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Late-onset depression: genetic, vascular and clinical contributions

I. HICKIE,[1] E. SCOTT, S. NAISMITH, P. B. WARD, K. TURNER, G. PARKER, P. MITCHELL AND K. WILHELM

From the School of Psychiatry, University of New South Wales, Sydney, Australia

ABSTRACT

Background. Neuropsychiatric research needs to examine the relationships between aetiological, genotypic and clinical risk factors and behavioural phenotypes. These relationships can now be examined in older patients with depressive disorders.

Methods. Key behavioural features, clinical and vascular risk factors and putative genotypes for late-onset neurodegenerative disorders and/or vascular disease were recorded in 78 older patients with depression (mean age = 54·9 years, S.D. = 14·1) and 22 healthy control subjects (mean age = 55·5 years, S.D. = 9·6).

Results. Two or more vascular risks were more common in older patients (65% *v.* 26% of control subjects, $P < 0{\cdot}01$), and in patients with late-onset disorders (82% *v.* 57% in patients with early-onset disorders, $P < 0{\cdot}05$). Patients with late-onset depression had a higher prevalence of the homozygous or heterozygous forms of the C677T mutation of the methylenetetrahydrofolate reductase enzyme (MTHFR)(74% *v.* 48% in patients with early-onset disorders, $P < 0{\cdot}05$). In a multivariate model, only presence of the MTHFR gene mutation predicted late-onset depression (odds ratio = 3·8, 95% CI = 1·1–12·9). Neither apolipoprotein E epsilon 4 or epsilon 2 was associated with depression, late-onset depression, cognitive impairment, or psychomotor change. Patients with apolipoprotein E epsilon 4 were less likely to have psychotic forms of depression.

Conclusions. Patients with late-onset depression had an increased rate of the C677T MTHFR gene mutation and other vascular risk factors. This suggests that a proportion of these patients may have genetically-determined and/or other vascular aetiologies. Patients at risk of these disorders may be assisted by currently-available preventative strategies.

INTRODUCTION

There has been a longstanding debate regarding the utility of sub-classifying depressive disorders in aetiological and treatment research (Carroll, 1989; Parker *et al.* 1994; Krishnan & McDonald, 1995). While some have argued that identification of key behavioural features (e.g. psychosis, psychomotor retardation, vegetative features, concurrent anxiety) is a necessary prerequisite in aetiological and/or treatment research (Parker *et al.* 1989, 1996*a*), others have suggested that no useful sub-classification will be achieved until relevant aetiological processes (and their behavioural consequences), have been identified (Krishnan *et al.* 1995). A third approach (Hickie, 1996) is to study the patterns of interaction between clinical risk factors, neurobiological correlates and key behavioural features such as psychosis or psychomotor change. This process relies on the simultaneous recording of multiple behavioural constructs (rather than simple diagnostic groups), clinical risk factors, and linked neurobiological or psychosocial markers. This process may maximize the chances of identifying common (or

[1] Address for correspondence: Professor Ian Hickie, Academic Department of Psychiatry, 7 Chapel Street, Kogarah, NSW 2217, Australia.

novel) pathways to disorder (Leboyer *et al.* 1998).

The diagnostic significance of psychomotor retardation, at least for the more severe depressive disorders, has received considerable attention (Widlöcher, 1983; Parker *et al.* 1990, 1995; Parker & Brotchie, 1992). For those patients treated by specialist psychiatry services it appears to provide meaningful differentiation with regard to a range of psychosocial (Parker *et al.* 1991; Boyce & Hickie, 1994) and neurobiological (Bench *et al.* 1993; Hickie *et al.* 1996*a*; Mitchell, 1996) correlates and prediction of response to biomedical treatments (Hickie *et al.* 1990; 1996*b*; Parker *et al.* 1996*b*; Flament *et al.* 1999). Additionally, those patients with melancholia who also have psychotic features present with clinically different forms of psychomotor change and respond preferentially to electroconvulsive therapy (Hickie *et al.* 1996*a*, *b*). Thus, they may represent another group with alternate pre-disposing neurobiological risk factors (Hickie *et al.* 1996*a*).

