Anosmia is very common in the Lewy body variant of Alzheimer’s disease

J M Olichney, C Murphy, C R Hofstetter, K Foster, L A Hansen, L J Thal, R Katzman

Background: Olfactory abnormalities are reported in Alzheimer’s disease and Parkinson’s disease. Anosmia appears to be common in dementia with Lewy bodies but not in pure Alzheimer’s disease. Objective: To determine whether anosmia improves discrimination between the Lewy body variant (LBV) of Alzheimer’s disease and “pure” Alzheimer’s disease.

Methods: 106 cases of necropsy confirmed pure Alzheimer’s disease (n = 89) or LBV (n = 17) were reviewed. All had received butanol odour threshold testing. Anosmia was defined as a score < 1.0 on a 0–9 point scale. Logistic regression analysis was used to model potential predictors (for example, parkinsonism, smoking, hallucinations) of neuropathological diagnosis and anosmia.

Results: LBV cases had an increased prevalence of anosmia (65%) compared with Alzheimer’s disease (23%; odds ratio (OR) = 6.3, p = 0.00045), or normal elderly people (6.7%). Within the dementia cases, the negative predictive value (92%) and specificity (78%) of anosmia were both good; sensitivity for detecting LBV was 65%, but the positive predictive value (PPV) was only 35%. Logistic regression models showed anosmia (OR = 5.4, p = 0.005) and visual hallucinations (OR = 7.3, p = 0.007) were strong independent predictors of Lewy body pathology. When anosmia was added as a core feature to consensus diagnostic criteria for probable Lewy body dementia, five additional cases of LBV were detected (29% increased sensitivity), but with four additional false positives (1% increased discrimination, 4% decreased specificity, 33% decreased PPV).

Conclusions: Anosmia is very common in LBV. Adding anosmia as a core feature improved sensitivity for detecting LBV, but did not improve discrimination between Alzheimer’s disease and LBV owing to a concomitant increase in false positives.
testing was generally carried out during either the mild or the moderate stage of the dementia. All selected cases met the CERAD neuropathological criteria for definite or probable Alzheimer’s disease, and the DSM-III R criteria for dementia. In addition, the LBV group had Lewy bodies present in the brain stem and cerebral cortex. Nearly all these cases satisfied NINCDS-ADRDA clinical criteria for either probable or possible Alzheimer’s disease at the time of olfactory testing. Cases with a clinical diagnosis of Parkinson’s disease with motor symptoms for more than 12 months before dementia onset were excluded, as recommended by the consensus clinical criteria for DLB. While cases with dementia and parkinsonism at entry into the ADRC were not excluded, all the LBV cases had a history of cognitive symptoms preceding any motor symptoms of parkinsonism. To reduce the neuropathological heterogeneity of our LBV group, we excluded cases (n = 3) with “pure” DLB (that is, symptoms preceding any motor symptoms of parkinsonism). 

Table 1: Demographic, clinical, and olfactory data for the patient groups

<table>
<thead>
<tr>
<th></th>
<th>LBV</th>
<th>AD</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>17</td>
<td>89</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>11M; 6F</td>
<td>51M; 38F</td>
<td>0.57</td>
</tr>
<tr>
<td>Age (years)</td>
<td>74.3 (5.7)</td>
<td>73.2 (8.3)</td>
<td>0.60</td>
</tr>
<tr>
<td>Education (years)</td>
<td>14.9 (2.6)</td>
<td>13.9 (3.5)</td>
<td>0.30</td>
</tr>
<tr>
<td>DRS</td>
<td>100.6 (20.4)</td>
<td>106.2 (21.8)</td>
<td>0.33</td>
</tr>
<tr>
<td>No of EPS</td>
<td>0.71 (1.16)</td>
<td>0.29 (0.81)</td>
<td>0.07</td>
</tr>
<tr>
<td>Current smoker</td>
<td>11.8%</td>
<td>11.9%</td>
<td>0.98</td>
</tr>
<tr>
<td>History of smoking</td>
<td>67.1%</td>
<td>68.7%</td>
<td>0.10</td>
</tr>
<tr>
<td>Anosmia</td>
<td>64.7% (11/17)</td>
<td>22.5% (20/89)</td>
<td>0.0004*</td>
</tr>
<tr>
<td>Odour threshold</td>
<td>1.79 (2.42)</td>
<td>4.10 (2.62)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Time interval (years), from testing to death</td>
<td>4.9 (3.3)</td>
<td>5.3 (2.8)</td>
<td>0.62</td>
</tr>
</tbody>
</table>

Values are mean (SD) or prevalence (%).

