Profiles of neuropsychological impairment in autopsy-defined Alzheimer’s disease and cerebrovascular disease

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Differentiating the cognitive effects of cerebrovascular disease, particularly small vessel disease, from those of Alzheimer’s disease is a difficult clinical challenge. An influential model of how subcortical cerebrovascular disease causes cognitive dysfunction posits that damage to frontostriatal loops impairs frontal lobe function, leading to predominant impairment of executive function and secondary impairments of associated cognitive functions such as memory. Consistent with this, neuropsychological studies of clinically diagnosed patients have reported that individuals with vascular dementia do better on memory tests and worse on executive function tests compared with patients with Alzheimer’s disease. This observation has led to the suggestion that predominant cognitive executive dysfunction might serve as a useful diagnostic marker for vascular dementia. We sought to test this idea in a series of cases with autopsy-defined pathologies. Subjects were 62 autopsied cases from a prospective study of vascular contributions to dementia. Using neuropathological features alone, 23 were diagnosed with Alzheimer’s disease (AD), 11 with cerebrovascular disease (CVD), 9 with both (mixed pathology) and 19 with normal elderly brain (NEB). Three psychometrically matched composite scales of different cognitive abilities were used: Verbal Memory, Nonverbal Memory and Executive Function. Analysis of group data showed that for Alzheimer’s disease memory scores were lower than Executive Function by nearly a standard deviation on average. In contrast, and contrary to the model, CVD was rather equally impaired on Executive Function, Verbal Memory and Nonverbal Memory. Individual patterns of cognitive impairment were examined by defining three profiles based on reliable differences between neuropsychological scores to characterize cases with predominant memory impairment, predominant executive dysfunction, and ‘other’ patterns. Analysis of individual impairment profiles showed that predominant memory impairment was present in 71% of Alzheimer’s disease while predominant executive dysfunction described only 45% of CVD. A stronger pattern emerged when cognitively normal cases were excluded; among the six cognitively impaired CVD patients four had predominant executive dysfunction and none had predominant memory impairment. This report, comprised of a substantial sample of autopsy confirmed cases, delineates the patterns of neuropsychological impairment associated with small vessel cerebrovascular disease and Alzheimer’s disease. While the findings show that memory loss usually exceeds executive dysfunction in patients with Alzheimer’s disease, the reverse is not the case in CVD. Taken as a whole, the results indicate that the cognitive effects of the small vessel cerebrovascular disease are variable and not especially distinct, thus raising question about the utility of executive impairment as a diagnostic marker for vascular dementia.

Keywords: Alzheimer’s disease; vascular dementia; memory performance; executive control; neuropathology

Abbreviations: DRS = Dementia Rating Scale; CERAD = Consortium to Establish a Registry for Alzheimer’s Disease; CVDPS = cerebrovascular disease parenchymal pathology score; HS = hippocampal sclerosis; AD = Alzheimer’s disease, defined by pathology; CVD = cerebrovascular disease, defined by pathology; NEB = normal elderly brain, defined by pathology

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Introduction

Cerebral infarcts and the histopathological markers of Alzheimer’s disease are the most common neuropathological findings in the ageing brain, a degree of one or both becoming virtually ubiquitous by the age of 90. One or both of these pathologies is thought to underlie the great majority of cases of dementia (and mild cognitive impairment) (Neale et al., 2001). Their clinical detection and especially their differential diagnosis, however, remain challenging.

Validation of a pattern of cognitive impairments that is specifically associated with small vessel ischaemic disease would be clinically and scientifically valuable. At present, our ability to detect evidence of ischaemic lesions, using neurological examination, MRI and clinical history far outstrips our ability to link those lesions to cognitive impairment. Even in the case when an ischaemic event is followed closely by a decline in function, it can be difficult to be certain that the clinical picture does not reflect a potentiation of underlying Alzheimer’s disease. If it could be shown that lacunar infarcts and white matter lesions typically produce cognitive symptoms that are distinguishable from those associated with Alzheimer’s disease it would be possible to make causal attributions with more certainty and clinical diagnosis would be advanced.

