Hippocampal Neuronal Atrophy and Cognitive Function in Delayed Poststroke and Aging-Related Dementias

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Background and Purpose—We have previously shown delayed poststroke dementia in elderly (≥75 years old) stroke survivors is associated with medial temporal lobe atrophy; however, the basis of the structural and functional changes is unknown.

Methods—Using 3-dimensional stereological methods, we quantified hippocampal pyramidal neuronal volumes and densities in a total of 95 postmortem samples from demented and nondemented poststroke survivors within our prospective Cognitive Function after Stroke study and subjects pathologically diagnosed with vascular dementia, Alzheimer disease, and mixed Alzheimer disease and vascular dementia syndrome.

Results—Hippocampal CA1 but not CA2 subfield neuron density was affected in poststroke, Alzheimer disease, vascular dementia, and mixed dementia groups relative to control subjects (P<0.05). Neuronal volume was reduced in the poststroke dementia relative to poststroke nondemented group in both CA1 and CA2, although there were no apparent differences in neuronal density. Poststroke nondemented neuronal volumes were similar to control subjects but greater than in all dementias (P<0.05). Neuronal volumes positively correlated with global cognitive function and memory function in both CA1 and CA2 in poststroke subjects (P<0.01). Degrees of neuronal atrophy and loss were similar in the poststroke dementia and vascular dementia groups. However, in the entorhinal cortex layer V, neuronal volumes were only impaired in the mixed and Alzheimer disease groups (P<0.05).

Conclusions—Our results suggest hippocampal neuronal atrophy is an important substrate for dementia in both cerebrovascular and neurodegenerative disease. (Stroke. 2012;43:808-814.)

Key Words: Alzheimer disease ■ hippocampus ■ poststroke dementia ■ stroke ■ vascular dementia

Patients with stroke who do not develop dementia as a direct result of a stroke have a 9-fold increased risk of developing delayed poststroke dementia (PSD),¹ which can affect up to 50% of all stroke survivors and is associated with poor long-term survival.²,³ However, the pathological processes that increase vulnerability of nondemented stroke survivors to cognitive decline are unknown. We have previously shown that medial temporal lobe atrophy (MTA) on MRI was a predictor of delayed PSD in elderly patients with stroke who were not cognitively impaired 3 months poststroke.⁴ Given that hippocampal atrophy is considered a sensitive marker of Alzheimer disease (AD),⁵ we postulated that MTA reflects the presence of asymptomatic Alzheimer pathology uncovered or exacerbated by ischemic injury. However, there is growing evidence for MTA and hippocampal degeneration associated with cerebrovascular disease in ischemic vascular dementia (VaD)⁶–⁸ and dementia caused by sporadic and familial small vessel disease,⁹–¹¹ although postmortem verification of neurodegenerative pathology was not available in most of these studies.

The basis of MTA and associated functional impairment in delayed PSD is unclear. In AD, the cause is generally thought to be hippocampal neurodegeneration, particularly in the CA1 subfield.¹²,¹³ This may also be true in PSD because CA1 neurons are vulnerable to ischemia and hypoperfusion.¹⁴,¹⁵ and human and experimental studies suggest there is significant CA1 neuron loss after ischemic stroke.¹⁴ Greater neurodegeneration in stroke survivors who developed delayed PSD may therefore account for more severe cognitive impairment compared with those who maintained normal cognitive function. However, loss of neurons is not the only factor that contributes to brain atrophy and functional decline. This has been demonstrated in the hippocampus, where although atrophy is strongly associated with memory impairment in...
AD and normal aging, there is limited neuron loss with age and neurodegeneration in AD makes only a weak contribution to tissue atrophy. Furthermore, conflicting reports of CA1 neuron loss in VaD suggest other mechanisms are involved. Volumetric or atrophic changes in neuronal morphology have also been suggested as a major contributory factor to gross structural and functional changes in dementia. This study therefore investigated the impact of cellular pathology on cognitive dysfunction in cerebrovascular and neurodegenerative diseases associated with MTA and dementia. Hippocampal pyramidal neuron density and soma volume were examined in relation to cognitive function in prospectively assessed stroke survivors who had developed delayed PSD or remained nondemented.

