Affective behavioural disturbances in Alzheimer's disease and ischaemic vascular disease

Rita Hargrave, Laurie C Geck, Bruce Reed, Dan Mungas

Abstract

***Objectives*—To investigate affective change in Alzheimer's disease and ischaemic vascular disease and examine the contribution of white matter disease to psychopathology in these dementias. Based on earlier studies, it was predicted that: (1) depression would be more prevalent and severe in ischaemic vascular disease; (2) psychomotor slowing would be more prevalent in ischaemic vascular disease; (3) apathy would be more prevalent in ischaemic vascular disease; and (4) The degree of white matter disease would be positively correlated with the severity of psychomotor slowing.**

***Methods*—Ratings of affective/behavioural states and white matter disease were compared in 256 patients with Alzheimer's disease and 36 patients with ischaemic vascular disease or mixed dementia with an ischaemic vascular component using analysis of variance (ANOVA) and linear regression models.**

***Results*—The findings were: (1) decreased affect/withdrawal was more prevalent and severe in patients with ischaemic vascular disease and patients with white matter disease; (2) psychomotor slowing was more severe in patients with ischaemic vascular disease and patients with white matter disease; and (3) differences between Alzheimer's disease and ischaemic vascular dementia groups in the degree of psychomotor slowing were independent of the severity of white matter disease.**

***Conclusions*—Future studies using structural and functional neuroimaging techniques would be helpful for examining the relation between neurobiological factors and affective/behavioural disturbances in dementia.**

(*J Neurol Neurosurg Psychiatry* 2000;**68**:41–46)

Keywords: dementia; behavioural disturbances; white matter disease

Department of Psychiatry, University of California, Davis, CA, USA
R Hargrave

Department of Neurology
B Reed
D Mungas

Nashua Clinic of New Hampshire, NH, USA
L C Geck

Correspondence to:
Dr Rita Hargrave, 4338 Leach Street, Oakland, CA 94602, USA.

Received 13 May 1998 and in final form 10 June 1999
Accepted 23 June 1999

Recent studies suggest that behavioural disturbances in dementia may vary according to the aetiology of the dementia. Although the types of behavioural disturbances in Alzheimer's disease and ischaemic vascular disease are similar, there are substantial differences in the symptom profiles of these two types of dementia.[1–6] Behavioural disturbances in Alzheimer's disease commonly include anxiety, agitation, psychosis, and personality change.[1 7–10] Ischaemic vascular disease is often associated with irritability, apathy, and blunted affect.[10–12] Patients with ischaemic vascular disease have greater severity of depression and anxiety than patients with Alzheimer's disease.[13]

A comparative analysis of behavioural disturbances in Alzheimer's disease and ischaemic vascular disease may provide clues about the underlying pathophysiology of affective/behavioural change in dementia. White matter abnormalities are associated with dementia, cognitive impairment, and functional impairment.[14–19] Although white matter change may contribute to the development of affective/behavioural changes in dementia, few studies have specifically examined this association.

The purpose of our study was to investigate affective change in Alzheimer's disease and ischaemic vascular disease and to examine the contribution of white matter disease to psychopathology in these dementias. Previous studies have examined discrete affective/behavioural occurrences (for example, hallucinations). Our study focused on continuous, ongoing behaviour patterns that reflect more stable affective or arousal states (for example, depressed affect or agitation). We were interested in continuous affective changes for two reasons. Firstly, affective changes in dementia exert a significant impact on a patient's and caregiver's quality of life and social interactions.[20] Secondly, ongoing affective/behaviour patterns may be related to measurable pathophysiological changes in the brain (for example, white matter disease). We developed a new behavioural rating instrument that focuses specifically on affective changes that occur in dementia and provides more comprehensive assessment of affect than is possible with other, existing instruments. Based on earlier studies, we predicted that: (1) depression would be more prevalent and severe in ischaemic vascular disease; (2) psychomotor slowing would be more prevalent in ischaemic vascular disease; (3) apathy would be more prevalent in ischaemic vascular disease; and (4) the degree of white matter disease would be positively correlated with the severity of psychomotor slowing.