A strong conceptual case can be made for the idea that subcortical cerebrovascular disease is likely to result in cognitive symptoms distinguishable from those of Alzheimer’s disease. The term subcortical cerebrovascular disease is used here to refer to the clinical presentation in which subcortical infarcts and white matter changes, but not large cortical infarcts are evident. Cortical microinfarcts may be present in these cases, but are not revealed until autopsy (White et al., 2002). There is evidence that both lacunar infarcts (Ishii et al., 1986) and white matter lesions (Tullberg et al., 2004), the two manifestations of subcortical cerebrovascular disease best visualized during life, occur predominantly in subcortical frontal lobe. Because the functioning of frontal cortex depends on the integrity of corticalstriatal loops that course through the frontal white matter (Alexander and Crutcher, 1990; Cummings, 1993), it is quite plausible that these types of lesions would produce deficits in working memory, executive control functions, and other cognitive abilities that are subserved by prefrontal cortex. In addition, there is evidence that subcortical cerebrovascular disease, even when located outside of these circuits, is associated with hypometabolism and other indicators of dysfunction in prefrontal cortex (Kwan et al., 1999; Tanaka et al., 2002; Reed et al., 2004a; Tullberg et al., 2004). Episodic memory is a complex, anatomically distributed cognitive function with significant inputs from prefrontal cortex (Fletcher and Henson, 2001; Desmond, 2004). However, while it is thus reasonable to expect that memory abnormality would accompany subcortical cerebrovascular disease, there is less reason to expect that these deficits would be severe. In contrast, severe loss of episodic memory function is well-established as the most prominent and, generally, first cognitive symptom of Alzheimer’s disease. As Alzheimer’s disease progresses into its later pathological stages frontal cortex is typically affected and with that executive functions and other neocortically mediated abilities are impaired as well. Generally, however, these changes trail behind the loss of memory, suggesting that the relative severity of executive function and memory impairments might serve diagnostically in early and middle disease states.

Many studies have used neuropsychological tests to evaluate this hypothesis in clinical samples. That literature, while by no means uniform, is supportive overall (Desmond, 2004). The critical problem with all such studies is the lack of neuropathological confirmation of clinical diagnosis. Because Alzheimer’s disease is so common, so variable in its clinical presentation (Villareal and Morris, 1999; Cummings, 2004), and impossible to exclude with certainty during life, and because vascular dementia, also heterogeneous, clearly can present with a gradual decline similar to that seen in patients with Alzheimer’s disease (Knopman et al., 2003; Reed et al., 2004b) errors of misclassification in both directions are inevitable in clinical series. Worse than random misclassification, however, is the distinct possibility that diagnosticians’ ideas of what the different behavioural features of vascular dementia and Alzheimer’s disease are will bias their diagnoses, thus creating circularity in the use of clinically diagnosed samples to test differences in behavioural features.

In this article, we report on an effort to use neuropsychological test scores to distinguish Alzheimer’s disease and cerebrovascular cases in pathologically diagnosed cases. Although neuropsychological domains other than memory and executive function have been examined as potentially differing between Alzheimer’s disease and vascular dementia, we chose these for two main reasons. The first was conceptual and based on the arguments above. The second was practical, based on methodological considerations. In prior work we have created and reported on composite neuropsychological scales for episodic memory and executive function (Mungas et al., 2003). These scales, developed using item response methods, have several psychometric advantages including linearity of measurement over a 4 SD range, of possessing equivalent, high levels of reliability across their range of measurement, and of being normed. They are thus particularly well-suited for examining comparative degrees of impairment, as differences between scale scores can confidently be attributed to differences in the underlying abilities tapped by these measures, as opposed to differences in the measurement characteristics of the tests themselves.

These were the hypotheses to be tested in autopsy defined cases: (i) cerebrovascular disease is associated with deficits of executive function that are more severe than...
episodic memory deficits; (ii) Alzheimer’s disease is associated with episodic memory impairments that are more severe than executive function deficits; (iii) neuropathological markers of Alzheimer’s disease correlate with episodic memory function; and (iv) neuropathological markers of cerebrovascular disease correlate with executive function. Prior work has suggested that in cases of mixed dementia Alzheimer’s disease pathology is a more important determinant of cognitive impairment than is cerebrovascular pathology (Reed et al., 2004b; Schneider et al., 2004; Chui et al., 2006) and thus we hypothesized that (v) mixed Alzheimer’s disease and cerebrovascular disease is associated with episodic memory impairments that are more severe than executive function deficits (similar to Alzheimer’s disease).

