Cognitive and Physiologic Correlates of Subclinical Structural Brain Disease in Elderly Healthy Control Subjects

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Context: Healthy elderly persons commonly show 4 types of change in brain structure—cortical atrophy, central atrophy, deep white-matter hyperintensities, and periventricular hyperintensities—as forms of subclinical structural brain disease (SSBD).

Objectives: To characterize the volumes of SSBD present with aging and to determine the associations of SSBD, physiology, and cognitive function.

Design: Cross-sectional study.

Setting: University of California, Los Angeles, Neuropsychiatric Institute.

Subjects: Forty-three community-dwelling healthy control subjects, aged 60 through 93 years.

Main Outcome Measures: Volumetric magnetic resonance imaging, neuropsychological testing, and quantitative electroencephalographic coherence (functional connectivity) between brain regions.

Results: Regression models demonstrated significant relationships between SSBD volumes, age, cognitive performance, and connectivity. Cortical and central atrophy and periventricular hyperintensities had significant associations with age while deep white-matter hyperintensities did not. Posterior atrophy showed stronger associations with age than did anterior atrophy. Only a subset of subjects at older ages showed large SSBD volumes; older subjects primarily showed increasing variance of SSBD. Although all subjects scored within the normal range on cognitive testing, SSBD volume was inversely related to performance, most notably on the Trail-Making Test part B and the Shipley-Hartford Abstract Reasoning test. Coherence had significant associations with SSBD. Path analysis supported mediation of the effects of deep white-matter hyperintensities and periventricular hyperintensities on cognition by altered connectivity. For several measures, cognitive performance was best explained by coherence, and only secondarily by SSBD.

Conclusions: Modest volumes of SSBD were associated with decrements in cognitive performance within the normal range in healthy subjects. Lower coherence was associated with greater volumes of SSBD and increasing age. Path analysis models suggest that brain functional connectivity mediates some effects of SSBD on cognition.
The converse association between structural changes and poorer cognitive function has also been reported. Nevertheless, there is not good agreement on the functional consequences of structural disease, since others have reported little or no association.

Some of these inconsistencies likely reflect limitations of the measurement techniques. Few studies have used precise methods to quantitate disease, though volume of damage is likely to be important. Instead they have used semiquantitative rating scales that yield nonvolumetric values and limit accuracy and reliability. Subjective judgments for “thresholds” of disease on multiple point scales (ie, 0-3, 9, or even 24 points) pose problems of systematizing what differentiates, for example, a 1 from a 2 rating. Accuracy may be limited by systematic overrating or underrating of pathologic abnormality, because raters must determine what constitutes sufficient change to be rated greater than 0; one study explicitly excluded some types of PVHs as a “normal variant.” Additionally, attention is not uniform in evaluating all types of SSBD, such as differentiating DWMHs from PVHs, leading to inconsistent conclusions.

A mechanism that may link SSBD to cognitive effects is disruption in the connectivity between brain regions. Quantitative electroencephalographic (QEEG) coherence can assess connections between regions and permit testing of this possible mechanism. Our past work linked white matter lesions with decreased coherence in both healthy subjects and and subjects with dementia.
In this project, we combined volumetric MRI measurements in healthy elderly subjects with neuropsychological assessments and coherence values to clarify the cognitive correlates of SSBD and to investigate a potential mechanism for these relationships. Figure 2 shows a path analysis model for evaluating whether SSBD’s effects on cognition arise from disruption in connectivity.

![Figure 2](http://archneur.jamanetwork.com/pdfaccess.ashx?url=/data/journals/neur/6988/)

During this study, we recruited 43 subjects from the community. All were at least 60 years old, were in good health, and had normal findings on neurological examination. Exclusion criteria included any history of an axis I psychiatric disorder; any poorly controlled medical illness that could affect brain function (eg, untreated hypothyroidism); current use of medications that could alter electroencephalographic activity (eg, benzodiazepines); current or past drug or alcohol abuse; and a history of head trauma, brain surgery, skull defect, stroke, or transient ischemic attacks. This study was approved by the University of California, Los Angeles, institutional review board; informed consent was obtained from all subjects. Demographic characteristics are given in Table 1, including age, sex, educational level, and health status (Cumulative Illness Rating Scale–Geriatrics). Subclinical structural brain disease measures were available from all 43 subjects. Because some subjects did not have usable QEEG recordings (eye-movement and/or muscle-tension artifacts), or declined to complete all cognitive tests, subsets of subjects (ranging from 28 to 43 subjects) were used for the analyses involving QEEG data and cognitive scores; sample sizes are indicated for each analysis (Tables 2, 3, and 4). Subjects with QEEG data were not statistically differ-