In addition to the accumulating body of literature focusing on psychomotor change, concurrent emphasis has been placed on the potential significance of genetic (Krishnan *et al.* 1996; Ohara *et al.* 1999), neuroimaging (Lesser *et al.* 1996; Steffens & Krishnan, 1998) and cerebrovascular (Krishnan & McDonald, 1995; Hickie & Scott, 1998) correlates of some types of depression, particularly those with initial onset after 50 years of age (late-onset depression). The discovery of the relationship between apolipoprotein E epsilon 4 (ApoE4) and neurodegenerative processes such as Alzheimer's disease (Betard *et al.* 1994) has provided the impetus for studying the relationship between ApoE4 and depressive disorders. However, to-date, such studies have been limited and have provided conflicting results (Krishnan *et al.* 1996; Heidrich *et al.* 1997; Schmand *et al.* 1998; Ohara *et al.* 1999). Consequently, it is still unclear whether any of the ApoE alleles constitute a specific risk factor to major depression, depression of late-onset, and/or depression characterized by cognitive impairment, psychotic features and/or psychomotor retardation.

By contrast, aetiological and neuroimaging research has identified vascular and behavioural features associated with late-onset depression (Salloway *et al.* 1996; Alexopoulos *et al.* 1997; Simpson *et al.* 1997; Lyness *et al.* 1998; Steffens *et al.* 1999; de Groot *et al.* 2000; Rao, 2000). Such patients are generally characterized by greater cognitive impairment, psychomotor change, absence of a family history of depression, anhedonia, risk factors to cerebrovascular disease and/or neuroimaging evidence of structural change within fronto-subcortical paths. The term 'vascular depression' has subsequently been promoted and proposes that some older individuals with underlying (typically small vessel) cerebrovascular disease are predisposed to late-onset depression (Alexopoulos *et al.* 1997; Steffens & Krishnan, 1998).

When considering particular genotypes associated with vascular risk, the apolipoprotein E epsilon 2 (ApoE2) isoform may be of significance as it has been linked to vascular disease generally and vascular dementia specifically (Betard *et al.* 1994; Skoog *et al.* 1998). Additionally, vascular risk (Moustapha & Robinson, 1998; Hankey & Eikelboom, 1999) and cognitive impairment (Kalmijn *et al.* 1999) have been independently linked to raised plasma homocysteine levels. Raised plasma homocysteine may result from interactions between the C677T mutation of the methylenetetrahydrofolate reductase enzyme (MTHFR) and dietary co-factors such as folate and vitamins B_6 and B_{12}(Jacques *et al.* 1996; Lalouschek *et al.* 1999). Such relationships have been reported in patients with both cardiovascular (Gallagher *et al.* 1996) and cerebrovascular (Markus *et al.* 1997) disease. Since the intake of dietary cofactors may be compromised in older persons and/or persons with depression with poor diets (e.g. folate, B_6, B_{12}), it is possible that those individuals with mutations of the MTHFR gene may be predisposed to cerebrovascular disease, and hence, late-onset depressive disorders (Hickie & Scott, 1998). Although patients with severe depression have been reported to have elevated total plasma homocysteine (Bottiglieri *et al.* 2000) as well as folate deficiencies (Fava *et al.* 1997), no prior research, to our knowledge, has investigated the relationship between the MTHFR gene mutation and late-onset depression.

The present study aimed to explore the 'vascular depression' concept further by examining the relationships between various depressive subtypes (which may be due to

different aetiological factors) and potential cognitive, familial, genetic and vascular risk factors in a sample of older patients with severe depression. Specifically, the aims were: (*i*) to determine whether depression subtyped on the basis of key behavioural (melancholic or psychotic) features is associated with cognitive, vascular, family history or genetic risk factors; (*ii*) to examine whether late-onset depression is associated with such risk factors; and, (*iii*) to determine whether genetic and/or vascular risk factors are predictive of any specific combination of behavioural features. It was hypothesized that late-onset depression would be associated with cognitive impairment, vascular risk factors, and an increased prevalence of genotypic features believed to be associated with vascular disease such as ApoE2 and presence of the MTHFR mutation.

METHOD

Subjects

Patients were included on the basis of participation in either an earlier longitudinal study ($N = 23$: Hickie *et al*. 1995, 1997) of patients with severe depressive disorders or a more recent study ($N = 55$) of the clinical correlates of functional and structural brain imaging. Patients recruited to the first study (sample 1) came from a specialist tertiary assessment service for mood disorders (Brodaty *et al*. 1993). They were more likely to be older, have more treatment-resistant and/or psychotic depression, have more medical risk factors to cerebrovascular disease and hence, more likely to exhibit structural changes on MRI (Hickie *et al*. 1995). Clinical assessment for sample 1 has been detailed elsewhere (Hickie *et al*. 1995). Patients in the second study (sample 2) were recruited from both a district-based mental health service and a specialist mood disorders unit, and were selected to be older. However, they were not selected for other factors likely to increase the chances of detecting vascular risk factors or neuroimaging abnormalities. Patients in both samples were excluded if there was any indication of neurodegenerative disorder, history of stroke, chronic alcohol abuse, or depression secondary to a major medical condition. The total study population consisted, therefore, of 78 patients (age range 28–83 years; mean = 54·9 years, S.D. = 14·1). The resultant combined sample was, therefore, enriched for older patients, patients with more severe disorders and patients with increased rates of risk factors to cerebrovascular disease.