Methods

SUBJECTS

Subjects were patients evaluated at the UC Davis Alzheimer's Disease Center (UCD-ADC) after a uniform clinical evaluation protocol. All patients are evaluated by a team of neurologists, geriatricians, neuropsychologists, nurses, and social workers. Routine dementia evaluation laboratory tests, other clinically indicated laboratory tests, and a CT or MRI study of the brain are obtained for each patient. Clinical findings, test results, and imaging films

Table 1 Demographic characteristics of sample

Age:		Sex (n (%)):	
mean (SD)	75.6	Female	258 (68.3)
Range	43–102	Male	120 (31.7)
		Diagnostic syndrome (n (%)):	
Education (y):		Dementia	346 (91.5)
mean (SD)	12.4 (3.4)	Other cognitive impairment	22 (5.8)
range	0-20	No cognitive impairment	5 (1.3)
		Diagnosis deferred	5 (1.3)
MMSE:		Aetiology (n (%)):	
mean (SD)	18.7(6.7)	Possible Alzheimer's disease	54 (14.6)
range	0–30	Probable Alzheimer's disease	202 (54.7)
		Possible + probable ischaemic vascular disease	15 (4.1)
Ethnicity (n (%)):		Mixed Alzheimer's disease-ischaemic vascular disease	20 (5.4)
White	307 (81.2)	Mixed ischaemic vascular disease-Parkinson's	1 (0.3)
Black	31 (8.2)	Other dementia	77 (20.8)
Hispanic	22 (5.8)		
Asian	8 (2.1)		
Other	10 (2.6)		

are reviewed in a multidisciplinary case conference and a consensus diagnosis is established. National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) diagnostic criteria are used for possible and probable Alzheimer's disease and California ADDTC criteria are used for possible and probable ischaemic vascular disease.[21 22]

Patients evaluated between September 1992 and November 1995 were included in this study. All patients signed informed consent forms which had been approved by the local internal review boards. All patients (n=378) received initial clinical evaluations and ratings of affective states. Table 1 presents the demographic characteristics of the patients.

Thirty six patients had possible or probable ischaemic vascular disease (n=15) or had a mixed dementia with an ischaemic vascular component (n=21). Among patients with ischaemic vascular disease, 20 had subcortical infarcts: 14 had basal ganglia infarcts, 10 had centrum semiovale infarcts, five had thalamic infarcts, and two had brainstem infarcts. Seven patients had cortical infarcts: four in the posterior cerebral artery distribution, two in the middle cerebral artery distribution and one in the anterior cerebral artery distribution. Two patients had both subcortical and cortical infarcts.

Table 2 Interrater reliability and principal component loadings of affect ratings

Variable	*Interrater r**	*Comp 1*	*Comp 2*	*Comp 3*	*Comp 4*
Anhedonia	0.70	0.80	0.35		
Apathy	0.680	0.79			−0.31
Social withdrawal	0.74	0.72			
Depressed affect	0.78	0.64	0.46		−0.53
Decreased affect	0.62	0.58			
Decreased humour	0.63	0.58			−0.42
Decreased energy	0.77	0.54			−0.52
Agitation	0.76		0.87		
Irritability	0.84		0.82		
Labile affect	0.84		0.80		
Anxious affect	0.79	0.35	0.71		
Hyperactivity	0.60		0.60	0.39	
Sweet craving	0.85			0.78	
Inappropriate humour	0.74			0.66	
Slowed movement	0.83				−0.84
Slowed thinking	0.67				−0.74
Interrater r†		0.80	0.88	0.69	0.89

Loadings <0.30 are not tabled. Principal components analysis based on 378 cases.
*Spearman *r* coefficients based on 35 cases.
†Pearson correlation coefficients based on 35 cases.

VARIABLES

Ratings of affect

The affect ratings utilised in this study constitute one component of the standard evaluation protocol of the UCD ADC. Ratings of 16 variables representing affect and relatively continuous, ongoing behavioural patterns were obtained as part of the routine evaluation. The variables were: (1) depressed affect,(2) anhedonia, (3) decreased energy, (4) anxious affect, (5) irritability, (6) agitation, (7) labile affect, (8) apathy, (9) social withdrawal, (10) decreased affective expression, (11) decreased humour, (12) hyperactivity, (13) slowed movement, (14) inappropriate humour, (15) sweet craving, and (16) slowed thinking. Quantitative methods for rating these variables were developed. Detailed definitions of each variable were created so that raters could objectively distinguish characteristics that at times have subtle differences. Variables were then rated according to a five point scale: 0=the affective/behaviour disturbance in question is not present; 1=the affective/behaviour disturbance is present but intensity is of a very mild degree; 2=present with intensity of mild degree; 3=present with intensity of moderate degree; 4=present with intensity of extreme degree. The intensity of a variable was rated based on the degree to which most people would regard the affective state/behaviour pattern as unusual or abnormal and the degree to which the behaviour is responsive to environmental change.