**Material and methods**

Subjects were selected from 92 consecutive autopsied cases from the Aging Brain project, a prospective, multi-site study of vascular contributions to dementia. The project enrolls subjects who are aged 55 years or older with evidence of small vessel cerebrovascular disease whose cognitive function falls between normal and mild dementia, as well as similar patients without vascular disease. Exclusion criteria include the diagnosis of a dementing illness other than Alzheimer’s disease or vascular dementia, history of major psychiatric illness, alcohol or substance abuse within the past 5 years or within the 5 years preceding onset of cognitive symptoms, significant head injury and unstable major medical conditions. Patients with imaging findings of cortical infarction at baseline are excluded from enrolment. Based on the neuropathological findings, those subjects who had significant non-Alzheimer’s or vascular neuropathology, such as Lewy bodies or severe cerebral amyloid angiopathy, were removed, as were patients missing neuropsychological test data, leaving a final sample of 62 cases.

All subjects underwent a uniform clinical evaluation consisting of a history and physical examination, laboratory tests appropriate for a dementia evaluation, neuropsychological testing and MRI studies of the brain. Clinical diagnosis was made at the local recruitment site by project clinicians using common diagnostic criteria. Clinical follow-up was attempted annually, and, when the patient was unable to return to clinic, basic information about clinical course and vascular events were obtained by telephone. Baseline evaluations were used for the present analyses, as those data were most complete and most representative of how patients might initially present. The lag from clinical evaluation to autopsy averaged 3.8 years and did not differ significantly between diagnostic groups. The research project was approved by the Institutional Review Boards at the University of Southern California, University of California Davis, VA Northern California Health Care System, University of California San Francisco and Rancho Los Amigos National Rehabilitation Center, Downey, California. Written informed consent was obtained following IRB-approved protocols.

**Neuropsychology**

Subjects received neuropsychological testing under a uniform protocol administered by psychometrists trained specifically in the project protocol. Test scores from the baseline evaluation were used in these analyses. The Mini Mental Status Examination (Folstein et al., 1975) and the Dementia Rating Scale (DRS) (Mattis, 1988) were used as standard clinical measures of global function. Profiles of domain-specific function were analysed using three composite scales, Verbal Memory, Executive Function and Nonverbal Memory. The development and characteristics of the first two scales has been previously described (Mungas et al., 2003). Nonverbal Memory, a new scale, was developed using the same methods and the same psychometric goals as were used for the other three. Briefly, item scores from a comprehensive neuropsychological test battery in a sample of 400 elderly persons who varied in cognitive status from cognitively normal to mildly demented served as the basis for scale development. Item response theory analytical methods (Hambleton et al., 1991) were used to create psychometrically matched scales. Within the item response theory framework, scales are matched when they demonstrate equivalent reliability (test information values) over a similar range of measured ability (theta). In the present case, the scales were constructed so as to have information values of about 14 over a −2.0 to +2.0 SD range of ability. In terms of classical test theory this translates to a reliability coefficient of 0.93 for each scale (Hambleton and Jones, 1993); it also means that the scales have linear measurement properties (an absence of floor or ceiling effects) over this broad range of cognitive function. Each scale was transformed so as to have a mean of 100 and a SD of 15. Donor items for Verbal Memory came from the Memory Assessment Scale (Williams, 1991) list learning task and emphasize delayed recall. Donor items for Executive Function consist of working memory and verbal fluency items and the Initiation—Perseveration subscale from the DRS, and Nonverbal Memory uses items from the Biber serial design learning test (Glosser, 1989).

Neuropsychological profiles that operationalize the concepts of predominant memory dysfunction and predominant executive dysfunction were defined using Verbal Memory, Nonverbal Memory and Executive Function. The probability that a difference between scores on two different scales is due to chance errors in measurement is a function of the reliability of each scale (Anastasi, 1988). Because scale reliabilities and standard deviations are matched, each of these scales has the same standard error of measurement, 3.97 points and the standard error of difference is 5.61 points. Thus, the probability is < 5% that a chance difference between scales’ scores will equal or exceed 11.00 points. Using this threshold, we defined three neuropsychological profiles: ‘Low Memory’ indicates that Verbal Memory or Nonverbal Memory was at least 11.0 points below Executive Function; ‘Low Executive’ means that Executive Function was at least 11.0 points below one the memory scales; ‘Other’ means that neither of these conditions applies and that Executive Function does not reliably differ from either memory scale.