Twenty-two control subjects (age range 40–74 years; mean = 55·5 years, S.D. = 9·6) were recruited from the local community via newspaper advertisement. They were screened by phone interview and by self-report measures for any lifetime history or current evidence of depressive disorders. They were required to be medically healthy with no overt or past history to suggest cerebrovascular disease. All control and patient subjects gave written informed consent prior to participation.

Clinical assessment

Clinical assessment consisted of a structured interview with a psychiatrist trained in the administration of the CORE assessment tool for rating psychomotor function (CORE) (Parker *et al*. 1994); a structured interview for assessment of patients with depressive disorders (generating DSM-IV depression diagnoses); and, the 21-item Hamilton Depression Rating Scale (HAM-D; Hamilton, 1960). In sample 2 subjects, family history of depression and other neuropsychiatric disorders was obtained from the patient and a close family member (when available). Specifically we sought evidence (presence/absence) of a first-degree relative having a history of likely depression and/or dementia.

All subjects with depression were subclassified by DSM-IV defined non-melancholic, melancholic or psychotic subtypes of depression. Those that had both melancholic and psychotic features were classified as being psychotic. Subjects were also classified by age of onset of depression (early-onset < 50 years or late-onset $\geqslant 50$ years). Age 50 was used as a cut-off in accordance with previous research (Krishnan *et al*. 1995) and with Steffens & Krishnan's (1998) 'vascular depression' specifier.

Vascular risk

Vascular risk factors were assessed from both interviews conducted by a research psychologist and a psychiatrist and from subject and informant self-reports. They included: history of diabetes; history of treated or untreated hypertension; past or present smoking history; cardiovascular disease; elevated cholesterol;

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Table 1. *Demographic, clinical, cognitive, vascular, genotypical and family history correlates of healthy control subjects and patients with depression*

	Control subjects *versus* patients with depression				
	Control subjects	Patients with depression	*F*	χ^2	*P*
Demographics					
Female†, %	59 (13/22)	68 (53/78)		0·6	NS
Age†, mean	55·5 (9·6)	54·9 (14·1)	0·0		NS
Age of onset†, Mean	—	40·1 (16·4)	—		—
Clinical					
Bipolar†, %	—	21 (16/78)	—		—
CORE‡	—	13·0 (8·5)	—		—
HAM-D‡	—	27·7 (6·6)	—		—
Cognitive‡					
MMSE, mean	28·6 (1·4)	27·8 (1·9)	3·0		NS
Simple RT, mean	0·279 (0·1)	0·409 (0·2)	13·7		***
Choice RT, mean	0·773 (0·1)	0·946 (0·2)	10·6		**
Vascular risk†					
0–1, %	74 (14/19)	35 (24/69)		9·2	**
⩾ 2, %	26 (5/19)	65 (45/69)			
ApoE genotype†					
Any E2, %	0 (0/22)	16 (12/76)		4·0	*
Any E4, %	41 (9/22)	25 (19/76)		2·1	NS
MTHFR†					
−, %	54 (12/22)	44 (33/75)		0·8	NS
+, %	46 (10/22)	56 (42/75)			
Family history‡					
Depression, %	19 (4/21)	47 (25/53)		4·9	*
Dementia, %	33 (7/21)	19 (10/53)		1·8	NS

Denominators may change with missing data.
† Sample 1 and 2 ($N = 78$ patients with depression).
‡ Sample 2 only ($N = 55$ patients with depression).
RT, Reaction time.
*$P < 0·05$; **$P < 0·01$; ***$P < 0·001$; NS, not significant.

and, family history of at least two vascular risk factors (including stroke and transient ischaemic attack). Each risk was given an equal weighting (0/1) and summed to give a total risk value (range 0–6). Those with two or more risks ($N = 45$) were subsequently distinguished from those with zero or one risk ($N = 24$).