Table: *Two sided p < 0.05.

AD, Alzheimer’s disease; DRS, dementia rating scale; EPS, extrapyramidal signs; F, female; LBV, Lewy body variant; M, male.

Olfactory stimuli and test procedures
Olfactory testing was generally done within one week of the annual neuropsychological tests described above. The odorant n-butyl alcohol was prepared in a series of 10 dilutions beginning with a 4% solution (by volume) in deionised water. N-butyl alcohol is often used in olfactory threshold testing because it is a potent stimulus for the olfactory nerve at concentrations which have no impact on the trigeminal nerve. Each successive dilution was one third the concentration of the preceding dilution. The odour threshold for butanol was determined separately for each nostril, using a two alternative, forced choice task with ascending concentrations, modified as in Murphy et al. Each pair of stimuli consisted of a blank and an odour stimulus. The subject sniffed each stimulus and then chose which of the two smelled stronger. In order to minimise the effects of adaptation, testing progressed from weaker to stronger concentrations with approximately 90 seconds between trials. An incorrect choice led to an increased concentration on the next trial. Correct choices led to presentation of the same concentration, to a criterion of four correct choices in a row. Two threshold determinations were made for each subject, one for each nostril, using a 0 to 9 point scale. An average score of <1.0 was considered “anosmia.” This threshold was chosen because 4% butyl alcohol is often strong enough to be detected by the trigeminal pathway, but this is rarely the case for a 1.33% solution. The mean odour threshold for 150 normal elderly controls (mean age, 71.6 years) tested at our ADRC was 5.75 (SE = 1.7). The prevalence of anosmia was 6.67% in these normal elderly controls, using the same criteria.

Neuropathology
The full neuropathological procedures of our ADRC and CERAD have been published previously. All neuropathological measures were made blind to clinical diagnoses and to olfactory and cognitive test scores. Neuritic plaques were assessed on thioflavin-S or Bielschowsky silver stains of cerebral neocortex. All cases in this report had sufficient neuritic plaque density to meet CERAD criteria for probable or definite Alzheimer’s disease. Lewy bodies were detected by either antiubiquitin or haematoxylin and eosin (H&E) staining. In addition to satisfying CERAD criteria for probable or definite Alzheimer’s disease, the presence of one or more Lewy bodies in both the brain stem and cerebral cortex was required for the neuropathological diagnosis of LBV. In none of the LBV cases were Lewy bodies confined to only the amygdala or visible only with anti-synuclein labelling. Modified Braak staging was carried out on all cases, using procedures we have described previously.
and the intergroup comparison failed to reach statistical significance. For comparison, the three cases of “pure” DLB had a mean of 1.67 extrapyramidal signs at the time of olfactory testing. There was no significant difference in the smoking history of the two groups, although there was a trend toward more ex-smokers in the Alzheimer group (table 1).

Anosmia was very common in LBV, present in 64.7% of LBV cases compared with 22.5% in Alzheimer’s disease—a highly significant group difference ($\chi^2 = 12.3; p = 0.00045$). If we had included the three cases with “pure” DLB at necropsy in this report, the results would be nearly identical (two of three had anosmia, meaning that 68% of the total LBV/DLB sample had anosmia). The mean (SD) odour threshold score was 4.0 (2.6) in Alzheimer’s disease, but only 1.8 (2.4) in LBV ($t$ test, $p = 0.001$). The distributions for olfactory threshold in LBV and Alzheimer’s disease are shown in fig 1 (all scores are rounded to the nearest integer; therefore scores of 1.5 were combined with 2.0 for the histogram figure). There was a modest correlation between odour threshold and DRS score ($r = 0.20$, $p = 0.04$), which was somewhat stronger ($r = 0.48$) and of marginal significance ($p = 0.052$) within the LBV cases. Only 23% of cases with anosmia (7/31) had one or more extrapyramidal signs, which was not significantly different than the prevalence of extrapyramidal signs in cases without anosmia (16%; $\chi^2 = 0.65, p = 0.42$). The relatively low prevalence of extrapyramidal signs is entirely unexpected, because patients with a clinical diagnosis of Parkinson’s disease were excluded. Eighteen per cent of the entire cohort had at least one extrapyramidal sign. There also was no significant relation between anosmia and the number of extrapyramidal signs present ($\chi^2 = 1.76, p = 0.78$).