### Subjects and Methods

#### Subject Selection and Clinical Diagnosis

The demographic details of the different subjects and pathological findings are presented in Table 1. Hippocampal tissue was analyzed from 36 poststroke subjects from the prospective Cognitive Function After Stroke (CogFAST) study as described previously. Stroke patients ≥75 years old were selected if they were not demented 3 months poststroke and did not exhibit disabilities that would prevent them from completing cognitive tests. They received annual clinical assessments and a neuropsychological test battery from baseline including the Cognitive Drug Research battery, the Mini-Mental State Examination, and the Cambridge Assessment of Mental Disorders in the Elderly, which generated subscores for various cognitive domains, including memory and executive function.

Subjects were diagnosed as demented if they met Diagnostic and Statistical Manual of Mental Disorders, Third Edition Revised criteria for dementia. Control subjects >75 years old were only selected if they demonstrated no evidence of cognitive impairment; however, they were not psychologically tested. Ethical approval was granted by local research ethics committees for this study (Newcastle on Tyne Hospitals Trust, UK) and permission for postmortem research using brain tissue was granted for this project.

### Neuropathological Examination

Final diagnoses of demented subjects were assigned based on established neuropathological diagnostic criteria. Briefly, hematoxylin and eosin staining was used for assessment of structural integrity and infarcts, Nissl and Luxol fast blue staining for cellular pattern and myelin loss, Bielschowsky silver impregnation for Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) rating of neuritic plaques, and tau immunohistochemistry for Braak staging of neurofibrillary tangles. A diagnosis of VaD was made when there were multiple or cystic infarcts, lacunae, microinfarcts, and small vessel disease and Braak stage <III. A diagnosis of AD was made when there was evidence of significant Alzheimer-type pathology (Braak Stage V–VI and moderate to severe CERAD score) and absence of significant vascular pathology. Subjects were diagnosed as “mixed” when there was evidence of concomitant VaD with AD, Lewy body pathology, or tauropathy. We found that 70% of delayed PSD cases met pathological criteria for VaD at autopsy with negligible neurodegenerative pathology. Global vascular pathology was assessed (V.D., R.K.) and calculated as the sum of ratings of vascular pathology in the hippocampus, frontal lobe, temporal lobe, and basal ganglia to generate a score /20 (Deramecourt et al, unpublished data).

### Tissue Acquisition

To investigate the effects of different disease processes, we also analyzed neurons in elderly control subjects and VaD, AD, and dementia with mixed AD and VaD pathology cases. Brain tissues were retrieved from the Newcastle Brain Tissue Resource (Newcastle, UK) except 4 control cases, which were obtained from the Medical Research Council London Brain Bank for Neurodegenerative Diseases (Institute of Psychiatry, London, UK). Brain tissue was cut from predefined, paraffin-embedded blocks of the hippocampus according to the Newcastle Brain Map. The coronal samples were taken between the level of the pregeniculate nucleus and the pulvinar at which the emergence of the ventricle is visible. Structural