**Neuropathology**

The neuropathology methods have been previously described (Vinters et al., 2000). After fixation in 10% neutral buffered formalin for at least 2 weeks, the brain was sectioned coronally at 5 mm using a rotary slicer and examined for macroscopic lesions. Tissue blocks were removed from representative regions, using a standardized blocking protocol. The protocol includes sections from anterior and posterior deep white matter, in addition to
sections recommended by the Consortium to Establish a Registry for Alzheimer Disease (CERAD) (Mirra et al., 1991), NIA and Reagan Institute Working Group (Hyman and Trojanowski, 1997), and the Consensus Conference on Dementia with Lewy bodies (McKeith et al., 1996). Tissue blocks were stained with haematoxylin–eosin, cresyl violet, Congo red and Bielschowsky silver. At the pathologist’s discretion, cases were also immunolabelled using primary antibodies against alpha-synuclein, ubiquitin, glial fibrillary acidic protein, phosphorylated tau and beta-amyloid. Each case was reviewed and rated at neuropathology consensus conference, which included two Board-certified neuropathologists (H.V.V., W.G.E.) who were blind to the clinical diagnoses.

The presence of the neuropathological lesions of Alzheimer’s disease were rated using standard methods and criteria: Braak and Braak stage (Braak and Braak, 1991) and CERAD plaque score (Mirra et al., 1991). These two scores were combined as recommended by the NIA-Reagan Institute criteria (Hyman and Trojanowski, 1997) to yield a likelihood rating of Alzheimer’s disease as either low, moderate or high. The severity of cerebrovascular ischaemic brain injury was rated using a scoring system developed in the course of this project. The total cerebrovascular parenchymal pathology score (CVDPS) (Vinters et al., 2000; Chui et al., 2006) reflects the extent of infarcts throughout the brain, including the hippocampus, subcortical grey nuclei, internal capsule, white matter, cortical grey matter, brainstem and cerebellum. Lacunar infarcts, microinfarcts and cystic infarcts are each counted separately in specified locations, and the count of each is normalized on a scale of 0–100. The 3 subscores are then summed to yield an overall score which has a mathematical maximum of 300. In practice, the project neuropathologists have judged 20 to be a score that reflects substantial ischaemic pathology. Acute strokes near the time of death were noted, but were not included in the CVDPS score. Hippocampal sclerosis (HS), defined as segmental neuronal dropout and gliosis in the pyramidal cell layer, was rated on a 0–3 scale.

**Results**

**Neuropathological classification of cases**

Subjects were categorized according to ratings of Alzheimer’s disease and ischaemic cerebrovascular pathology. Thus, cases were classified as pathology-defined Alzheimer’s disease when the likelihood of Alzheimer’s disease was ‘high’ or ‘moderate’ by NIA-Reagan Institute criteria unless the CVDPS score was 20 or higher in which case a diagnosis of Mixed pathology applied. Cases with a CVDPS score of 20 or greater were classified as cerebrovascular disease (CVD) when the NIA-Reagan Institute rating was ‘low’ likelihood of Alzheimer’s disease. Subjects with low CVDPS scores and low NIA-Reagan Institute ratings and an absence of any other significant pathology (e.g. hippocampal sclerosis, Lewy bodies) were classified as NEB. The resulting distribution of cases was 23 AD, 11 CVD, 9 Mixed and 19 NEB. Table 1 shows the demographic characteristics of these groups along with their CVDPS, Braak stage, and CERAD plaque scores. The groups did not differ in age or education but differed significantly, by design, on the neuropathology measures. Comparing overall severity is more complex. The three disease groups match rather closely in average on the omnibus cognitive measures DRS ($P > 0.6$), nor did the disease groups differ on the Mini Mental State ($P > 0.15$, means for AD, CVD, and Mixed $= 22.4, 24.4$ and 19.7, respectively), but considerable variability in severity is present in all groups. Cognitively normal cases were present in the AD and CVD groups (but not in Mixed), and both cognitively impaired and demented cases were present in NEB. Cognitively normal cases were proportionately more frequent in CVD (45%) than in AD (4%).

**Neuropathological correlates of neuropsychological scales**

Simple bivariate regressions were done regressing each cognitive score on Braak stage, CERAD score and CVDPS. Strong negative correlations were found between Braak stage and scores on Verbal Memory ($R^2 = 0.20, P < 0.0002$), Nonverbal Memory ($R^2 = 0.21, P < 0.0002$) and between CERAD score and Verbal Memory ($R^2 = 0.21, P < 0.0002$) and Nonverbal Memory ($R^2 = 0.25, P < 0.0001$). HS correlated modestly with the memory measures (Spearman rank order correlations for Verbal Memory $= -0.22, P < 0.09$; for Nonverbal Memory $= -0.32, P < 0.01$). CVDPS did not correlate with Verbal Memory or Nonverbal Memory ($P > 0.3$ for both variables). Executive Function did not correlate with any of the pathology variables.