Interrater reliability of ratings was empirically tested by having tape recorded interviews with caregivers of 35 patients independently rated by two raters. Spearman *r* coefficients were calculated to assess interrater reliability for each variable. These reliability coefficients are presented in table 2. The mean interrater *r* was 0.74 (SD 0.08). Principal components analysis of the 16 ratings, based on the overall sample of 378 participants, yielded four components accounting for 66.4% of total variance. Rotated component loadings are shown in table 2. These components seem to measure decreased affect/withdrawal (component 1), agitation/irritability (component 2), disinhibition (component 3), and psychomotor speed (component 4). Interrater reliability components for coefficients component scores are presented in table 2. These results demonstrate very acceptable levels of interrater reliability, particularly for measuring complex phenomena.

Clinical ratings were based on semistructured caregiver interviews and information from detailed behaviour questionnaires completed by the caregivers. Ratings referred to a 1 month period preceding the interview. Ratings were made by doctoral level professionals with formal training in the assessment process.

Ratings of white matter disease

Neuroimaging films of each patient were reviewed by a UCD ADC neurologist and quantitative ratings were made for selected variables. We were particularly interested in the degree of white matter abnormality in this

Table 3 Demographic characteristics of probable Alzheimer's disease and ischaemic vascular dementia groups

		Group	
Variable	*Parameter*	*Alzheimer's disease*	*Ischaemic vascular disease*
Age	mean (SD)	75.5 (8.0)	77.6 (7.5)
Education (y)	mean (SD)	12.2 (3.2)	12.3 (3.6)
MMSE	mean (SD)	18.4 (6.4)	18.7 (6.5)
Sex	% Female	76.4	69.4
	% Male	23.6	30.6

study. This variable was rated on a four point scale: 0=no white matter change beyond that expected on the basis of the patient's age; 1=mild white matter abnormality; 2=moderate abnormality; 3=severe abnormality. The same scale was used for rating CT images and MRI images. Interrater reliability was tested by having two neurologists independently rate films of 18 patients (10 MRI , 8 CT). The Spearman *r* coeffient comparing the two ratings of degree of white matter abnormality was 0.83, indicating good interrater agreement.

DATA ANALYSIS

JMP Statistical Discovery software was used for data analyses.[23] Data analyses considered three primary questions: (1) the relation of diagnosis (Alzheimer's disease *v* dementia with an ischaemic vascular component (ischaemic vascular disease)) to affect ratings; (2) the relation of white matter disease to affect; and (3) the interactive effects of diagnosis and white matter disease. For each analysis, a multivariate analysis of variance (MANOVA) was used in which component scores from each of the four principal components underlying the 16 affect ratings were dependent variables. These component scores are uncorrelated, linear combinations of the 16 affect ratings optimally weighted to provide a measure of each dimension, and the simple correlation of a given rating with a component score is equal to the loading of that rating on that component. The primary variable(s) of interest were included as independent variables. Sex, age, education, and mini mental state examination (MMSE) score were added as independent variables to control for effects of demographic variables and overall degree of dementia. *t* Tests were used to test for group differences in age, education, and MMSE scores. A χ^2 test was used to test for group differences in sex. If the overall multivariate effect for all four dependent variables was significant, then individual univariate analyses of variance (ANOVAs) were performed for each of the four component scores. Secondary analyses were performed to examine effects on the 16 individual affect ratings. Bonferroni correction methods were used to adjust the significance level for multiple comparisons (p=0.05/16=0.0031).

Results

AFFECT RATING DIFFERENCES BETWEEN ALZHEIMER'S DISEASE AND ISCHAEMIC VASCULAR DEMENTIA

The first step of data analysis involved comparing patients with probable Alzheimer's disease (n=195) with patients in the ischaemic vascular dementia group (n=36). Table 3 shows demographic characteristics of patients in these groups. Groups did not significantly differ in age, education, MMSE scores, or sex.