### Table 1. Demographic Details of Groups Analyzed*

<table>
<thead>
<tr>
<th>Maximum no. of subjects analyzed (total = 95)</th>
<th>Control</th>
<th>PSND</th>
<th>PSD</th>
<th>VaD</th>
<th>Mixed</th>
<th>AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>81 (72–92)</td>
<td>84 (78–94)</td>
<td>88 (80–98)</td>
<td>86 (71–97)</td>
<td>84 (72–94)</td>
<td>84 (70–91)</td>
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<td>Braak stage</td>
<td>NPD</td>
<td>2.6 (1–5)</td>
<td>2.6 (0–4)</td>
<td>2.1 (1–4)</td>
<td>5.1 (4–6)</td>
<td>5.2 (4–6)</td>
</tr>
<tr>
<td>CERAD</td>
<td>NPD</td>
<td>1.5 (0–2)</td>
<td>1 (0–3)</td>
<td>1.3 (0–2)</td>
<td>2.6 (2–3)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Vascular pathology</td>
<td>NPD</td>
<td>12.6 (7–16)</td>
<td>11.9 (8–17)</td>
<td>13 (12–14)</td>
<td>3 (6–14)</td>
<td>N/A</td>
</tr>
<tr>
<td>PMD, h</td>
<td>Mean (± 2 SE)</td>
<td>25 (7)</td>
<td>46 (12)</td>
<td>48 (13)</td>
<td>43 (10)</td>
<td>36 (11)</td>
</tr>
<tr>
<td>Fixation duration, wk</td>
<td>Mean (± 2 SE)</td>
<td>15 (4)</td>
<td>11 (3)</td>
<td>8 (2)</td>
<td>12 (6)</td>
<td>17 (5)</td>
</tr>
<tr>
<td>Section thickness, μm</td>
<td>Mean (± 2 SE)</td>
<td>24.1 (1.6)</td>
<td>26.3 (0.3)</td>
<td>27 (0.3)</td>
<td>27.1 (0.6)</td>
<td>26.2 (0.7)</td>
</tr>
</tbody>
</table>

PSND indicates nondemented poststroke subjects; PSD, delayed poststroke dementia; VaD, vascular dementia; “mixed” Alzheimer, and vascular dementia; AD, Alzheimer disease; CERAD, Consortium to Establish a Registry for Alzheimer’s Disease; PMD, postmortem delay; NPD, no pathological diagnoses; ECV, entorhinal cortex Layer V.

*Maximum number in control group ECV n=8, PSND CA2 n=20, and ECV n=20; PSD CA2 n=21 and ECV n=11; VaD CA2 n=12 and ECV n=11; mixed CA2 n=12 and ECV n=11; AD CA2 n=13 and ECV n=12. Total no. in CA1 n=95, in CA2 n=82 and ECV n=73.
neuromaging did not detect differences in the degree of MTA in the left versus right hemisphere; therefore, sections were taken from either the left or right hippocampus in each case provided there were no apparent gross lesions. At least 3 30-μm sections per case were cut using a Shandon FineneE+ rotary microtome. Sections were cut using the Nissl method and checked for quality, staining consistency, and penetration. Slides were coded so the investigators (E.G., H.B.) were blind to disease group. To minimize differential tissue effects from processing and staining, all cases were collected, treated, and analyzed in a standardized manner, allowing accurate and valid comparisons to be made.

**Stereological Analysis**
Pyramidal neurons were analyzed in hippocampal areas CA1, CA2, and entorhinal cortex Layer V (ECV), except 13 cases in which CA2 and 22 cases where ECV was not present or suitable for analysis (Table 1). Sections were imaged using a Zeiss Axioptan Photomicroscope with a Pixellink PL-B623CP color digital camera linked to a computer. The reference area was defined by the investigator with a ×2.5 objective lens using stereological analysis software (Visiopharm Integration System, Hørsholm, Denmark). At this magnification, CA1 and CA2 were easily distinguishable because CA1 was broader with lower neuron density than CA2. The entorhinal cortex was defined according to Insausti et al.31 Layer V was identified as a band of darkly stained large- to medium-sized pyramidal neurons superficially bordered by cell-sparse Layer IV as described by Canto et al.32

