Affective behavioural disturbances in Alzheimer's disease and ischaemic vascular disease
Rita Hargrave, Laurie C Geck, Bruce Reed and Dan Mungas

doi:10.1136/jnnp.68.1.41

Updated information and services can be found at:
http://jnnp.bmjjournals.com/cgi/content/full/68/1/41

These include:

References
This article cites 38 articles, 17 of which can be accessed free at:
http://jnnp.bmjjournals.com/cgi/content/full/68/1/41#BIBL

2 online articles that cite this article can be accessed at:
http://jnnp.bmjjournals.com/cgi/content/full/68/1/41#otherarticles

Rapid responses
You can respond to this article at:
http://jnnp.bmjjournals.com/cgi/eletter-submit/68/1/41

Email alerting service
Receive free email alerts when new articles cite this article - sign up in the box at the top right corner of the article

Topic collections
Articles on similar topics can be found in the following collections

Other Neurology (3509 articles)
Other Psychiatry (815 articles)
Dementia (487 articles)

Notes

To order reprints of this article go to:
http://www.bmjjournals.com/cgi/reprintform

To subscribe to Journal of Neurology, Neurosurgery, and Psychiatry go to:
http://www.bmjjournals.com/subscriptions/
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

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.

Patients with ischaemic vascular disease have greater severity of depression and anxiety than patients with Alzheimer’s disease. 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. 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. Secondly, ongoing affective/behavioural 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

<table>
<thead>
<tr>
<th>Age:</th>
<th>Sex (n (%))</th>
<th>Male</th>
<th>Female</th>
<th>Total (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD):</td>
<td>75.6</td>
<td>73.6</td>
<td>74.4</td>
<td>258 (68.3)</td>
</tr>
<tr>
<td>Range</td>
<td>43–102</td>
<td>52–102</td>
<td>43–102</td>
<td>120 (31.7)</td>
</tr>
</tbody>
</table>

Diagnostic syndrome (n (%)):
- Dementia: 346 (91.5)
- Other cognitive impairment: 22 (5.8)
- No cognitive impairment: 5 (1.3)
- Diagnosis deferred: 5 (1.3)

MMSE:
- Mean (SD): 18.7 ± 6.7
- Range: 0–30

Ethnicity (n (%)):
- White: 307 (81.2)
- Black: 31 (8.2)
- Hispanic: 22 (5.8)
- Asian: 8 (2.1)
- Other: 10 (2.6)

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) anxiety, (3) decreased energy, (4) anxious affect, (5) irritability, (6) agitation, (7) labile affect, (8) apathy, (9) social withdrawal, (10) decreased affective expression, (11) decreased humoured, (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 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 for each variable. The variables were then rated utilizing in this study constituting 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) anxiety, (3) decreased energy, (4) anxious affect, (5) irritability, (6) agitation, (7) labile affect, (8) apathy, (9) social withdrawal, (10) decreased affective expression, (11) decreased humoured, (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 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 for each variable. The variables were then rated utilizing in this study constituting 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) anxiety, (3) decreased energy, (4) anxious affect, (5) irritability, (6) agitation, (7) labile affect, (8) apathy, (9) social withdrawal, (10) decreased affective expression, (11) decreased humoured, (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 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.
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 coefficient 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 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. r Tests were used to test for group differences in age, education, and MMSE scores. A χ² 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 differences in 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.

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 interaction 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.

ANOVA 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=-0.26, 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
Affective changes in dementia

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Alzheimer’s disease</th>
<th>Ischaemic vascular dementia</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apathy</td>
<td>1.09 (0.10)</td>
<td>1.71 (0.20)</td>
<td>0.005</td>
</tr>
<tr>
<td>Anhedonia</td>
<td>1.09 (0.10)</td>
<td>1.46 (0.18)</td>
<td>0.002</td>
</tr>
<tr>
<td>Decreased affect</td>
<td>1.28 (0.10)</td>
<td>1.93 (0.20)</td>
<td>0.003</td>
</tr>
<tr>
<td>Social withdrawal</td>
<td>1.47 (0.10)</td>
<td>2.47 (0.21)</td>
<td>0.001</td>
</tr>
<tr>
<td>Decreased energy</td>
<td>0.61 (0.08)</td>
<td>1.07 (0.16)</td>
<td>0.009</td>
</tr>
<tr>
<td>Decreased humour</td>
<td>1.06 (0.09)</td>
<td>2.26 (0.19)</td>
<td>0.001</td>
</tr>
<tr>
<td>Slowed thinking</td>
<td>1.69 (0.09)</td>
<td>2.48 (0.19)</td>
<td>0.001</td>
</tr>
<tr>
<td>Depressed affect</td>
<td>1.03 (0.09)</td>
<td>1.15 (0.18)</td>
<td>0.53</td>
</tr>
<tr>
<td>Hyperactivity</td>
<td>1.31 (0.10)</td>
<td>1.99 (0.19)</td>
<td>0.06</td>
</tr>
<tr>
<td>Irritability</td>
<td>1.31 (0.10)</td>
<td>1.53 (0.20)</td>
<td>0.31</td>
</tr>
<tr>
<td>Labile affect</td>
<td>0.87 (0.10)</td>
<td>0.96 (0.20)</td>
<td>0.66</td>
</tr>
<tr>
<td>Anxious affect</td>
<td>1.39 (0.09)</td>
<td>1.03 (0.19)</td>
<td>0.08</td>
</tr>
<tr>
<td>Hyperactivity</td>
<td>0.83 (0.09)</td>
<td>0.89 (0.19)</td>
<td>0.76</td>
</tr>
<tr>
<td>Sweet craving</td>
<td>1.02 (0.10)</td>
<td>1.20 (0.21)</td>
<td>0.41</td>
</tr>
<tr>
<td>Inappropriate humour</td>
<td>0.23 (0.05)</td>
<td>0.32 (0.11)</td>
<td>0.43</td>
</tr>
</tbody>
</table>

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.

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<0.001) had no significant 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
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. Greater prevalence of decreased affect/withdrawal in patients with white matter disease is consistent with earlier studies of dementia and strokes. 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. 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.

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.

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 ischae-
mic focal vascular disease. Studies utilising func-
tional 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 Califor-
Explain how to answer the question: What is the focus of the research described in the text?

The focus of the research described in the text is the progression of affective change in dementia and the relation between infarct location and severity of psychomotor slowing in ischemic focal vascular disease. The study was performed at the University of California, Davis Alzheimer’s Disease Center and supported by grants from the National Institute on Aging. The research utilized functional imaging techniques such as PET to assess the relationship between affect patterns and changes to function of specific cortical and subcortical structures.