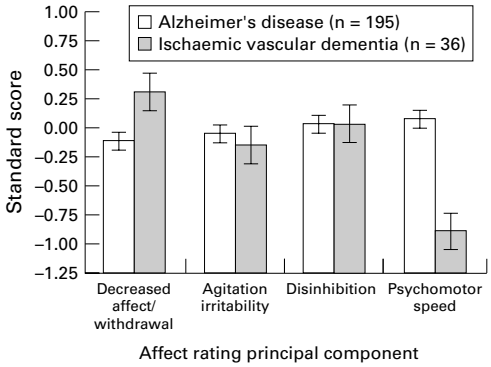

Figure 1 Means (SEM) on affect rating components for Alzheimer's disease and ischaemic vascular dementia groups. Values are expressed in standard score units with a mean of "0" and SD if "1" based upon the overall subject sample.

A MANOVA was performed on the four affect rating components comparing the probable Alzheimer's disease group with the ischaemic vascular disease group, controlling for effects of sex, age, education, and MMSE. The Alzheimer's disease-ischaemic vascular disease effect in the overall model was significant (F (4, 219)=9.6, p<0.001, Wilk's lambda=0.98), indicating that there was a statistically significant group difference for at least one of the four dependent variables. Figure 1 presents adjusted group means and standard errors of the mean for each dependent variable.

ANOVAs were then performed for each dependent variable using the same five independent variables (Alzheimer's disease-ischaemic vascular disease, sex, age, education, MMSE). Significant Alzheimer's disease-ischaemic vascular disease group differences were noted for component 1 (decreased affect/ withdrawal) (F=5.4; df=1, 222; p<0.03), with these characteristics present to a greater degree in in patients with ischaemic vascular dementia. Demographic variables and MMSE were not significantly related to this component. Component 4 (psychomotor speed) showed highly significant Alzheimer's disease-ischaemic vascular disease differences, (F=32.8; df=1, 222; p<0.001), with significantly slower psychomotor speed for the ischaemic vascular disease group. Sex (F(1, 222)=32.8 p<0.002; M female=-0.18, M male=-0.63) and MMSE (F=16.0; df=1, 222; p<0.001; r=0.26) effects were also significant. Alzheimer's disease-ischaemic vascular disease effects for the two other dependent variables were not significant.

Separate ANOVAs were performed using the 16 affect rating variables as dependent variables and including the five independent variables used in the above analyses. Bonferroni correction with a p value of 0.003 (0.05/16=0.0031) was used to control for the number of comparisons. Adjusted group means and standard errors for each variable, and significance levels of group differences are presented in table 4. Results are consistent with

Table 4 Means and p values for Alzheimer's disease-ischaemic vascular dementia comparisons

	Group mean (SEM)		
Variable	*Alzheimer's disease*	*Ischaemic vascular dementia*	*p Value*
Apathy	1.31 (0.10)	2.02 (0.20)	0.002
Anhedonia	1.09 (0.10)	1.71 (0.20)	0.005
Decreased affect	0.83 (0.08)	1.46 (0.18)	0.002
Social withdrawal	1.28 (0.10)	1.93 (0.20)	0.003
Decreased energy	1.47 (0.10)	2.47 (0.21)	0.001
Decreased humour	0.61 (0.08)	1.07 (0.16)	0.009
Slowed movement	1.06 (0.09)	2.26 (0.19)	0.001
Slowed thinking	1.69 (0.09)	2.48 (0.19)	0.001
Depressed affect	1.03 (0.09)	1.15 (0.18)	0.53
Agitation	1.00 (0.10)	1.09 (0.19)	0.66
Irritability	1.31 (0.10)	1.53 (0.20)	0.31
Labile affect	0.87 (0.10)	0.96 (0.20)	0.66
Anxious affect	1.39 (0.09)	1.03 (0.19)	0.08
Hyperactivity	0.83 (0.09)	0.89 (0.19)	0.76
Sweet craving	1.02 (0.10)	1.20 (0.21)	0.41
Inappropriate humour	0.23 (0.05)	0.32 (0.11)	0.43

previous results. Several variables with loadings of 0.50 or greater on component 1 (decreased affect/withdrawal) and all variables defining component 4 (psychomotor speed) showed significant group differences. The ischaemic vascular disease group consistently showed higher scores on these ratings. None of the variables on the agitation/irritability or the disinhibition components differentiated the two groups. The depressed affect rating, which loaded on both component 1(decreased affect/withdrawal) and component 2 (agitation/irritability) components, clearly did not significantly differ across groups.