Cognitive functioning

As part of a wider assessment of cognitive functioning (sample 2 only), the Mini-Mental Status Examination (MMSE) (Folstein *et al.* 1975) and a reaction time task (Huppert, 1987) were administered. The reaction time task consisted of two elements. The first (simple RT) measured the mean time taken (seconds) for subjects to respond by pressing a central button to 20 presentations of a single digit ('0') at varying intervals. The second (choice RT) measured the mean time taken (seconds) to respond to 40 presentations of a series of four digits ('1–4') by pressing the corresponding button. Subjects used their preferred hand. MMSE data was only included for those patients with adequate English speaking skills.

ApoE and MTHFR genotyping

Genotypes of ApoE and MTHFR were determined by PCR-based methods as described previously (Wang *et al.* 1995; Wilcken *et al.* 1996). There are three possible MTHFR genotypes: homozygous and heterozygous for the C677T mutant allele or absence of the mutation. Given the small number of homozygous patients ($N = 9$), the heterozygous and homozygous groups were pooled with subsequent analyses comparing those 'at risk' (MTHFR+: $N = 42$) *versus* those without the mutation (MTHFR−: $N = 33$). Since the presence of at least one ApoE2 and ApoE4 allele was of primary interest, subjects were classified as either positive or negative for ApoE2 (ApoE2+: $N = 12$;

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ApoE2−: $N = 64$) and/or ApoE4 (ApoE4+: $N = 19$; ApoE4−: $N = 57$).

Statistical analyses

Statistical analyses were performed using one-way analysis of variance and Pearson χ^2 for continuous and categorical data respectively. Multiple comparisons between DSM-IV subtypes were Bonferroni-adjusted.

RESULTS

Patients with depression *versus* control subjects

Table 1 illustrates the demographic, diagnostic, cognitive, vascular, genotypic and family history characteristics of patients with depression as compared to control subjects. While there were no differences between groups in terms of age, sex distribution, or overall cognitive function (MMSE), patients with depression had significantly longer simple and choice RTs, increased family history rates of depression, more than two vascular risks and a greater prevalence of the ApoE2 allele. The latter, however, may reflect the absence of this allele in control subjects. In fact, the prevalence of the ApoE2 allele in patients with depression (16%) is generally consistent with the rate in the Australian population (12·4%, Henderson *et al.* 1995).

DSM-IV behavioural subtypes

In reference to diagnostic subtypes, Table 2 shows that patients with psychotic features had significantly more severe depression (HAM-D), and greater clinically assessed psychomotor change (CORE) than the melancholic and the non-melancholic subjects. With increasing depression severity (i.e. non-melancholic, melancholic, psychotic) there was a gradient increase in the age of onset of depression and the number of vascular risk factors. This was only significant

Table 2. *Demographic, clinical, cognitive, vascular, genotypical and family history correlates of clinical subtypes of patients with depression*

	Clinical subtype						Multiple comparisons[1]		
	PSY	MEL	NMEL	*F*	χ^2	*P*	PSY–MEL	PSY–NMEL	MEL–NMEL
Demographics									
Female†, %	58 (11/19)	68 (23/34)	76 (19/25)		1·6	NS			
Age†, mean	58·8 (13·4)	55·2 (12·9)	51·3 (15·7)	1·6		NS			
Age of onset†, mean	48·5 (16·2)	40·8 (16·6)	32·7 (13·0)	5·6		**		**	
Clinical									
Bipolar†, %	16 (3/19)	24 (8/34)	20 (5/25)		0·5	NS			
CORE‡	25·2 (6·9)	13·3 (6·9)	7·7 (6·8)	13·7		***	**	***	*
HAM-D‡	36·4 (2·9)	27·2 (5·3)	24·8 (6·9)	10·7		***	**	***	
Cognitive									
MMSE‡, mean	27·8 (2·0)	27·6 (1·8)	28·2 (1·9)	0·5		NS			
Simple RT‡, mean	0·500 (0·2)	0·416 (0·2)	0·361 (0·1)	2·1		NS			
Choice RT‡, mean	0·987 (0·2)	0·982 (0·2)	0·867 (0·2)	1·6		NS			
Vascular risk†									
0–1, %	18 (3/17)	28 (9/32)	60 (12/20)		8·4	*		**	
⩾2, %	82 (14/17)	72 (23/32)	40 (8/20)						
ApoE genotype†									
Any E2, %	12 (2/17)	15 (5/34)	20 (5/25)		0·6	NS			
Any E4, %	6 (1/17)	35 (12/34)	24 (6/25)		5·3	NS			
MTHFR†									
−, %	35 (6/17)	45 (15/33)	48 (12/25)		0·7	NS			
+, %	65 (11/17)	55 (18/33)	52 (13/25)						
Family history‡									
Depression, %	43 (3/7)	40 (12/30)	63 (10/16)		2·2	NS			
Dementia, %	29 (2/7)	20 (6/30)	13 (2/16)		0·9	NS			