**Group neuropsychological profiles**

In order to test the hypotheses that the neuropsychological profile in CVD is one of relatively greater executive

**Table 1** Demographics, neuropathology ratings and clinical severity measures in pathology-defined groups

<table>
<thead>
<tr>
<th>Group (N)</th>
<th>Age</th>
<th>Education</th>
<th>Sex m/f</th>
<th>Braak and Braak</th>
<th>CERAD N/S/M/F</th>
<th>CVDPS</th>
<th>Clinical syndrome</th>
<th>DRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD (23)</td>
<td>791 (78)</td>
<td>14.7 (3.2)</td>
<td>14:9</td>
<td>5.3 (0.8)</td>
<td>1/5/3/14</td>
<td>5.1 (6.1)</td>
<td>1/4/17</td>
<td>118.8 (17.5)</td>
</tr>
<tr>
<td>CVD (11)</td>
<td>76.7 (7.5)</td>
<td>15.4 (2.7)</td>
<td>7:4</td>
<td>1.4 (1.2)</td>
<td>7/4/0/0</td>
<td>78.2 (47.1)</td>
<td>5/1/5</td>
<td>119.3 (23.9)</td>
</tr>
<tr>
<td>Mixed (9)</td>
<td>794 (6.7)</td>
<td>14.4 (2.9)</td>
<td>5:4</td>
<td>5.1 (1.2)</td>
<td>0/1/4/4</td>
<td>579 (31.6)</td>
<td>0/0/9</td>
<td>112.1 (14.1)</td>
</tr>
<tr>
<td>NEB (19)</td>
<td>773 (75)</td>
<td>13.1 (3.3)</td>
<td>11:8</td>
<td>1.4 (1.2)</td>
<td>13/6/0/0</td>
<td>4.6 (6.6)</td>
<td>11/3/5</td>
<td>130.2 (19.0)</td>
</tr>
</tbody>
</table>

For clinical syndrome, CN = cognitively normal; MCI = mild cognitive impairment; D = dementia. These are clinical diagnoses, established at case conference based on all available information. CERAD refers to the CERAD senile plaque rating; N = none, S = sparse, M = moderate, F = frequent. DRS is the Mattis Dementia Rating Scale score.
dysfunction whereas in AD memory dysfunction is relatively greater, a repeated measures MANOVA was run using Verbal Memory, Nonverbal Memory and Executive Function as dependent measures. The main effect for group was significant \(F(3,55) = 7.5, P = 0.0003\) as were the main effect for scale \(F(2,51) = 9.0, P = 0.0005\) and the group \(\times\) scale interaction \(F(3,53) = 6.5, P = 0.0008\). The pattern of the interaction was partly consistent with the hypotheses, as can be seen in Fig. 1; Verbal Memory and Nonverbal Memory are lower than Executive Function for AD while, conversely, Executive Function is lower than Verbal Memory (although not Nonverbal Memory) in CVD. Average differences between Executive Function and the memory scales in AD were large, approximately 15 points (one SD) for each memory scale. However, differences were small in the CVD group where Executive Function averaged (one SD) for each memory scale. The population mean for each scale is 100 and the SD is 15.

**Individual neuropsychological profiles**

In order to examine individual patterns of memory and executive dysfunction three neuropsychological profiles were defined: Low Memory, Low Executive and Other (see Material and methods). Each subject was characterized by one of these three profiles. Groups defined by these profiles were closely matched on age and education and did not differ on overall severity of cognitive impairment as measured by the DRS total score.

Table 2 shows the distribution of individual neuropsychological profiles. Results for AD were broadly consistent with the hypothesis: most (71%) had the Low Memory profile while only 10% showed a Low Executive profile. In contrast, the distribution for CVD is less distinctive: although Low Memory described only 18% of cases and Low Executive is the most common profile, Low Executive described less than half (45%) and 36% of cases fit neither pattern. Low Executive was nearly as common in NEB (39%) as in CVD (45%). The Mixed cases had the essentially the same predominance of Low Memory profiles as did the AD cases (67%), and Low Executive was modestly more common (22%) than in AD (10%). Figure 2 plots the profiles of each individual CVD case, illustrating the substantial heterogeneity within this group.