RELATION OF AFFECT RATINGS AND WHITE MATTER CHANGES

The next phase of data analysis examined the relation of affect ratings to semiquantitative ratings from neuroimaging depicting varying degrees of white matter disease. All subjects with neuroimaging data were included in these analyses. Analyses were similar to those used to compare diagnostic groups. Firstly, a multivariate general linear model was used in which the four component scores were dependent variables. White matter disease was the primary independent variable, and sex, age, education, and MMSE were also included as secondary independent variables. The overall white matter disease effect was significant, ($F(4,275)=3.6$; $p<0.008$ Wilk's lambda=0.95), so individual ANOVAs were performed with each of the four component scores. Figure 2 shows the relation between white matter disease ratings and component scores. Component score means were calculated for patients with white matter disease ratings of 0, 1, 2, and 3 and these means and standard errors are presented in fig 2.

Analyses were performed using each affect rating as a dependent variable and white matter disease, sex, age, education, and MMSE as independent variables. Significant white matter disease effects were found for decreased energy ($p<0.001$), slowed movement ($p<0.002$), and apathy ($p<0.003$). Consistent with Alzheimer's disease-ischaemic vascular disease analyses, individual variables from the decreased affect/withdrawal and psychomotor speed components were significantly influenced by degree of white matter disease. Variables from agitation/irritability and disinhibition components were not significantly related.

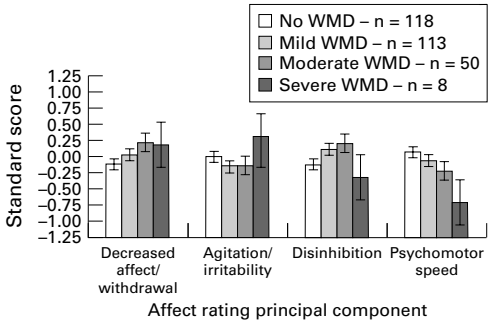

Figure 2 Means and standard errors of means of affect rating principal components across categories of white matter disease (WMD). Values are expressed in standard score units with a mean of "0" and standard deviation if "1" based upon the overall subject sample.

INTERACTIVE EFFECTS OF DIAGNOSIS AND WHITE MATTER DISEASE ON AFFECT

A final group of analyses was performed to determine if Alzheimer's disease-ischaemic vascular disease and white matter disease have independent and interactive effects on affect. These analyses were performed using scores from component 1 (decreased affect/withdrawal) and component 4 (psychomotor speed) because these two components were both related to Alzheimer's disease-ischaemic vascular disease and white matter disease. Patients with neuroimaging data who had either the diagnosis of probable Alzheimer's disease (n=153) or an ischaemic vascular disease component to their dementia (n=30) were used for these analyses. Patients were divided into two groups based on white matter disease ratings: (1) those with a score of 0 or 1 (no to mild white matter disease; Alzheimer's disease n=137, ischaemic vascular disease n=14), and (2) those with a score of 2 or 3 (moderate to severe white matter disease; Alzheimer's disease n=16, ischaemic vascular disease n=16). None of the patients with Alzheimer's disease had severe white matter disease. Each of the two component scores was entered as a dependent variable. Independent variables were the Alzheimer's disease-ischaemic vascular disease main effect, the white matter disease group main effect, the Alzheimer's disease-ischaemic vascular disease by white matter disease group interaction effect, and covariates sex, age, education, and MMSE. Adjusted group means and standard errors of the decreased affect/withdrawal and psychomotor speed component scores are presented in figs 3 and 4.

The Alzheimer's disease-ischaemic vascular disease ($F(1, 172)=1.7$, $p<0.20$) and white matter disease group ($F(1, 172)=1.7$, $p<0.18$) main effects and their interaction ($F<1.0$) were not significant for the decreased affect/withdrawal component. The lack of significance for either main effect is noteworthy because both Alzheimer's disease-ischaemic vascular disease and white matter disease change were related to this component in

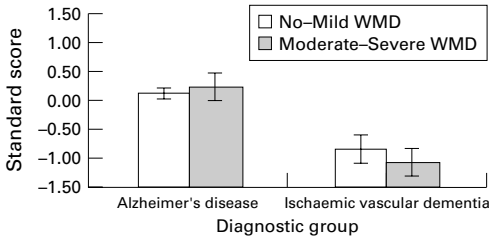

Figure 3 Means and standard errors of means on the decreased affect/withdrawal component for groups defined by degree of white matter disease (no WMD or mild WMD versus moderate or severe WMD). Values are expressed in standard score units with a mean of "0" and standard deviation if "1" based upon the overall subject sample.