A motorized stage (Prior ProScan II; Prior Scientific Instruments Ltd, Cambridge, UK) with an accuracy of 1 μm was used to take up a uniform random sampling procedure within the reference area to select approximately 33 frames from each of the 3 sections per case. Frames were viewed at ×100 magnification using an oil immersion objective with a numeric aperture of 1.25. The optical dissector method was used for estimation of neuron density.33 Based on x–y axis length, each dissector frame had an area of 2548.66 μm². A Heidenhain z-axis microrator (Heidenhain GB Ltd, London, UK), accurate to 0.5 μm, was used to precisely measure dissector depth and tissue section thickness, which was recorded every 10 frames (mean, 26.3 μm). Each dissector probe had a z-axis depth of 18 μm, excluding a guard volume ±4 μm. Pyramidal neurons were identified using established criteria, that is, characteristic triangular soma, Nissl-stained cytoplasm, and darkly stained single nucleolus.34 A pilot study was performed to ensure that the neurons were sampled in sufficient numbers to provide precise estimates based on the mean coefficient of error. Approximately 150 neurons were analyzed per subfield per case, ensuring that the average sampling error reached a satisfactory level.35 The soma volume of each sampled neuron was measured using an independent uniform random orientated nucleator probe (Figure 1).36

**Statistical Analyses**
Statistical analyses were carried out using SPSS Version 17.0. Significance was set at P<0.05. The Shapiro-Wilk test was used to check for normal distribution and data nonnormally distributed were analyzed using nonparametric tests. Group means were compared using the Kruskal-Wallis test. Pairwise analyses were performed using the Mann-Whitney U Test. The Wilcoxon signed rank test was used for comparison of related means. Correlations were assessed using Spearman rank correlation. Pearson χ² test or Fisher exact tests were used to determine associations between categorical data.

**Results**
There were no differences in the mean age or the distribution of males and females between groups. Poststroke cases were divided into 2 groups based on cognitive status at their final assessment (mean 7.6 months before death) to allow comparison between nondemented stroke survivors (PSND) and those who developed delayed PSD (Tables 1 and 2). We found no apparent differences in the Braak stage, CERAD score, vascular pathology scores, or time from stroke to death between PSND and PSD groups (Table 1). There was no association between Braak stage ≥2 and delayed PSD. Sixty-three percent (n=10) of delayed PSD cases met pathological criteria for a final diagnosis of VaD; the remainder were mixed AD and VaD. There were no associations between lesion location and delayed PSD (Fisher exact test P=0.743). The coefficient of error values for neuronal densities were CA1 P=0.06, CA2 P=0.002, ECV P=0.02, and for neuronal volumes were CA1 P=0.04, CA2 P=0.02, ECV P=0.05 demonstrating a high level of precision. Period of postmortem delay or length of fixation (up to 40 weeks) was not found to influence neuronal density or volume results among the various groups (P>0.05).

**Neuronal Densities**
As shown in Figure 2, neuronal density was different between all regions CA2>ECV>CA1 (P<0.001) and positively correlated between CA1 and CA2 and CA1 and ECV (r=0.311, Table 2.

<table>
<thead>
<tr>
<th></th>
<th>PSND</th>
<th>PSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from baseline- death (mo)</td>
<td>Mean (± 2 SE)</td>
<td>63.5 (22)</td>
</tr>
<tr>
<td>Total CAMCOG score (/100)</td>
<td>Mean (range)</td>
<td>88.6 (76–99)</td>
</tr>
<tr>
<td>Memory subscore (/27)</td>
<td>Mean (± 2 SE)</td>
<td>17 (1.6)</td>
</tr>
<tr>
<td>Executive function subscore (/28)</td>
<td>Mean (± 2 SE)</td>
<td>22 (0.8)</td>
</tr>
<tr>
<td>Hemisphere with visible lesion on CT</td>
<td>(right, left, both, none)</td>
<td>(5, 2, 5, 6)</td>
</tr>
</tbody>
</table>

PSND indicates nondemented poststroke subjects; PSD, delayed poststroke dementia; CAMCOG, Cambridge Assessment of Mental Disorders in the Elderly.
CA1 neuronal density was different among the groups (P<0.001). Compared with control subjects, CA1 neuronal density was reduced in the PS group (P=0.025), PSND (P=0.027), VaD (P=0.012), mixed (P<0.001), and AD groups (P=0.001).

In CA1, the mixed dementia and AD groups had lower neuronal density than the PSND group (P<0.001 and P=0.015, respectively). Surprisingly, there was no difference in CA1 neuronal density between the PSD and PSND groups (P=0.643). CA2 and ECV neuronal densities were not different between groups (P=0.562 and P=0.303, respectively); however, there were trends for lower ECV neuronal density in the mixed group compared with control subjects and PSND groups (P=0.083 and P=0.08, respectively).