Denominators may change with missing data.
[1] Bonferroni-adjusted (PSY, psychotic; MEL, melancholic; NMEL, non-melancholic).
† Sample 1 and 2 (psychotic $N = 19$, melancholic $N = 34$, non-melancholic $N = 25$).
‡ Sample 2 only (psychotic $N = 7$, melancholic $N = 32$, non-melancholic $N = 16$).
*$P < 0·05$; **$P < 0·01$; ***$P < 0·001$; NS, not significant.

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Table 3. *Demographic, clinical, cognitive, vascular, genotypical and family history correlates of patients with depression by age of onset*

	Age of onset[1]				
	Early-onset	Late-onset	*F*	χ^2	*P*
Demographics†					
Female, %	74 (40/54)	54 (13/24)		3·0	NS
Age, mean	49·9 (12·8)	65·8 (10·3)	36·9		***
Age of onset, mean	31·2 (10·0)	60·0 (8·0)	117·5		***
Clinical					
Psychotic†, %	19 (10/54)	38 (9/24)		3·3	NS
Bipolar†, %	28 (15/54)	4 (1/24)		5·7	*
CORE‡, mean	12·0 (8·2)	15·5 (9·1)	1·8		NS
HAM-D‡, mean	28·1 (6·5)	26·5 (7·0)	0·6		NS
Cognitive					
MMSE, mean	27·8 (1·7)	27·7 (2·3)	0·0		NS
Simple RT, mean	0·394 (0·14)	0·448 (0·18)	1·3		NS
Choice RT, mean	0·907 (0·21)	1·057 (0·24)	4·9		*
Vascular risk†					
0–1, %	43 (20/47)	18 (4/22)		3·9	*
⩾ 2, %	57 (27/47)	82 (18/22)			
ApoE genotype†					
Any E2, %	14 (7/52)	21 (5/24)		0·7	NS
Any E4, %	29 (15/52)	17 (4/24)		1·3	NS
MTHFR†					
−, %	52 (27/52)	26 (6/23)		4·3	*
+, %	48 (25/52)	74 (17/23)			
Family history‡					
Depression, %	51 (20/39)	36 (5/14)		1·0	NS
Dementia, %	18 (7/39)	21 (3/14)		0·1	NS

Denominators may change with missing data.
[1] Early-onset, onset < 50 years of age; late-onset, onset ⩾ 50 years of age.
† Sample 1 and 2 (Early-onset $N = 54$, late-onset $N = 24$).
‡ Sample 2 only (Early-onset $N = 40$, late-onset $N = 15$).
*$P < 0·05$; ***$P < 0·001$; NS, not significant.

in comparisons between psychotic and non-melancholic subtypes. There was no difference in cognitive performance between diagnostic subtypes.

Late-onset depression

In comparison to patients with early-onset depression, a significantly larger proportion of patients with late-onset depression had two or more vascular risk factors, as well as a significantly higher prevalence of the 'at risk' MTHFR genotype (Table 3). They were also less likely to have bipolar disorder. Although patients with late-onset depression had significantly longer choice RTs, this was not significant after controlling for age.

Vascular risk

Patients with two or more vascular risk factors were older (mean age = 57·4, S.D. = 13·5) than patients with zero or one vascular risk (mean age = 50·5, S.D. = 12·9; $F_{1,67} = 4·3$, $P < 0·05$). Additionally, those with two or greater risk factors had later ages of onset (mean age of onset = 43·8, S.D. = 16·6) than patients with zero or one vascular risk factor (mean age of onset = 34·7, S.D. = 16·0; $F_{1,67} = 4·8$, $P < 0·05$). No other clinical, genetic, cognitive or family history features were associated with vascular risk.

MTHFR and ApoE associations

Those patients with the 'at risk' MTHFR genotype demonstrated significantly slower simple RT (Table 4). The presence of an ApoE4 allele demonstrated no pattern of association with any clinical or cognitive feature (Table 5). However, those with the allele were less likely to be psychotic than those without the allele. Presence of the ApoE2 allele had no specific pattern of associations.