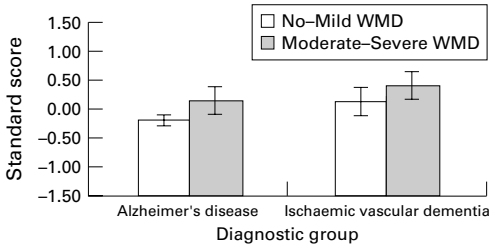

Figure 4 Means and standard errors of means on the psychomotor slowing component for groups defined by degree of white matter disease (no WMD or mild WMD versus moderate or severe WMD. Values are expressed in standard score units with a mean of "0" and standard deviation if "1" based upon the overall subject sample.

previous analyses. This difference in results is likely due to removal from each of the main effects of shared variance that is related to the dependent variable, thereby weakening the relation of both independent variables with the dependent variable. Results show the same general trend in which white matter disease corresponds to higher scores on this component (fig 3) but the degree of group differences failed to reach statistical significance.

For psychomotor speed, the Alzheimer's disease-ischaemic vascular disease main effect was significant ($F(1,172)=28.6$, $p<0.001$), but the white matter disease group main effect and the interaction effect were not significant (Fs<1.0). These results indicate that there are very striking Alzheimer's disease-ischaemic vascular disease differences in psychomotor speed that are independent of degree of white matter disease. Conversely, white matter disease effects previously found were likely related to confounding effects of Alzheimer's disease-ischaemic vascular disease on the white matter disease variable.

Discussion

Our study provides additional information on psychopathology in dementia and the influence of vascular disease on affective states/behavioural changes in Alzheimer's disease and ischaemic vascular disease. There were three main findings: (1) decreased affect/withdrawal was more prevalent and severe in patients with ischaemic vascular disease and in patients with white matter disease; (2) psychomotor slowing was more prevalent among patients with ischaemic vascular disease and patients with white matter disease; and (3) the degree of psychomotor slowing in ischaemic vascular disease was independent of the severity of white matter change. Secondary findings were: (1) psychomotor slowing was more severe in men than women and (2) psychomotor slowing was associated with lower MMSE scores in both Alzheimer's disease and ischaemic vascular disease.

The findings of higher scores on component 1 (decreased affect/withdrawal) among patients with ischaemic vascular disease supports our original hypotheses about depression and apathy and has been reported by other investigators.[11 12 21 22] Greater prevalence of decreased affect/withdrawal in patients with white matter disease is consistent with earlier studies of dementia and strokes.[11 12 21 22] Our data show a quantitative relation between degree of white matter disease and severity of apathy, decreased affect, and social withdrawal. A direct quantitative relation of this nature has not been previously reported in the literature. Higher prevalence of psychomotor slowing among patients with ischaemic vascular disease and patients with white matter disease is consistent with earlier studies.[11 21 24] Although the specific pathophysiology of apathy, depression, or psychomotor slowing is unknown, recent studies suggest that these symptoms may be due to pathological changes in the frontal-subcortical pathways and frontal lobe perfusion deficits and dysfunction of dopaminergic, serotonergic, and noradrenergic neurotransmission.[11 21 24–32]

Greater psychomotor slowing in ischaemic vascular disease than in Alzheimer's disease independent of the severity of white matter was an unexpected finding. The absence of a positive correlation between the severity of psychomotor slowing and degree of white matter disease has not been previously reported. Our results suggest that additional neuroanatomical and neurochemical factors beyond severity of white matter disease may contribute to greater psychomotor slowing in ischaemic vascular disease. For example, effects of discrete infarcts in specific subcortical structures may be more important than white matter changes in producing psychomotor slowing. Our sample of patients with ischaemic vascular disease was not large enough to examine the correlation of psychomotor slowing with infarcts in specific structures.