The odour threshold test, by itself, achieved 65% sensitivity and 78% specificity for LBV in our cohort (table 2, first row). While the negative predictive value (NPV) was high (92%), the positive predictive value (PPV) was only 35% (the pre-test probability of LBV was 16% in this sample). There was no significant relation between anosmia and the Alzheimer pathological stage in LBV. The proportion of cases with anosmia was 60% (3/5) for Braak stages I–II, 60% for stages III–IV, and 71% (5/7) for stages V–VI. When we required that only anosmia in non-smokers be considered a “pathological” risk factor for LBV, the sensitivity fell from 65% to 29% overall (5/17), but with improvements in specificity (92%), PPV, and overall discrimination (table 2: compare rows 1 and 2).

The consensus criteria for probable DLB (which requires the presence of two or more core features) had 100% specificity and PPV (3/3) in our cohort, but the NPV was less impressive (89/103), with low sensitivity (3/17). It should be kept in mind that this very low sensitivity partly reflects, first, that these criteria were applied when the patients were mostly in the mild stage of dementia; second, that our ADRC largely comprised referred patients with an Alzheimer’s disease-like phenotype; and third, that any cases diagnosed with Parkinson’s disease before dementia onset were excluded. Sensitivity would have been higher if we had taken the last clinical diagnosis before death, as is customary in cliniconeuropathological studies. Next, we tested the extent to which adding anosmia as a core feature might improve the diagnostic accuracy of established consensus criteria for the diagnosis of DLB. Adding anosmia resulted in the detection of five additional probable DLB cases, but at the cost of four additional false positive cases. While overall diagnostic accuracy was not significantly improved, sensitivity increased by 29%, with a fall in specificity of 4% (table 2, compare rows 4 and 5). The less stringent criteria for possible DLB resulted in somewhat improved sensitivity (9/17), but
lower overall discrimination (76%), specificity (81%), and PPV (35%). Adding anosmia as a core feature, sufficient for the diagnosis of possible DLB % (table 2, row 7), resulted in good sensitivity (76%) but mediocre specificity (63%), a low PPV (28%), and an overall diagnostic accuracy of only 65%. The highest diagnostic accuracy overall (90%) was achieved by adding anosmia in a non-smoker as a core feature to consensus criteria for probable DLB % (row 5 of table 2), which produced an excellent specificity (88/89), high PPV (7/8), but only mediocre sensitivity (7/17).

The logistic regressions modelling the neuropathological presence of Lewy bodies showed that only anosmia (odds ratio (OR) = 5.4 (95% confidence interval (CI), 1.67 to 30.12), p = 0.0049) and visual hallucinations (OR = 7.3 (1.71 to 31.08), p = 0.0072) were strong independent predictors for LBV. The number of parkinsonian signs, keeping in mind that cases with a clinical diagnosis of Parkinson’s disease were excluded, was not a significant independent predictor.

The regression models for anosmia showed three significant independent variables: neuropathological Lewy bodies (OR = 5.67 (95% CI, 1.75 to 18.09), p = 0.0035), low DRS score (OR = 0.98 (0.96–1.00), p = 0.049), and high education (OR = 1.24 (1.06–1.45), p = 0.0066). This relation between anosmia and higher education could reflect the fact that such individuals have a greater neuropathological burden by the time they become demented. When the time interval from olfactory testing to death was added as an independent variable, it remained in the model (B = −0.24 (95% CI, −0.42 to −0.05), p = 0.01) replacing DRS score. This is likely to reflect the co-linear relation present between DRS and survival (r = 0.33, p = 0.001).