### Table 1. Demographic and Clinical Features for 43 Healthy Elderly Subjects*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>75.2 (6.9)</td>
</tr>
<tr>
<td>Sex, F/M</td>
<td>24/19</td>
</tr>
<tr>
<td>Ethnicity/race, W/B</td>
<td>42/1</td>
</tr>
<tr>
<td>Educational level, y</td>
<td>15.6 (2.4)</td>
</tr>
<tr>
<td>Health status (Cumulative Illness Rating Scale–Geriatrics) score*</td>
<td>4.0 (2.9)</td>
</tr>
<tr>
<td>Folstein Mini-Mental State Examination score**</td>
<td>29.0 (1.2)</td>
</tr>
<tr>
<td>Hamilton Depression Rating Scale score***</td>
<td>4.9 (4.9)</td>
</tr>
<tr>
<td>Hachinski scale for risk of ischemic dementia score****</td>
<td>0.58 (0.82)**</td>
</tr>
</tbody>
</table>

*Data are given as mean (SD) unless otherwise stated.

**Hachinski scores were skewed: median equals 0; interquartile range, 0-1.

***Folstein Mini-Mental State Examination score.

†Hachinski scale for risk of ischemic dementia score.

### Table 2. Relationship of SSBD and Cognitive Function*

<table>
<thead>
<tr>
<th>SSBD Measure</th>
<th>Trails A Test (n = 35)</th>
<th>Trails B Test (n = 35)</th>
<th>BNT (n = 36)</th>
<th>FAS Test (n = 36)</th>
<th>SHAR Test (n = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DWMH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total region</td>
<td>−0.044</td>
<td>0.297†</td>
<td>−0.285†</td>
<td>−0.154</td>
<td>−0.214</td>
</tr>
<tr>
<td>Anterior region</td>
<td>−0.011</td>
<td>0.322†</td>
<td>−0.299†</td>
<td>−0.170</td>
<td>−0.265</td>
</tr>
<tr>
<td>Posterior region</td>
<td>−0.078</td>
<td>0.215</td>
<td>−0.231</td>
<td>−0.110</td>
<td>−0.112</td>
</tr>
<tr>
<td>PVH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total region</td>
<td>0.039</td>
<td>0.328†</td>
<td>−0.158</td>
<td>−0.156</td>
<td>−0.329†</td>
</tr>
<tr>
<td>Anterior region</td>
<td>−0.020</td>
<td>0.367†</td>
<td>−0.189</td>
<td>−0.204</td>
<td>−0.416‡</td>
</tr>
<tr>
<td>Posterior region</td>
<td>0.067</td>
<td>0.303†</td>
<td>−0.146</td>
<td>−0.179</td>
<td>−0.297†</td>
</tr>
<tr>
<td>sCSF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total region</td>
<td>0.207</td>
<td>0.506†</td>
<td>−0.137</td>
<td>−0.004</td>
<td>−0.323†</td>
</tr>
<tr>
<td>Anterior region</td>
<td>0.198</td>
<td>0.406†</td>
<td>−0.071</td>
<td>0.077</td>
<td>−0.284‡</td>
</tr>
<tr>
<td>Posterior region</td>
<td>0.203</td>
<td>0.547†</td>
<td>−0.173</td>
<td>−0.057</td>
<td>−0.330†</td>
</tr>
<tr>
<td>vCSF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total region</td>
<td>0.243</td>
<td>0.410†</td>
<td>−0.035</td>
<td>−0.047</td>
<td>−0.222</td>
</tr>
<tr>
<td>Anterior region</td>
<td>0.246</td>
<td>0.415†</td>
<td>−0.062</td>
<td>−0.011</td>
<td>−0.233†</td>
</tr>
<tr>
<td>Posterior region</td>
<td>0.229</td>
<td>0.284†</td>
<td>−0.021</td>
<td>−0.080</td>
<td>−0.185</td>
</tr>
</tbody>
</table>

*SSBD indicates subclinical structural brain disease; Trails A, Trail Making Test to measure sequencing abilities; Trails B, Trail Making Test to measure attention and speed; BNT, Boston Naming Test; FAS, controlled word association; SHAR, Shipley-Hartford Abstract Reasoning test; DWMH, deep white-matter hyperintensities; PVH, periventricular hyperintensities; sCSF, sulcal cerebrospinal fluid; vCSF, ventricular CSF. Pearson correlation values are shown for the relationships between changes in volumes and performance on cognitive tests. Regarding the correlation signs, higher scores on the BNT and SHAR test indicate better performance, whereas higher scores on Trails A and B indicate poorer performance; correlations are in the predicted directions (greater SSBD volume is associated with poorer performance).