Greater psychomotor slowing among men than women has not been previously reported. Sex differences in psychomotor slowing persisted even after adjustments for age, education, and MMSE scores. Previous studies of sex differences in Alzheimer's disease have yielded conflicting results. Some investigators have reported sex differences in cognitive deficits, mood disorders, behavioural disorders, and brain metabolism.[33–36] Other studies report no consistent sex differences in the clinical presentation of Alzheimer's disease.[37 38]

Future research is needed to validate our results and examine the contribution of additional demographic and neurobiological factors to the pathophysiology of affective states/behavioural disturbances in dementia. Future research could consider issues such as (1) the relation between infarct location and

the progression of affective change in dementia and (2) the relation between infarct location and severity of psychomotor slowing in ischaemic vascular disease. Studies utilising functional imaging techniques such as PET might be valuable for relating affect patterns and changes to function of specific cortical and subcortical structures.

This work was performed at the University of California, Davis Alzheimer's Disease Center at 1771 Stockton Blvd, Suite 2005, Sacramento, California 95816.This study was supported in part by grants AG10220 and AG10129 and AG12435 from the National Institute on Aging, Bethesda, MD, and by the California Department of Health Services Alzheimer's Disease Program, contracts 91–13044 and 91–13045.

1 Cummings JL, Mega M, Gray K, *et al*. The neuropsychiatric inventory: comprehensive assessment of psychopathology in dementia. *Neurology* 1994;**44**:2308–14.
2 Marin RS, Biedrzycki RC, Firinciogullari S. Reliability and validity of the apathy evaluation scale. *Psychiatric Research* 1991;**38**:143–62.
3 Cohen D, Eisdorfer C, Gorelick P, *et al*. Psychopathology associated with Alzheimer's disease and related disorders. *J Gerontol* 1993;**48**:M255–60.
4 Dian L, Cummings JL, Petry S, Hill S. Personality alterations in multi-infarct dementia. *Psychosomatics* 1990; **31**:415–19.
5 Swearer JM, Drachman DA, O'Donell BF. Troublesome and disruptive behaviors in dementia: relationships to diagnosis and disease severity. *J Am Geriatr Soc* 1988;**36**:784–90.
6 Bucht G, Adolfsson R, Winbald B. The comprehensive psychopathological rating in patients with dementia of the Alzheimer type and multi-infarct dementia. *Acta Psychiatr Scand* 1983;**68**:263–70.
7 Tariot PN, Mack JL, Patterson MB, *et al*. The behavioral symptoms rating scale for dementia of the consortium to establish a registry for Alzheimer's disease. *Am J Psychiatry* 1995;**152**:1349–57.
8 Deutsch LH, Rovner BW. Agitation and other noncognitive abnormalities in Alzheimer's disease. In: Davidson M, ed. *Psychiatr Clin North Am* 1991:341–51.
9 Petry S, Cummings JL, Hill MA, *et al*. Personality alterations in dementia of the Alzheimer type. *Arch Neurol* 1988;**45**:1187–90.
10 Cummings JL, Petry S, Dian L, *et al*. Organic personality disorder in dementia syndromes: an inventory approach. *J Neuropsychiatry Clin Neurosci* 1990;**2**:261–7.
11 Sultzer DL, Levin HS, Mahler ME, *et al*. Assessment of cognitive, psychiatric and behavioral disturbances in patients with dementia: the neurobehavioral rating scale. *J Am Geriatr Soc* 1992;**40**:549–55.
12 Krasuski JS, Gaviria M. Neuropsychiatric sequelae of ischemic cerebrovascular disease: clinical and neuroanatomic correlates and implications for the concept of dementia. *Neurol Res* 1994;**16**:241–250.
13 Sultzer DL, Levin HS, Mahler ME. A comparison of psychiatric symptoms in vascular dementia and Alzheimer's disease. *Am J Psychiatry* 1993;**150**:1806–12
14 Leys D, Soetaert G, Petit H, *et al*. Periventricular and white matter magnetic resonance imaging hyperintensities do not differ between Alzheimer's disease and normal aging. *Arch Neurol* 1990;**47**:524–7.