The multiple linear regression models for odour threshold score showed that a shorter time interval before death (B = 0.31 (95% CI, 0.15 to 0.48), p = 0.0001), the presence of Lewy bodies (B = −2.07 (−3.35 to −0.79), p = 0.002), and high education (B = −0.12 (−0.26 to 0.01), p = 0.08) were all significant predictors of poorer (lower) odour threshold scores for the entire patient group.

Comparisons of the pure Alzheimer’s disease cases with anosmia versus those without by t test showed no intergroup difference in Braak stage (for example, mean neurofibrillary pathology stage = 5.50 vs 5.48; p = 0.95). Pure Alzheimer patients with anosmia tended to survive a shorter period than Alzheimer patients without anosmia (means: 4.02 vs 5.65 years; p = 0.019). Analogous t tests in LBV showed no significant differences in Braak stage (means: 3.82 vs 3.17; p = 0.49) or survival interval (means: 4.4 vs 5.9 years; p = 0.37) between those with anosmia (n = 10) and those without anosmia (n = 7). A trend for lower DRS scores in the anosmic LBV cases (94.3 (22.6) vs 112.3 (7.3) in those without anosmia) did not reach statistical significance (t = 1.88, p = 0.08), perhaps owing to the small sample size.

### DISCUSSION
Anosmia was a very common finding, present in nearly two thirds of our necropsy confirmed LBV cases. This is the second clinicopathological study we are aware of that has reported increased anosmia in dementia cases with Lewy bodies, and the first to quantify threshold with a rigorous psychophysical procedure that corrects for response bias. McShane et al reported that nine of their 22 dementia cases with Lewy bodies (41%) had anosmia, using a 1.7% lavender oil solution as their stimulus. Sixteen (73%) of their Lewy body cases also met CERAD criteria for probable or definite Alzheimer’s disease, and they found a similar prevalence of anosmia in pure DLB and in Lewy body cases with superimposed Alzheimer pathology (which we label as “Lewy body variant”). Using a butanol odour threshold test, we found 65% of LBV cases had anosmia. This suggests that anosmia is one of the most common clinical signs in LBV, a patient group which remains difficult to diagnose when only minimal extrapyramidal signs are present early in the disease course. In this regard, it should be noted, however, that anosmia appeared to be relatively independent of extrapyramidal signs in our dementia cohort which excluded cases with a clinical diagnosis of Parkinson’s disease (for example, there was no relation between anosmia and the number of extrapyramidal signs present). A limitation of the present study is that most patients did not receive the UPDRS at the time of olfactory testing. Thus patient examinations before 1993 may not have been as sensitive to mild extrapyramidal signs as are cut off scores of ≥2 on motor UPDRS items. Furthermore, we did not consider UPDRS scores of 1 as definite extrapyramidal signs as they are common in both Alzheimer’s disease and elderly normal control groups. Previous studies in Parkinson’s disease have also found that olfactory deficits appear to be independent of disease duration and the severity of extrapyramidal signs. Likewise, we found anosmia and visual hallucinations to be independent predictors of Lewy bodies. Thus adding anosmia to the established consensus diagnostic criteria is likely to increase sensitivity markedly, even in cohorts with relatively mild dementia.

### Table 2
Diagnostic accuracy of anosmia and other clinical criteria for the detection and discrimination of Lewy body variant cases

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity*</th>
<th>Specificity†</th>
<th>PPV</th>
<th>NPV</th>
<th>Discrimination (LBV v AD)</th>
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<tr>
<td>Anosmia</td>
<td>65 (11/17)</td>
<td>78 (69/89)</td>
<td>35  (11/31)</td>
<td>92 (69/75)</td>
<td>75 (80/106)</td>
</tr>
<tr>
<td>Anosmic non-smoker</td>
<td>29 (5/17)</td>
<td>92 (82/89)</td>
<td>42  (5/12)</td>
<td>87 (82/94)</td>
<td>82 (87/106)</td>
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<td>Consensus probable DLB</td>
<td>18 (3/17)</td>
<td>100 (89/89)</td>
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</tr>
<tr>
<td>Consensus possible DLB</td>
<td>53 (9/17)</td>
<td>81 (72/89)</td>
<td>35  (9/26)</td>
<td>90 (72/80)</td>
<td>76 (81/106)</td>
</tr>
<tr>
<td>Consensus possible DLB or anosmia</td>
<td>76 (13/17)</td>
<td>63 (56/89)</td>
<td>28 (13/46)</td>
<td>93 (56/60)</td>
<td>65 (69/106)</td>
</tr>
<tr>
<td>Consensus possible DLB or anosmic non-smoker</td>
<td>59 (10/17)</td>
<td>74 (66/89)</td>
<td>30 (10/33)</td>
<td>90 (66/73)</td>
<td>72 (76/106)</td>
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All values given are percentages with exact proportions in parentheses.