†P<.05.

‡P<.01.
Table 3. Regression Models of SSBD and Age as Predictors of Cognition*

<table>
<thead>
<tr>
<th>Model</th>
<th>Predictors</th>
<th>r²</th>
<th>F</th>
<th>P Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trails B Test</td>
<td>5 Age, DWMH, vCSF, sCSF, and PVH</td>
<td>0.453</td>
<td>4.80</td>
<td>.003</td>
</tr>
<tr>
<td></td>
<td>4 Age, DWMH, vCSF, and sCSF</td>
<td>0.450</td>
<td>6.13</td>
<td>.001</td>
</tr>
<tr>
<td></td>
<td>3 Age, DWMH, and sCSF</td>
<td>0.435</td>
<td>8.00</td>
<td>.001</td>
</tr>
<tr>
<td></td>
<td>2 Age and sCSF</td>
<td>0.399</td>
<td>10.60</td>
<td>.001</td>
</tr>
<tr>
<td></td>
<td>1 Age</td>
<td>0.329</td>
<td>16.15</td>
<td>.0005</td>
</tr>
</tbody>
</table>

SHAR Test

<table>
<thead>
<tr>
<th>Model</th>
<th>Predictors</th>
<th>r²</th>
<th>F</th>
<th>P Values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 Age, DWMH, vCSF, sCSF, and PVH</td>
<td>0.355</td>
<td>3.30</td>
<td>.017</td>
</tr>
<tr>
<td></td>
<td>4 Age, DWMH, vCSF, and sCSF</td>
<td>0.351</td>
<td>4.19</td>
<td>.008</td>
</tr>
<tr>
<td></td>
<td>3 Age, DWMH, and vCSF</td>
<td>0.344</td>
<td>5.60</td>
<td>.003</td>
</tr>
<tr>
<td></td>
<td>2 Age and DWMH</td>
<td>0.337</td>
<td>8.39</td>
<td>.001</td>
</tr>
<tr>
<td></td>
<td>1 Age</td>
<td>0.320</td>
<td>16.02</td>
<td>.0005</td>
</tr>
</tbody>
</table>

*SSBD indicates subclinical structural brain disease; Trails B, Trail-Making Test; DWMH, deep white-matter hyperintensities; vCSF, ventricular cerebrospinal fluid; sCSF, sulcal cerebrospinal fluid; PVH, periventricular hyperintensities; SHAR, Shipley-Hartford Abstract Reasoning. 

Table 4. Correlations of Coherence with SSBD and Cognition*

<table>
<thead>
<tr>
<th>Measure</th>
<th>Prerolandic Area</th>
<th>Postrolandic Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>PVH</td>
<td>12 (R)‡</td>
<td>12 (R), †16§</td>
</tr>
<tr>
<td>DWMH</td>
<td>12 (R)‡</td>
<td>16†</td>
</tr>
<tr>
<td>sCSF</td>
<td>...</td>
<td>16 (L)†</td>
</tr>
<tr>
<td>vCSF</td>
<td>12 (L)†</td>
<td>12†</td>
</tr>
<tr>
<td>Trails A</td>
<td>8 (L)‡</td>
<td>8 (R)†</td>
</tr>
<tr>
<td>Trails B</td>
<td>12†</td>
<td>16 (L)†</td>
</tr>
<tr>
<td>BNT</td>
<td>8 (R)†</td>
<td>...</td>
</tr>
<tr>
<td>FAS test</td>
<td>12 (L)†</td>
<td>...</td>
</tr>
<tr>
<td>SHAR test</td>
<td>...</td>
<td>16 (L)‡</td>
</tr>
</tbody>
</table>