Because differential diagnosis of dementia is only a clinical issue in patients who present with cognitive impairment, a subset of cases with MCI or dementia at the time of baseline examination was defined. Table 2 shows the distribution of neuropsychological profiles in these 41 cases (19 AD, 6 CVD, 9 Mixed, 7 NEB). This distribution is more distinctive than that obtained among all cases: in AD 79% had Low Memory versus 5% with Low Executive while in CVD 67% had Low Executive and none had Low Memory.

The diagnostic sensitivity of the Low Executive profile as a test for the presence of vascular cognitive impairment/vascular dementia can be calculated as its sensitivity for the pathological diagnosis CVD. So calculated (among patients with cognitive impairment or dementia only), the sensitivity is 0.67, (CI = 0.24 – 0.94) specificity is 0.86 (CI = 0.69 – 0.95) and the positive likelihood ratio is 4.7 (CI = 1.7–12.5).

**Neuropsychological profiles and neuropathological abnormalities**

A series of analyses compared Low Executive versus Low Memory cases on neuropathological measures of Alzheimer’s disease and cerebrovascular disease. Low Memory had higher Braak and Braak scores \((P < 0.01)\) and higher CERAD scores \((P = 0.002)\) but did not differ from Low Executive on CVDPS \((P > 0.3)\). The mean HS score was slightly higher for Low Memory cases but it did not differ significantly from those of other profiles. Perhaps more importantly, HS did not account for Low Memory profiles among the CVD cases. Of the five that had any degree of HS, including two with moderate or severe ratings, none had Low Memory profiles.

**Table 2 Distribution of neuropsychological test profiles within diagnostic groups**

<table>
<thead>
<tr>
<th>Group (N)</th>
<th>Low Memory profile</th>
<th>Low Executive profile</th>
<th>Other profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>All complete cases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AD (21)</td>
<td>71</td>
<td>10</td>
<td>19</td>
</tr>
<tr>
<td>CVD (11)</td>
<td>18</td>
<td>45</td>
<td>36</td>
</tr>
<tr>
<td>Mixed (9)</td>
<td>67</td>
<td>22</td>
<td>11</td>
</tr>
<tr>
<td>NEB (18)</td>
<td>33</td>
<td>39</td>
<td>28</td>
</tr>
<tr>
<td>Cases with clinical cognitive impairment or dementia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AD (19)</td>
<td>79</td>
<td>5</td>
<td>16</td>
</tr>
<tr>
<td>CVD (6)</td>
<td>0</td>
<td>67</td>
<td>33</td>
</tr>
<tr>
<td>Mixed (9)</td>
<td>67</td>
<td>22</td>
<td>11</td>
</tr>
<tr>
<td>NEB (7)</td>
<td>57</td>
<td>29</td>
<td>14</td>
</tr>
</tbody>
</table>

Tabled values are row percentages. Three cases lacked complete data and are omitted.
Discussion

This study evaluated the idea that the neuropathological changes of Alzheimer’s disease and subcortical cerebrovascular disease cause distinctive, dissociable patterns of neuropsychological impairment such that memory failure is predominant in Alzheimer’s disease, and executive dysfunction is predominant in subcortical cerebrovascular disease. This hypothesis was supported with respect to Alzheimer’s disease, as the data show moderate to strong associations between Alzheimer’s disease and predominant memory impairment. Pathologically defined cases of Alzheimer’s disease had verbal and non-verbal memory scores that averaged about 1 SD lower than their executive function scores, and classification of cases according to neuropsychological profiles revealed that predominant memory loss described 71% of cases. Likely reflecting the strong effects of Alzheimer’s disease pathology, Mixed cases were neuropsychologically similar to Alzheimer’s disease. A more complex pattern emerged with respect to cerebrovascular disease, in part because even relatively severe cerebrovascular disease at autopsy was often not associated with clinically significant cognitive impairment. Among all pathologically-defined cerebrovascular cases executive function scores averaged only 0.3 SD (and non-significantly) lower than the memory scales and the neuropsychological profile of predominant executive dysfunction described less than half of the cases. Additionally, CVDPs did not correlate with Executive Function, nor were CVDPs scores elevated in the Low Executive group. However, when cognitive impairment was present the neuropsychological profile of prominent executive dysfunction described two-thirds of cases. Because the number of cases with vascular dementia or cognitive impairment is small and this profile is also found in NEB and AD, its potential as a diagnostic marker is unproven.