* Sensitivity to LBV cases.
† Specificity for non-LBV cases.
AD, Alzheimer’s disease; DLB, dementia with Lewy bodies; LBV, Lewy body variant; NPV, negative predictive value (absence of Lewy bodies); PPV, positive predictive value (presence of Lewy bodies).

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  AD, Alzheimer’s disease; DLB, dementia with Lewy bodies; LBV, Lewy body variant; NPV, negative predictive value (absence of Lewy bodies); PPV, positive predictive value (presence of Lewy bodies).

- Figure 1: Discrimination of Lewy body variant cases

  Discrimination (LBV v AD) = 5.65 (95% CI, 5.3 to 6.0), p = 0.001

  Sensitivity to LBV cases = 88/89 (97.8%), Specificity for non-LBV cases = 90/106 (85.7%), PPV = 85/94 (90.4%), NPV = 89/88 (99.1%).
Despite the high prevalence of anosmia in LBV, we did not find that this symptom in itself produced satisfactory discrimination between LBV and Alzheimer’s disease. When we added anosmia as a core feature to the consensus diagnostic criteria for probable DLB, we found—as did McShane et al.—an increase in sensitivity with a decreased specificity and little change in overall diagnostic accuracy. We were able to achieve the highest diagnostic accuracy when we only considered the finding of anosmia in those without a history of smoking as a core feature for the criteria for probable DLB. While these modified criteria had around 90% accuracy in discriminating between LBV and pure Alzheimer’s disease, and a good PPV (78%), the sensitivity was only modest (7/17). Overall, the accuracy was not significantly better than that of the established criteria for probable DLB (87%). These criteria are conservative and resulted in most of the LBV cases being classified as Alzheimer’s disease, but did achieve a PPV of 100%. Perhaps discrimination could be improved further by specialist evaluations to rule out other common medical aetiologies of anosmia in the elderly (for example, nasal disease, paranasal sinus disease, viral infection, trauma).28 29

An argument could well be made that unexplained anosmia might be more appropriate as a supportive feature than a core feature for DLB. It should be noted that for several purposes (for example, enrolling large samples of LBV patients for clinical drug trials; or if specific highly effective treatments are found for LBV), it could be advantageous to improve detection sensitivity, even at substantial loss of specificity. In this regard, we achieved the highest sensitivity (76%) when we added anosmia to the criteria for possible DLB, but at the cost of a low positive predictive value.

Caution is advised in applying these findings to other cohorts, such as those with Parkinson’s disease. Reliable data on sensitivity, specificity, and the positive and negative predictive value of a diagnostic tool can only be obtained in a cohort that is representative of the population in which it is to be used. Our ADRC is a referral centre for dementia cases, most of whom have an Alzheimer’s disease-like phenotype. If anosmia were used to discriminate LBV from our normal elderly, for example, 65% sensitivity and 93% specificity would be attained.

Regarding the underlying pathophysiology of anosmia in LBV, it seems likely that the Lewy body burden in areas such as the anterior olfactory nucleus, orbitofrontal, and anterior cingulate cortices could account for the increased anosmia in LBV. Neuropathological changes in the amygdala and entorhinal cortex are particularly severe in LBV, both of these regions often having spongiform neuropil vacuolisation.28 Braak et al showed that the anterior olfactory nucleus is one of the main predilection sites for α-synuclein pathology in the earliest stages of Parkinson’s disease.31 By the middle stages, Lewy body pathology begins to appear as well in the piriform, entorhinal, and other olfactory cortices. Anosmia in LBV is unlikely to be primarily a result of Alzheimer’s disease pathology. Specifically, neurofibrillary tangles are much less abundant and less widespread in LBV than in pure Alzheimer’s disease.32 As in the results of McShane et al., we found no relation between the Braak stage of Alzheimer pathology and anosmia in our LBV sample. However, McShane and colleagues did find that anosmia was related to higher cortical Lewy body scores and to greater Lewy body density in the cingulate gyrus.