15 Kertesz A, Polk M, Carr T. Cognition and white matter changes on magnetic resonance imaging in dementia. *Arch Neurol* 1990;**47**:387–91.
16 Harrell LE, Duvall E, Folks DG, *et al*. The relationship of high-intensity signals on magnetic resonance images to cognitive and psychiatric state in Alzheimer's disease. *Arch Neurol* 1991;**48**:1136–40.
17 Erkinjuntti T, Benavente O, Eliasziw M, *et al*. Diffuse vacuolization(spongiosis) and arteriosclerosis in the fronal matter occurs in vascular dementia. *Arch Neurol* 1996;**53**:325–32.
18 Ishijima M, Imazu O, Kitamura S, *et al*. Clinico-pathological evaluation of leukoariosis in Alzheimer's disease. *Japanese Journal of Geriatrics* 1996;**33**:744–53.
19 Teri L, Rabins P, Whitehouse P, *et al*. Management of behavior disturbance in Alzheimer disease: current knowledge and future directions. *Alzheimer Dis Assoc Disord* 1992;**6**:77–88.
20 McKhann G, Drachman D, Folstein M. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. *Neurology* 1984;**34**:939–43.
21 Chui HC, Victoroff JI, Margolin D, *et al*. Criteria of the diagnosis of ischemic vascular dementia proposed by the State of California Alzheimer's disease diagnostic and treatment centers. *Neurology* 1992;**42**:473–80.
22 Gupta SR, Naheedy MH, Young JC, *et al*. Periventricular white matter changes and dementia. *Arch Neurol* 1988;**45**: 637–41.
23 SAS Institute. *JMP statistical discovery software, version 3.1*. Cary, NC: SAS Institute, 1995.
24 Starkstein SE, Robinson RG, Honig MA. Mood changes after right hemisphere lesion. *Br J Psychiatry* 1989;**45**:725–30.
25 Brown FW, Lewine RJ, Hudgins PA, *et al*. White matter hyperintensity signals in psychiatric and nonpsychiatric subjects. *Am J Psychiatry* 1992:**149**;620–5.
26 Wolfe N, Linn R, Babikian VL, *et al*. Frontal systems impairment following multiple lacunar infarcts. *Arch Neurol* 1990;**47**:1045–59.
27 Gainotti G. Emotional behavior and hemispheric side of the lesion. *Cortex* 1972;**8**:41–55.
28 Robinson RG, Kubos KL, Starr LB. Mood disorders in stroke patients: Importance of location of lesion. *Brain* 1984;**107**:81–93.
29 Sinyor D, Jacques P, Kaloupek DG. Poststroke depression and lesion location: an attempted replication. *Brain* 1986;**109**:537–46.
30 Galaynker II, Roane DM, Miner CR, *et al*. Negative symptoms in patients with Alzheimer's disease. *American Journal of Geriatric Psychiatry* 1995;**3**:52–9.
31 Ebmeirer L, Glabus MF, Prentice N, *et al*. A voxel based analysis of cerebral perfusion in dementia and depression old age. *Neuroimage* 1998;7:199–208
32 Starkstein SE, Sabe L, Vazqueez S, *et al*. Neuropsychological, psychiatric and cerebral perfusion correlates of leukoaraiosis. *J Neurol Neurosurg Psychiatry* 1997:**63**:66–73
33 Buckwalter JG, Sobel E, Dunn ME, *et al*. Gender differences on a brief measure of cognitive functioning in Alzheimer's disease. *Arch Neurol* 1993;**50**:757–60.
34 Cohen D, Eisendorf C, Gorelick P, *et al*. Sex differences in the psychiatric manifestations of Alzheimer's disease. *Journal of American Geriatric Society* 1996;**41**:229–32.
35 Cooper JK, Mungas D, Weiler PG. Relation of cognitive status and abnormal behaviors in Alzheimer's disease *Journal of American Geriatric Society* 1990;**38**:867–70.
36 Teri L, Borsen S, Kiyak HA. Behavioral disturbance, cognitive dysfunction and functional skill. *Journal of American Geriatric Society* 1989;**37**:109–17.
37 Paolo AM, Troster A, Glatt SL, *et al*. Influence of demographic variables in the dementia rating scale. *J Geriatr Psychiatry Neurol* 1995;**8**:38–41.
38 Eisendorfer C, Cohen D, Paveza G. An empirical evaluation of the global deterioration scale for scaling Alzheimer's disease. *Am J Psychiatry* 1988;**149**:1–6.
39 Wragg RE, Jeste DV. Neuroleptics and alternatives: management of behavioral symptoms and psychosis in Alzheimer's disease and related conditions. *Psychiatr Clin North Am* 1988;**11**:185–213.
40 Kitagaki H, Mori E, Hirono N, *et al*. Alteration of white matter MR signal intensity in fronto temporal dementia. *AJNR Am J Neuroradiol* 1997;**18**:367–78.