*SSBD indicates subclinical structural brain disease; PVH, periventricular hyperintensities; DWMH, deep white-matter hyperintensities; sCSF, sulcal cerebrospinal fluid; vCSF, ventricular cerebrospinal fluid; Trails A, Trail-Making Test; DWMH, deep white-matter hyperintensities; SHAR, Shipley-Hartford Abstract Reasoning; BNT, Boston Naming Test; FAS test, controlled word association; SHAR, Shipley-Hartford Abstract Reasoning; and ellipses, not applicable. Subclinical structural brain disease measures showed significant correlations with connectivity in the corticolimbic coherence measures (prerolandic and postrolandic) (n = 33). Cognitive performance measures also showed significant correlations with connectivity in the coherence measures (n = 28 for all tests except FAS test (n = 29)). Numbers indicate the center frequency of each band (e.g., 8 Hz = 6-12 Hz; 12 Hz = 10-14 Hz; and 16 Hz = 14-18 Hz); unilaterality in the finding, if present, is denoted by “R” and “L.”

MRI METHODS

Brains were imaged using a 1.5-T scanner (Signa; GE Medical Systems, Milwaukee, Wis). Parameters included a 256 × 256 window, 3-mm slices, no interslice space, and a double–echo sequence with the following: echo time, 3000 milliseconds; repetition time, 16 milliseconds; and echo time, 3000 milliseconds; repetition time, 80 milliseconds. Data were processed with standard segmentation protocols, using the MRX software package. This software has shown sensitivity and reliability for detecting age-related changes.

Segmentation of brain, ventricular spaces, and lesions was performed in 4 steps, by operators blinded to clinical and QEEG data. First, an outline (mask) of the cerebral hemispheres was created for each scan plane, to delineate brain parenchyma from other structures and to eliminate the latter from further examination. Second, the operator selected sample points of each specific tissue and fluid type: sulcal cerebrospinal fluid (sCSF), normal cortical and subcortical gray matter, normal white matter, DWMHs, PVHs, and ventricular fluid (vCSF). The computer then classified all volume elements (voxels) according to these sample points via the signal intensity in both echo sequences.

Third, these automated tissue segmentations were reviewed for accuracy and misclassifications were corrected. The operator searched for misclassifications from partial volume effects at the boundary between segments (e.g., brain and CSF). Finally, voxels for each tissue were summed and converted to milliliter values. Data were evaluated for the whole brain and for anterior and posterior regions separately. These were divided by a vertical plane bisecting the line between the genu and splenium of the corpus callosum, drawn where that distance was smallest.

The use of the MRX software package has been investigated by Sandor and colleagues, who reported high interrater reliability using manually drawn regions and good reproducibility of data from multiple scans on the same subjects.

EEG METHODS

Recordings were performed while subjects rested in the eye-closed, maximally alert state, as previously detailed. Subjects were alerted by the technicians at the emergence of any sign of drowsiness. A parietal electrode (Pz)—referential montage was used with electrodes placed according to the 10-20 system. Signals were digitally recorded (bandpass width, 0.3-70 Hz) and analyzed with the QND system (Neurodata Inc, Pasadena, Calif). This system allowed for off-line reformatting to bipolar channels for coherence calculations (Figure 3). The first 20 to 32 seconds of artifact-free data were selected for processing by a technician, with selections confirmed by a second technician (both blinded to subject identity). Data were analyzed with a sample rate of 256 samples per second per channel with a fast Fourier transform (1024 points) to calculate values for coherence in 4-Hz frequency bands.

Figure 3. Coherence was computed to detect alterations in functional connectivity between regions connected by known neuroanatomical pathways. Corticolimbic connectivity was assessed in prerolandic (A) and postrolandic (B) networks (modified from Leuchter et al). Left hemisphere pathways are shown here; measures were calculated separately from both hemispheres. Dots indicate electrodes; arrows, pathways; and gray areas, electrode pairs at the ends of the pathways.
wide bands previously examined (6-10 Hz, 10-14 Hz, and 14-18 Hz).\textsuperscript{2,3,13,43}

**COHERENCE**

Coherence measures the similarity between signals at different locations, and is analogous to the square of a correlation coefficient between 2 EEG channels.\textsuperscript{29} High values (near 1) indicate much shared activity between the 2 channels, while low values (near 0) indicate little shared activity. Computationally, coherence is a function of the power spectra for 2 channels, \( x \) and \( y \), at any given frequency \( f \):

\[
C_{xy}(f) = \frac{|S_{xy}(f)|^2}{S_x(f)S_y(f)}
\]

or the square of the cross-spectrum of the 2 channels divided by the product of the spectra of the individual channels.