While anosmia was not as common in Alzheimer’s disease as in LBV, hyposmia was quite common in Alzheimer’s disease (mean olfactory threshold 4.10 ± 5.75 in elderly controls). Several other studies have shown impaired odour threshold in Alzheimer’s disease using standard psychophysical measurements.2 23 33 Our analyses suggest that it was the fairly common finding of anosmia in Alzheimer’s disease that limited our ability to discriminate LBV from Alzheimer cases more accurately. Discrimination was improved somewhat by only considering anosmia in non-smokers to be a likely sign of a neurodegenerative disorder such as LBV or DLB. The 22.5% prevalence of anosmia in our Alzheimer cohort is in line with the 16% prevalence reported by McShane et al.4 It has been shown in a cohort with “questionable Alzheimer’s disease” (comparable to mild cognitive impairment)44 that smell identification tests are more sensitive to early Alzheimer pathology than are odour threshold tests.35 Not only is odour identification impaired in mild Alzheimer’s disease,35 36 but it has been recently shown to be reduced in carriers of the apolipoprotein E4 allele, who have an increased genetic risk of Alzheimer’s disease.37 Those at genetic risk show a decline in odour identification over time38 and those at risk for Alzheimer’s disease (because of mild cognitive impairment) and who have both impaired odour identification and an unawareness of their deficits are more apt to go on to develop the disease.39 Patients with LBV40 and diffuse Lewy body disease41 have also been reported to show impairments in odor identification. Odour identification was introduced at our ADRC subsequent to odour threshold and odour memory testing and thus is not available for many of the cases reported here. The lack of odour identification testing in all of our LBV cases is a limitation of the present study.

Some previous studies in Alzheimer cohorts have found that anosmic patients have somewhat greater disease severity than patients without anosmia.22 In the present study we also found a relation between anosmia and dementia severity, but the correlation was modest in the entire cohort, and driven mostly by the LBV group. Other previous studies of olfactory threshold in clinical Alzheimer cohorts, without neuropathological confirmation, have reported that both anosmia20 and a fast decline in olfactory sensitivity42 were associated with more rapid progression of dementia. It is unknown whether some of these patients may have had LBV or if anosmia in Alzheimer’s disease reflects more severe Alzheimer pathology in the olfactory cortices. Our present results favour the latter, in that Alzheimer cases with anosmia had shorter survival than cases without anosmia, and poor odour thresholds were associated with shorter survival in the entire (predominantly Alzheimer’s disease) cohort. Fully resolving this issue will require larger quantitative clinicopathological studies. Longitudinal characterisation of olfactory deficits (for example, anosmia, hyposmia, or olfactory naming deficits) may provide useful clinical measures for tracking disease progression in patients with mild Alzheimer’s disease with high education and premorbid intellectual abilities, factors that decrease the sensitivity of conventional neuropsychological tests.

Conclusions
The present study, although limited in sample size, suggests that anosmia may be one of the most common clinical findings in cases with necropsy confirmed LBV. While anosmia is fairly sensitive to LBV, it is also occasionally present in mild Alzheimer’s disease, which limits its predictive value in discriminating between these two disorders. The present study is limited by sample size, and further research of olfactory function in larger dementia cohorts with necropsy data appears warranted in an attempt to improve the detection of DLB. Diagnosing DLB during life is particularly challenging when there is significant comitant Alzheimer’s disease pathology.5 Anosmia deserves further consideration as a supportive feature or core feature to aid in the diagnosis of LBV or DLB.
ACKNOWLEDGEMENTS

Supported by grants from the National Institutes of Health (AG04085, AG08203, P50 AG05131, and AG08313) and the State of California ADCC. We wish to thank Brock Riggins and James Gatherswright for technical support, and the Department of Veteran’s Affairs.

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Competing interests: none declared

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