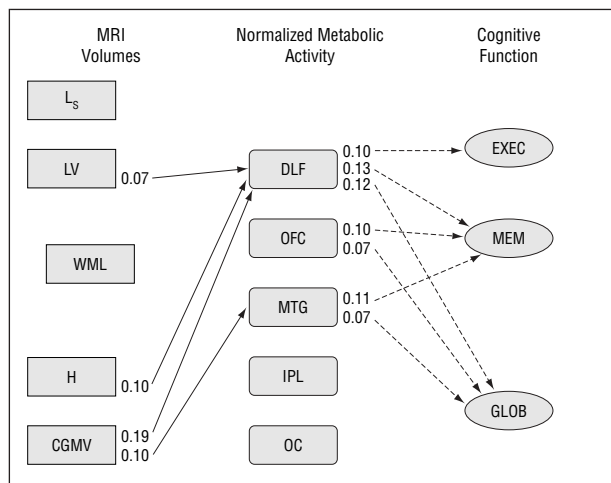


**Figure 1.** Relationships between anatomical measurements, regional cerebral glucose metabolism, and cognitive function. Coefficients represent significant  $R^2$  values. Analyses are generally bivariate; see “Methods” section for details. CGMV indicates cortical gray matter; DLF, dorsolateral prefrontal cortex; EXEC, executive function; GLOB, global cognitive function; H, hippocampus; IPL, inferior parietal lobule; LV, lacunes; L<sub>s</sub>, strategic lacunes; MEM, memory; MTG, middle temporal gyrus; OC, occipital cortex; OFC, orbital frontal cortex; WML, white matter lesions.

## RESULTS

### GLUCOSE METABOLIC RATES

Bivariate regressions were performed for the 35 subjects with glucose metabolic rates (Table) testing the relationships between metabolic rates, lacunar volume (LV), WML, hippocampal volume (H), and cortical gray matter volume (CGMV). Lacunes in cognitively strategic locations (L<sub>s</sub>) (thalamus and caudate) were also examined. Both single hemisphere and bilateral averaged VOIs were examined, but the pattern of results for bilateral regions was mirrored in the results for unilateral regions and so only the results for bilateral regions are reported. As shown in **Figure 1**, L<sub>s</sub> was selectively associated with rCMRglc in DLF ( $R^2=0.15$ ;  $P<.02$ ); the effect did not approach significance in any other VOI. However, the association was not unique to L<sub>s</sub>, as LV showed the same relationship with DLF ( $R^2=0.15$ ;  $P<.02$ ) but was not related to any other VOI. White matter lesions negatively correlated with rCMRglc in every VOI, most strongly in DLF where it explained 37% of the variance. The CGMV correlated with rCMRglc in DLF ( $R^2=0.11$ ;  $P=.047$ ) and orbital frontal cortex (OFC) ( $R^2=0.13$ ;  $P=.03$ ). Hippocampal volume was not associated with rCMRglc in any VOI or with whole brain metabolism. Follow-up multiple regression analyses were run using LV, WML, H, and CGMV, which are moderately intercorrelated (range, 0.28–0.61). Those analyses showed that the WML effect was not reduced by adding the other MRI measures, whereas LV and CGMV had no effect that was statistically independent of WML. The effect of LV on DLF was not modified substantially by adding CGMV to the model. Although WML and cognitive function correlate (see later information), addition of the GLOB scale score to the models did not substantially alter the pattern of bivariate results between WML and metabolic rates.



**Figure 2.** Summary of relationships between normalized cortical metabolism, structural pathological changes, and cognitive function. Coefficients represent significant  $R^2$  values. Nonsignificant values are omitted. CGMV indicates cortical gray matter; DLF, dorsolateral prefrontal cortex; EXEC, executive function; GLOB, global cognitive function; H, hippocampus; IPL, inferior parietal lobule; LV, lacunes; L<sub>s</sub>, strategic lacunes; MEM, memory; MTG, middle temporal gyrus; OC, occipital cortex; OFC, orbital frontal cortex; WML, white matter lesions.

Associations between regional metabolic rates and cognitive function were examined in a series of regression analyses. Age and education were generally associated with both the cognitive measures (predictably) and the metabolic measures (unexpectedly). Controlling for age and education, no relationships between rCMRglc and the cognitive variables was significant, although trends ( $P < .10$ ) toward significance for the association between DLF and EXEC scale score and between OFC and EXEC scale score were present. In each case, adding the frontal rCMRglc to the model explained an additional approximate 5% of the variance in EXEC scale score.

### ACTIVITY RATIOS

Results of analogous analyses using normalized regional count ratios and all 62 cases are shown in **Figure 2**. The LV but not L<sub>s</sub> correlated with normalized DLF ( $R^2=0.07$ ;  $P=.04$ ). Both H ( $R^2=0.10$ ;  $P=.01$ ) and CGMV ( $R^2=0.19$ ;  $P<.001$ ) also correlated with normalized DLF. Of the 3 MRI variables, only CGMV had an effect on DLF that was statistically independent of the others. White matter lesions showed no relationship to normalized metabolic activity in any region, presumably because its generalized effects were present in both the numerator and denominator of the ratios. The CGMV correlated with normalized MTG ( $R^2=0.10$ ;  $P<.03$ ).