Thatcher et al\textsuperscript{44} measured the information transmitted through corticocortical fibers by averaging coherence values among recording sites overlying their distribution. By combining coherence values from bipolar channels overlying known structures,\textsuperscript{2} this measure can assess functional connectivity in these areas of interest. We previously used this approach to study disruption of connectivity in complex networks of corticocortical and corticosubcortical fibers (eg, prerolandic, frontal cortex [Figure 3A]) and the projections of the visual and association cortex in the postrolandic area (Figure 3B);\textsuperscript{2} subjects with vascular dementia showed reductions in coherence in these networks. In the present study, we measured coherence in the prerolandic and postrolandic regions. As in our previous work,\textsuperscript{2} values were multiplied by 10 and log-transformed to minimize skew and kurtosis. We limited our examination to frequencies above 6 Hz, because these bands have shown a consistent association between decreased coherence and impaired cognition.\textsuperscript{2}

**COGNITIVE MEASURES**

We assessed cognition with measures previously shown to be sensitive to structural changes. Boone et al\textsuperscript{41,43} found that frontal measures are particularly sensitive to significant white matter disease. The work of Heaton and colleagues\textsuperscript{46,47} with patients who have multiple sclerosis suggests that measures of attention, incidental memory, and psychomotor function are also useful. Consequently, we used the Trail-Making Tests\textsuperscript{46-50} to measure attention and processing speed (Trails A) and sequencing abilities (Trails B). We used the Controlled Oral Word Association Test (FAS test, named for its stimuli)\textsuperscript{51} to measure verbal fluency and semantic memory retrieval. The Shipley-Hartford Abstract Reasoning test\textsuperscript{52} was used to assess complex abstracting ability. The Boston Naming Test\textsuperscript{53} was used as a measure of confrontational naming.

**STATISTICAL METHODS**

Statistical analyses were performed using SPSS Analytic Software, Version 10.1 (SPSS Inc, Chicago, Ill.). Continuous outcome data were analyzed with linear regression models and \( t \) tests. Differences in SSBD variance between age groups were examined with the Levene test for equality of variance. The test of parallelism was used to evaluate the homogeneity of regression slopes. Path analysis\textsuperscript{49} was used to test whether the effects of SSBD on cognition were mediated by coherence. Regression equations from the hypothesized path model were used to test whether (1) the independent variable (SSBD) affected the mediator variable (connectivity), (2) the independent variable affected the dependent variable (cognition), and (3) the mediator variable (connectivity) affected the outcome variable. If all 3 conditions were met, and the path coefficient of the independent variable to the dependent variable was smaller than the path coefficient of the mediator to the dependent variable when cognition was regressed on both connectivity and SSBD, one could conclude that the hypothesized mediation was present.\textsuperscript{53}

**RESULTS**

**EFFECTS OF AGE ON VOLUMES OF STRUCTURAL CHANGE**

Significant linear relationships were found between age and central atrophy (\( r_{43} = 0.47, P = .001 \)), cortical atrophy (\( r_{43} = 0.46, P = .002 \)), and PVHs (\( r_{43} = 0.47, P = .002 \)), but not with DWMHs (\( r_{43} = 0.22, P = .15 \)) (Figure 4). Scatterplots revealed that, collectively, the older individuals had more SSBD than the younger subjects, but larger volumes were not inevitable: many subjects older than 75 years exhibited small volumes that were comparable to those in adults younger than 75 years. A primary finding was the increased variability in SSBD volumes for those older than 75 years, with a subgroup of subjects showing much greater volumes than those seen in the 60- to 75-year-old age group. Using the Levene test, this increase in variance was significant for DWMHs (\( F_{41} = 9.17, P = .004 \)) and PVHs (\( F_{41} = 4.93, P = .03 \)) but not for vCSF (\( F_{41} = 3.67, P = .14 \)) or sCSF (\( F_{41} = 0.02, P = .89 \)).

Because DWMH was not associated with age, its relationship with other factors was examined. Deep white-matter hyperintensity volume was significantly correlated with health state (CIRS-G, \( r_{41} = 0.54, P < .01 \)) and total PVH volume (\( r_{41} = 0.49, P < .001 \)). Deep white-matter hyperintensity volume was not correlated with Hachinski scores in our subject pool, though this may reflect the limited range for the latter scale in these subjects.