The association between the Low Memory profile and Alzheimer’s disease pathology is supported by the strong correlations between each of the memory scales and pathological measures of Alzheimer’s disease. Even with an average lag of 3.8 years between the time of memory testing and the time of autopsy, correlations between memory tests and the extent of neurofibrillary tangles and neuritic plaques ranged from 0.45 to 0.50.

It is not likely that the modest association between vascular pathology and executive dysfunction is simply a measurement problem. Although the scale Executive Function is not widely known, it is psychometrically robust and has substantial, published validity data. Executive Function has been shown to be associated with metabolic activity in dorsolateral prefrontal cortex (Reed et al., 2004a), hypometabolism of dorsolateral prefrontal cortex predicts subsequent decline in Executive Function (Reed et al., 2005), Executive Function correlates with volume of lacunes, volume of thalamic lacunes, and volume of white matter lesions in cross sectional analyses, and longitudinal increases in lacunar volume and white matter lesions correlates with declining Executive Function (Mungas et al., 2001, 2005). Thus, although it is possible that a measure that incorporated other components of executive function might have yielded other results, this scale clearly taps important aspects of executive function, and has been shown to be associated with frontal lobe...
integrity. It is more likely that small vessel cerebrovascular disease, at least to the extent that we are currently capable of quantifying pathologically, does not have the same magnitude of impact on executive function as the changes of Alzheimer’s disease have on memory.

Consistent with this, we found little evidence that co-morbid cerebrovascular disease modifies the cognitive presentation of Alzheimer’s disease. The level of Alzheimer’s disease pathologies as graded by Braak staging and CERAD ratings was no different in the Mixed group than in the AD group. Even with the addition of ‘significant’ cerebrovascular pathology, the global impairment scores for the Mixed group were only slightly and non-significantly lower than those of the AD group. Additionally, the mean neuropsychological profiles of the Mixed and AD groups were virtually identical, as was the proportion of individual cases within each group that fit a Low Memory profile. Despite the addition of vascular pathology the Low Executive profile was only modestly more common in the Mixed than in the AD group. This suggests that once the pathology of Alzheimer’s disease extends to neocortex and Alzheimer’s disease is consequently considered diagnostically very likely (Hyman and Trojanowski, 1997), its effects are overwhelming and not much coloured by modest levels of CVD.

The extent to which executive dysfunction predominates in our subcortical cerebrovascular cases is at least as strong as what has been previously reported in the clinical literature, which is to say that the findings in that literature are not as strong as might be supposed. Although comparisons of clinically diagnosed Alzheimer’s disease and vascular dementia/cognitive impairment cases very consistently report greater memory impairment in Alzheimer’s disease and rather consistently report executive dysfunction in vascular cases (Mendez and Ashland-Mendez, 1991; Kertesz and Clydesdale, 1994; Lafosse et al., 1997; Lamar et al., 1997; Matsuda et al., 1998; Lukatela et al., 2000; Desmond, 2004; Graham et al., 2004), this does not logically require that executive abilities be worse than memory abilities in the vascular cases. It could equally well be that memory tends to be more impaired than executive function in mild and moderate Alzheimer’s disease, while in vascular dementia the two domains are relatively equally affected. In fact, the relatively few studies that report data in a manner that permit profiles to be constructed show variable evidence of a mild predominance of executive dysfunction in cerebrovascular disease. For example, a recent report comparing Alzheimer’s disease and vascular dementia on an extensive battery of neuropsychological tests (Graham et al., 2004) showed that of nine executive function measures, vascular dementia cases were worse on four but five did not differ between groups. Based on the most sensitive scales in the battery, the frequency of memory and executive impairments was very similar among the vascular cases (for memory 79% of cases; for executive 74% of cases). In another study that compared neuropsychological profiles in mild/moderate and severely demented vascular dementia groups (Paul et al., 2001) mean scores on the executive scale were no worse than those for the memory scale for either group. A third study that used composite neuropsychological scales to examine impairment in TIA/stroke patients (Sachdev et al., 2004) did find that executive function was the lowest scale overall and, compared with verbal memory, was about −1.0 Z score units lower on average. However, it was only about 0.25 Z lower than visual memory and the scales for working memory and attention, functions that are often lumped in the executive domain, were actually higher than visual memory. Finally, a study using verbal fluency as the executive function test found that fluency was worse than memory recall for the vascular cases, but that the average difference was less than half a standard deviation (Schmidtke and Hull, 2002). Thus, none of these clinical studies support the idea that subcortical cerebrovascular disease is consistently accompanied by predominant or severe executive impairment. Clouding the interpretation of these studies is the likelihood of undiagnosed Alzheimer’s disease in an unknown proportion of the patients.