Correlations between normalized regional metabolic activity and cognitive function were examined in a series of regression analyses. Simple bivariate models were used because neither education nor age was consistently related to both the independent or dependent variables and controlling for these variables did not change the results. The GLOB scale score correlated with normalized DLF ( $R^2=0.12$ ;  $P<.01$ ), OFC ( $R^2=0.07$ ;  $P=.04$ ), and MTG ( $R^2=0.07$ ;  $P=.047$ ). The MEM scale score correlated with normalized DLF ( $R^2=0.13$ ;  $P<.01$ ), OFC ( $R^2=0.10$ ;  $P=.01$ ), and

MTG ( $R^2=0.11$ ;  $P<.01$ ). The EXEC scale score correlated only with normalized DLF ( $R^2=0.10$ ;  $P<.03$ ).

Relationships between MRI volumes and cognitive function were also tested. Controlling for age and education (which were generally related to both independent and dependent variables), GLOB scale score correlated with H ( $\Delta R^2=0.09$ ;  $P<.005$ ) and CGMV ( $\Delta R^2=0.10$ ;  $P<.003$ ). The MEM scale score correlated with H ( $\Delta R^2=0.28$ ;  $P<.001$ ) and CGMV ( $\Delta R^2=0.14$ ;  $P<.001$ ). The EXEC scale score correlated with LV ( $\Delta R^2=0.08$ ;  $P=.006$ ), WML ( $\Delta R^2=0.08$ ;  $P=.008$ ), and CGMV ( $\Delta R^2=0.15$ ;  $P<.001$ ). Multivariate models incorporating demographics and metabolic and MRI data were complex and unstable.

### COMMENT

In these data, the functional impact of subcortical lesions was strongest in prefrontal cortex, particularly in DLF. Lacunes correlated with hypometabolism in DLF exclusively, and effects of WML on metabolic rates, while generalized, were strongest in DLF. In addition, lacunes and WML both correlated with diminished executive function. Although the anatomical substrate of executive dysfunction is complex and distributed, executive dysfunction and dysfunction of prefrontal cortex are closely linked.<sup>34</sup> Some prior studies of regional blood flow or metabolism have found prominent frontal hypoactivity in patients with lacunes or WML,<sup>14,35-37</sup> but others have not.<sup>38,39</sup> Methods, diagnostic criteria, and subject samples differ greatly between these studies, although the precise source of the discrepant findings is not clear.

Interestingly, both prefrontal hypometabolism and executive dysfunction were also associated with cortical atrophy. Temporoparietal metabolism, which is characteristically abnormal in AD, was not correlated with cortical atrophy, suggesting that in this sample (with much CVD), cortical atrophy was not simply a consequence of AD. Prior studies from this research program, using samples that overlap with this one, indicate that cortical atrophy is found in IVD,<sup>30,33</sup> even when AD is absent.<sup>30</sup> Although AD is undoubtedly a major cause of cortical atrophy, it is likely that CVD is also a cause of cortical atrophy even when cortical ischemic changes are not appreciated on MRI. Thus, dysfunction of prefrontal cortex in CVD is likely not solely a consequence of ischemic damage concentrated in frontothalamic tracts but may also reflect a vulnerability of frontal cortex to widely distributed pathological changes.

The correlations between regional metabolism and cognitive function also appear to reflect multiple brain pathological changes. Memory performance correlated with metabolism in MTG, as one might predict in AD. But memory scores also correlated with metabolism in frontal lobe. Memory tests demand executive as well as mnemonic abilities,<sup>40</sup> and functional MRI activation patterns during episodic memory tests frequently involve frontal lobe as well as medial temporal lobe.<sup>41</sup> The contributions of executive dysfunction in patients

with CVD may lead to impairment on memory tests,<sup>25</sup> a mechanism that is consistent with the present data. Because dysfunction both of medial temporal lobe and frontal lobe lead to impairments of executive function and memory, it is not surprising that metabolic activity in both regions also correlated with global cognitive ability.

An additional important finding is that WML were associated with global reductions in cortical metabolic rates. There are few previous data on this point, and the findings have been variable. For example, 3 studies<sup>23,38,39</sup> failed to find this relationship, but for various reasons, results were ambiguous in each case. A recent, large sample study of subjects without dementia found results comparable with the present study in that the extent of periventricular white matter hyperintensities correlated negatively with whole brain metabolism.<sup>36</sup>

White matter lesions probably diminish the efficiency of neural transmission and, consequently, functionally reduce cortical connectivity. This is one possible cause of the widespread hypometabolism of cortex we observed. Alternatively, WML may reflect disseminated small-vessel disease in cortex (eg, microscopic infarctions). Studies of cognitive speed and executive function show WML effects even in cognitively normal elderly individuals.<sup>10</sup> The metabolic findings of this study further strengthen the case that these lesions are not entirely benign.

We found no evidence that strategic lacunes are of special importance in causing cognitive impairment. It might be that more precise localization of lacunes within subcortical nuclei and particular white matter tracts would reveal location effects. Although single strategic lacunes were rare, lacunes predominantly occur in thalamus, basal ganglia, or frontal white matter,<sup>42</sup> and thus, lacunes may damage frontothalamic circuits whether or not a "strategic" lacune can be identified.

In conclusion, these data give qualified support to a model that explains cognitive failure in small-vessel CVD in terms of damaged frontothalamic circuits. Qualifications include the fact that lacunes per se do not appear to be an especially potent cause of cortical dysfunction. White matter lesions are also important, and both may be markers of more generalized CVD. Also, the effects of subcortical CVD on cortical metabolism are not restricted to the frontal lobes, and the effects of frontal hypometabolism may not be confined to executive function. Finally, WML and lacunes often occur in a setting of concomitant cortical and hippocampal atrophy that often represents effects of AD, although CVD may also cause atrophy of these structures. Regardless of etiology, both changes are likely deleterious to cognition. Thus, lacunes and WML contribute a frontal emphasis in the complexly determined clinical picture of vascular dementia.

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