To evaluate regional differences, we regressed age against SSBD volumes separately for the anterior and posterior regions. Different relationships were found for the atrophy measures but not for the white matter changes (lines in Figure 4). Regression slopes were significantly different for anterior vs posterior sCSF and vCSF, with age-related atrophy seen more prominently in the posterior regions. In contrast, the slopes for DWMHs and PVHs were not significantly different for the anterior and posterior regions. The same process was used to evaluate lateral differences and age; no differences were found between the right and left hemispheres.

**EFFECT OF SSBD ON COGNITIVE FUNCTION**

Whole-brain SSBD volumes showed significant relationships with cognitive performance; larger SSBD volumes were associated with poorer performance, seen most strongly with Trails B performance (Table 2). A regional analysis (Table 2) revealed more similarities than differences between the anterior and posterior regions. For example, Trails B performance was significantly correlated with both anterior and posterior measures of PVHs, sCSF, and vCSF but was associated only with anterior DWMHs.

**JOINT RELATIONSHIP OF SSBD AND AGE WITH COGNITIVE PERFORMANCE**

Regression models incorporated age and SSBD variables to predict cognitive function (Table 3). After age entered
the model, sCSF was the most important structural variable in accounting for the variance in Trails B performance, followed by DWMHs. In contrast, after age had entered the model, DWMH was the best structural variable for predicting performance on abstract reasoning (Shipley-Hartford Abstract Reasoning test), followed by vCSF. While age clearly was important, the structural measures further explained the variance in performance.

RELATIONSHIP OF SSBD AND FUNCTIONAL CONNECTIVITY, AND OF CONNECTIVITY WITH COGNITION

Increasing PVH volumes were associated with significantly lower values of coherence in prerolandic and postrolandic regions, as was the case for DWMHs and vCSF (Table 4). In contrast, the only significant association for sCSF was with postrolandic coherence, the region with the greatest volumes of sCSF.

All cognitive measures showed associations with coherence, but with differing patterns of association (Table 4). For example, Trails A performance showed significant associations with coherence in both prerolandic and postrolandic regions, while Trails B showed a pattern of multiple significant relationships with connectivity in the both areas.

PATH ANALYSIS MODEL OF RELATIONSHIPS BETWEEN SSBD, CONNECTIVITY, AND COGNITION

To link these observations, we used a path analysis model to test whether the effects of SSBD on cognition are mediated through disrupted connectivity. To build this
The relationships in this model support the hypothesis model as exerting a physical influence through SSBD vol-

tive performance; consequently, age was placed in the

association. The central focus of this model is the po-

but none of the other parameters showed a significant

were seen for central and cortical atrophy and PVHs. There

diation role at the trend level for atrophy.

SSBD on cognitive function are mediated through im-

lations with coherence. Fourth, our path analysis mod-

cognitive function in the normal range. Third, SSBD also

these healthy subjects had modest volumes of SSBD and

factors of most types of SSBD on cognition, even though

these healthy subjects had modest volumes of SSBD and

cognitive function in the normal range. Third, SSBD also

affected functional connectivity, with significant corre-

lations with coherence. Fourth, our path analysis models

support the conclusion that effects of white-matter

SSBD on cognitive function are mediated through impair-

ment of functional connections, and support this med-

iation role at the trend level for atrophy.

The strongest relationships between SSBD and age

were seen for central and cortical atrophy and PVHs. There

was a regional difference for atrophy, with greater promi-

nence over the posterior brain regions, both cortically and
centrally; in contrast, white-matter changes did not show

a regional difference. These findings are consistent with

prior reports of atrophy and aging in healthy subjects, but
extend them with the finding of regional differences. The
regional prominence of posterior atrophy with age in healthy
subjects is, to our knowledge, a new finding and is particu-
larly intriguing given that Alzheimer disease is commonly
associated with atrophy and hypometabolism in posterior
regions.

The increased variability of SSBD in our older sub-
jects is compatible with prior reports from Jernigan et
al2,63 and Goldstein et al.44 A clinical implication is that
increasing volumes of structural change with aging are
not inevitable; some of our most aged subjects showed
small amounts of SSBD. Of note, deep white-matter hy-

perintensity volume was not significantly related to age
but was related to health status. The differing patterns
of association for PVHs and DWMHs suggest that these
white matter changes may be pathophysiologically re-
lated but are not identical.