Consideration of the pathology found in subcortical cerebrovascular disease suggests that episodic memory impairment will be commonly seen in subcortical cerebrovascular disease and that sometimes memory impairment will match or exceed executive dysfunction. Cerebrovascular disease may affect hippocampus and other medial temporal lobe structures (Vinters et al., 2000; Jellinger, 2005), causing a vascular ‘hippocampal sclerosis’ (Jellinger, 2005) with consequent memory failure. In addition, it is clear from experimental brain imaging studies that there are important contributions of frontal lobe regions to the episodic memory system (Buckner et al., 1996; Buckner et al., 2000; Fletcher and Henson, 2001; Bunge et al., 2004). It is likely that there are multiple mechanisms of clinical memory failure (Reed et al., 2000). The fact that hippocampal sclerosis, in our vascular series, did not produce predominant memory loss may only mean that other brain systems were compromised to similar degrees by the vascular pathology of those patients.

There are several major methodological strengths of the present study. The first is that pathology is verified by autopsy. We are not aware of any previous study characterizing the cognitive deficits of vascular dementia or vascular cognitive impairment in autopsy confirmed cases. Additionally, all cases were evaluated under a single neuropathology protocol that involved an extensive evaluation of vascular lesions, and all cases were reviewed by multiple neuropathologists who made cases ratings at consensus case conference. All clinical data were collected prospectively under a single protocol. The neuropsychological measures have several desirable psychometric features that ensure that differences on scales reflect differences on the underlying cognitive functions, free of test-induced artefact. The vascular and Alzheimer’s disease cases were well-matched demographically, and closely
matched on dementia severity as measured by the DRS, which assesses multiple cognitive domains including aspects of executive function. The fact that vascular cases were less likely to be diagnosed as demented even while scoring similarly to the Alzheimer’s disease cases on this omnibus measure perhaps reflects the central role of memory failure in daily function and the definition of dementia.

Several limitations should also be acknowledged. One is that generally only one hemisphere of the brain was examined neuropathologically (the other was frozen). This obviously introduces a degree of misestimation of the true extent of ischaemic lesions in these cases. The problem is likely to be one of random error rather than bias (systematic over- or under-estimation) as the CVDPS is a scaled measure and absolute levels of pathology are not relevant to the analyses we performed. We acknowledge that the definitions of neuropsychological profiles are to some extent arbitrary. The particular definitions we used have the advantages of being explicitly defined in terms of the reliability of the component scales, and of being based on scales that are psychometrically matched. A substantial limitation on the generalizability of the findings relates to the composition of the parent cohort. By design cases with cortical pathology were excluded. By circumstance the recruitment emphasized (although it was not entirely confined to) patients who presented for evaluation at university-based memory clinics, clinics that tend to be referred patients who clinically appear to have Alzheimer’s disease. These two factors together likely acted to filter out cases with more severe cerebrovascular disease, certainly excluded cases with overt cortical infarcts, and hence may have muted the cognitive impact of vascular lesions. The sample size for each of the groups, especially the cognitively impaired vascular group, is small and replication of these findings in other samples is highly desirable. It is particularly uncertain whether similar findings would emerge in patients with more clinically pronounced cerebrovascular disease (patients with stroke and TIA, for example). And, while the data do not reveal any clear relationship of the profiles to overall severity, numbers are small and such a relationship may exist. It may be, for example, that effects of vascular pathology are more pronounced in mild cognitive impairment than in normal or demented cases.

The present findings hint that the profile of neuropsychological impairment, particularly a pattern of predominant memory loss as a marker of Alzheimer’s disease, may prove to be a useful feature for differentiating pure vascular cases from those with co-morbid Alzheimer’s disease in MCI/dementia. However, the fact that the extent of ischaemic pathology does not correlate well with severity or pattern of neuropsychological impairments, and the wide confidence intervals around our estimates of sensitivity and specificity argue against incorporating the neuropsychological pattern as a diagnostic feature for vascular dementia or vascular cognitive impairment at this time.

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References


Cognitive profiles in autopsied vascular dementia