Neuronal Volumes

We found neuronal volume was different across all areas (CA2>CA1>ECV; P<0.001; Figure 3). Providing consistency in our results, neuronal volume was correlated in all 3 areas (CA1 versus CA2 r=0.406, P<0.001; CA1 versus ECV r=0.231, P=0.05; CA2 versus ECV r=0.311 P=0.012).

CA1 neuronal volume was different among all groups (P=0.015). Compared with control subjects, CA1 neuronal volume was reduced in VaD (P=0.047), mixed dementia (P=0.039), and AD (P=0.037). Compared with the PSND group, CA1 neuronal volume was reduced in all dementia groups (PSD P=0.028, VaD P=0.026, mixed P=0.009, and AD P=0.01). However, there was no difference in neuronal volume between the PSND group and control subjects (P=0.785).

CA2 neuronal volume was different among all groups (P=0.002). Compared with control subjects, CA2 neuronal volume was reduced in all dementia groups (PSD P=0.014, VaD P=0.021, mixed P=0.003, and AD P=0.016). Compared with the PSND group, CA2 neuron volume was reduced in all dementia groups (PSD P=0.009, mixed P=0.003, and AD P=0.019), and there was a trend to significance with the VaD group (P=0.08). We did not find any differences between the PSND and control subjects (P=0.959). A negative correlation was found between CA2 neuronal volume and age (r=−0.246, P=0.031).

ECV neuronal volumes were different among all groups (P<0.001). ECV neuron volumes were reduced compared with control subjects and PSND in mixed dementia (P=0.001 and P<0.001, respectively) and AD (P=0.008 and P=0.019, respectively). There were no differences found among the PS, VaD, and control groups. We did not find differences in neuronal volume or density between the PS cases that were classified as “VaD” or “mixed” (data not shown). There were no differences in neuronal volume or density between male and female subjects.

Poststroke Neuronal Volume and Cognitive Function

Final total Cambridge Assessment of Mental Disorders in the Elderly scores were positively correlated with neuronal volume in CA1 (r=0.399, P=0.01) and CA2 (r=0.445, P=0.007; Table 2; Figure 4). CA2 neuronal volume was positively correlated with total memory (r=0.481, P=0.006), recent memory (r=0.692, P<0.001), remote memory (r=0.428, P=0.016) and attention Cambridge Assessment of
Mental Disorders in the Elderly subscores ($r=0.379$, $P=0.035$). There were trends to significant correlations between CA2 neuronal volume and learning ($r=0.352$, $P=0.052$). ECV neuronal volume was correlated with remote memory subscores ($r=0.372$, $P=0.043$). We did not find correlations between neuronal density and cognitive function.

Neurodegenerative Pathology
CA1 neuron density was negatively correlated with Braak stage and CERAD score across all groups ($r=-0.379$, $P=0.002$ and $r=-0.0392$, $P=0.001$) even where Braak staging was not diagnostic for AD.28 CA2 and ECV neuronal volume were negatively correlated with Braak stage ($r=-0.392$, $P=0.003$ and $r=-0.395$, $P=0.004$) and CERAD score ($r=-0.261$, $P=0.059$ and $r=-0.419$, $P=0.002$). There were no correlations between vascular pathological burden and neuronal volumes or between neurodegenerative or vascular pathology and neuronal density.