Our findings suggest that SSBD is associated with
decrements in cognitive performance even in a healthy
elderly control population, seen most strongly with the
Trails B task. Trail-Making Tests are thought to reflect
executive function65,66 and Boone et al21 reported on the
sensitivity of executive tasks to white-matter disease
throughout the brain. Trail-making performance has pre-
viously been reported to be affected by age in healthy
adults67 and by deterioration in the integrity of white-
matter tracts,17 but without the volumetric data needed to
test whether SSBD might be mediating the effect of age.
Our data do suggest a mediating role for SSBD on the dec-
rement in performance with aging. Our subjects had a
high average level of education; while this may be a limi-
tation for generalizing, it suggests that even subjects with
presumably high brain reserve68,69 show detectable changes
in cognition from SSBD as they age.

Volumes of SSBD showed influences on coherence,
consistent with our previous reports in other popula-
tions30,31 and with the intrahemispheric coherence find-
ings of Koyama et al70 and of Duffy et al71 using inter-

hemispheric coherence. While Geschwind and Kaplan72
and Geschwind73 advanced the idea that a process of “dis-
nexxion” underlay the deficits in their clinical popula-
tions, our data suggest that changes in connectivity may
occur during asymptomatic aging. This is also sup-
ported by recent observations by O’Sullivan et al17 using
diffusion tensor imaging. Our findings support a patho-
physiological model in which the effects of SSBD pro-
duce disturbances in information processing.

Coherence was significantly related to cognitive per-
formance, with intriguing differences among the tests for
patterns of connectivity. The Trails B task depends on
numerous processing steps, and showed multiple asso-
ciations with connectivity variables, while the related but
simpler Trails A task showed fewer associations, sug-

gest that the performance of the Trails B test may de-

mand more complex integrative processing. A limita-
tion of our study is that these were resting-state EEGs:
task-activated QEEG recordings might reveal addi-
tional relationships.

Our findings indicate a series of relationships between
structural changes, age, cognition, and connectivity. First,
while volume of some types of SSBD was strongly asso-
ciated with increasing age, this association was not seen
uniformly across types of change or brain region. Fur-

thermore, variance in the volumes of SSBD increased with
age, with only a subset of the oldest-old subjects show-
ing volumes of change significantly greater than the
younger-old age group. Second, there were detectable ef-

fets of most types of SSBD on cognition, even though
these healthy subjects had modest volumes of SSBD and
cognitive function in the normal range. Third, SSBD also
affected functional connectivity, with significant corre-

lations with coherence. Fourth, our path analysis models

support the conclusion that effects of white-matter

SSBD on cognitive function are mediated through imp-

airment of functional connections, and support this me-

iation role at the trend level for atrophy.

The relationships in this model support the hypothesis
that altered connectivity does mediate the effects of white-
matter disease on cognition.

**Figure 5.** The mediation hypothesis was examined using path analysis. A, The results for total white-matter disease burden (total WMD) support a mediation role for disturbances in connectivity (total COH or coherence) in WMD’s effects on cognition (Trails B). Path a indicates the standardized path coefficient $\beta = .51$, $P = .002$; b, $\beta = .45$, $P = .02$; c, $\beta = .34$, $P = .005$; and d, $\beta = .30$, $P = .048$. B, This mediation is not supported for the effects of atrophy (total atrophy) on cognition (total COH). Path a indicates $\beta = .45$, $P = .004$; b, $\beta = .31$, $P = .044$; c, $\beta = .41$, $P = .011$; and d, $\beta = .26$, $P = .08$.
The relationships between structural damage, coherence, and cognition in the path analysis model support our hypothesis that the effects of SSBD on cognition are mediated by disruptions in neuronal connectivity. To our knowledge, this is the first demonstration of a mechanism that integrates structural and functional connectivity data to explain the cognitive consequences of subtle structural damage in normal aging. The relationship between structural damage and disconnection is more clearly established for disturbances in white-matter structures than for those involving gray matter, so these findings are consistent with prior observations. These findings are also largely consistent with previous work in dementia subjects.

In this group of healthy elderly subjects, even small amounts of SSBD were seen to produce detectable changes in QEEG measures and decrements in cognitive performance. For some forms of SSBD, the adverse effect on cognition seems to be mediated via disruption in connectivity between brain regions, though other factors are also important. We conclude that these mild degrees of structural change can no longer be presumed to be inconsequential for cognitive function.

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