Discussion
Our results provide novel evidence that reduced neuronal volume or “neuronal atrophy” is associated with cognitive impairment in delayed PSD and other aging-related dementias with both vascular etiology and AD. Pyramidal neuronal volumes in the hippocampal subfields CA1 and CA2 were 10% to 20% smaller in delayed PSD, VaD, mixed, and AD groups compared with cognitively normal elderly subjects (online only Supplementary Table, http://stroke.ahajournals.org). Interestingly, the PSND group had neuronal volumes similar to control subjects, whereas neuronal volumes in the delayed PSD group were 20% smaller than PSND. Because the PS groups had comparable vascular and negligible Alzheimer-type lesion burden, neuronal atrophy appears as a selective pathological feature discriminating nondemented and demented elderly stroke survivors. This suggests that reduced neuronal volume reflects mechanistic change occurring in some PS survivors accelerating cognitive decline. This was supported by the positive correlation between neuronal volumes and cognitive test scores in stroke survivors. Furthermore, because neuronal volumes were reduced in VaD, AD, and mixed dementia, our results suggest that mechanisms causing neuronal atrophy are associated with cognitive decline in both cerebrovascular disease and neurodegenerative disease.

In agreement with the well-documented differential vulnerability of the entorhinal cortex to AD pathology,37 neuronal volumes in Layer V of the entorhinal cortex were negatively correlated with Braak stage and were reduced in AD and mixed dementia but not affected in PSD and VaD. The finding that neuronal volume and density changes in the delayed PSD group were similar to those in VaD supported clinico-pathological findings that delayed PSD is associated with vascular-type dementia driven by vascular rather than Alzheimer or other neurodegenerative pathology.29

We found that CA2 neuronal volumes were related to various memory Cambridge Assessment of Mental Disorders in the Elderly (CAMCOG) scores ($r=0.445$, $P=0.007$). CA2 neuronal volumes versus total CAMCOG memory subscores ($r=0.481$, $P=0.006$), x indicates post-stroke demented; o, poststroke nondemented.
subsequent estimation of total cell number within the structure using the desirable “fractionator” method.32 Because density measures are based on the relationship between the numerator (the cell counts) and denominator (extracellular matrix), the effect of tissue processing cannot be ruled out. However, all sections were processed and handled in a standardized manner, allowing valid comparisons to be made as any introduced artifact would be common to all sections. Our results were consistent with the literature describing significant loss of CA1 neurons in VaD and AD.9,17 We were surprised to find significantly decreased neuronal density in the CA1 of the PSND group compared with control subjects and no significant difference in CA1 neuron density between PS groups because we expected greater neuron loss to explain progression to PSD. This suggests an important role for mechanisms causing neuronal atrophy in cognition even after neuron loss. However, because we have shown that delayed PSD patients have greater MTA than nondemented stroke survivors on MRI,43 the PSD neuronal density measurements may be affected by tissue atrophy bringing surviving neurons closer together. Because the neurodegenerative dementia we studied are associated with MTA, the true level of neuron loss is likely to be greater than our results suggested and closer to values reported in previous studies.17 The greatest reduction in CA1 neuron density was found in the mixed AD and VaD groups, which supports clinicopathological studies demonstrating that coexistence of vascular and Alzheimer-type pathology has an additive effect on cognition.44

Conclusions
Our results provide novel evidence of hippocampal neuronal atrophy in delayed PSD, VaD, mixed AD and VaD, and AD. ECV neuronal volumes were only reduced in the mixed and AD groups, which was consistent with the known vulnerability of the ECV to AD pathology. Hippocampal CA1 and CA2 neuronal volumes were significantly reduced in delayed PSD subjects compared with nondemented stroke survivors and were related to global cognitive function as well as learning and memory function. However, there were no differences in hippocampal neuronal density between nondemented and demented stroke survivors. Our findings suggest that even after significant neurodegeneration, therapeutic strategies to maintain or restore functional morphology in surviving neurons could prevent further cognitive decline in PS and aging-related dementias.

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Disclosures
None.

References


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### SUPPLEMENTAL MATERIAL

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<th>Controls</th>
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<th>VaD</th>
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S1. Disease group means as percentage of control group mean. Abbreviations: ‘All PS’ = All post-stroke subjects, PSND = non-demented post-stroke subjects, PSD = delayed post-stroke dementia, VaD = vascular dementia, ‘mixed’ mixed Alzheimer’s and vascular dementia, AD= Alzheimer’s disease.