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Table 4. *Associations between demographic, clinical, cognitive, and vascular risk factors and presence or absence of the 'at risk' forms of the MTHFR gene mutation*

	MTHFR[1]				
	MTHFR−	MTHFR+	*F*	χ^2	*P*
Demographics†					
Female, %	58 (19/33)	76 (32/42)		2·9	NS
Age, mean	54·0 (15·3)	55·9 (13·6)	0·3		NS
Age of onset, mean	37·2 (16·2)	42·2 (16·7)	1·7		NS
Clinical					
Psychotic†, %	18 (6/33)	27 (11/42)		0·7	NS
Bipolar†, %	21 (7/33)	21 (9/42)		0·0	NS
CORE‡, mean	13·7 (8·3)	13·7 (8·3)	0·2		NS
HAM-D‡, mean	28·3 (6·9)	27·3 (6·5)	0·3		NS
Cognitive					
MMSE, mean	28·0 (1·7)	27·6 (6·5)	0·4		NS
Simple RT, mean	0·358 (0·1)	0·452 (0·2)	5·7		*
Choice RT, mean	0·885 (0·2)	0·998 (0·2)	3·4		NS
Family history‡					
Depression, %	57 (13/23)	38 (11/29)		1·8	NS
Dementia, %	9 (2/23)	28 (8/29)		2·9	NS

Denominators may change with missing data.
[1] MTHFR−, no MTHFR gene mutation; MTHFR+, presence of the 'at risk' forms of the MTHFR gene mutation.
† Sample 1 and 2 (MTHFR− $N = 33$, MTHFR+ $N = 42$).
‡ Sample 2 only (MTHFR− $N = 23$, MTHFR+ $N = 29$).
*$P < 0{\cdot}05$; NS, not significant.

Table 5. *Associations between demographic, clinical, cognitive and vascular risk factors and presence or absence of the ApoE2 and ApoE4 alleles*

	ApoE2[1]					ApoE4[2]				
	E2−	E2+	*F*	χ^2	*P*	E4−	E4+	*F*	χ^2	*P*
Demographics†										
Female, %	69 (44/64)	58 (7/12)		0·5	NS	68 (39/57)	63 (12/19)		0·2	NS
Age, mean	55·0 (14·0)	55·4 (15·8)	0·0		NS	55·9 (14·2)	52·4 (14·3)	0·9		NS
Age of onset, mean	39·5 (16·5)	43·9 (16·9)	0·7		NS	41·8 (17·6)	35·2 (11·9)	2·3		NS
Clinical										
Psychotic†, %	23 (15/64)	17 (2/12)		0·3	NS	28 (16/57)	5 (1/19)		4·3	*
Bipolar†, %	19 (12/64)	33 (4/12)		1·3	NS	21 (12/57)	21 (4/19)		0·0	NS
CORE‡, mean	13·3 (8·9)	11·7 (7·8)	0·3		NS	13·2 (8·6)	12·6 (8·6)	0·0		NS
HAM-D‡, mean	28·0 (6·6)	26 (6·4)	0·7		NS	27·8 (6·7)	27·4 (6·4)	0·0		NS
Cognitive‡										
MMSE, mean	27·7 (1·9)	28·7 (1·4)	1·8		NS	27·8 (1·9)	28·0 (1·7)	0·0		NS
Simple RT, mean	0·400 (0·2)	0·449 (0·2)	0·8		NS	0·411 (0·2)	0·399 (0·1)	0·0		NS
Choice RT, mean	0·952 (0·2)	0·919 (0·2)	0·2		NS	0·961 (0·3)	0·905 (0·2)	0·6		NS
Family history‡										
Depression, %	47 (21/45)	50 (4/8)		0·0	NS	44 (7/39)	57 (8/14)		0·8	NS
Dementia, %	22 (10/45)	0 (0/8)		2·2	NS	23 (9/39)	7 (1/14)		0·2	NS

Denominators may change with missing data.
[1] ApoE2−, no ApoE2 alleles; ApoE2+, at least one ApoE2 allele.
[2] ApoE4−, no ApoE4 alleles; ApoE4+, at least one ApoE4 allele.
† Sample 1 and 2 (ApoE2− $N = 64$, ApoE2+ $N = 12$; ApoE4− $N = 57$, ApoE4+ $N = 19$).
‡ Sample 2 only (ApoE2− $N = 45$, ApoE2+ $N = 9$; ApoE4− $N = 40$, ApoE4+ $N = 14$).
* $P < 0{\cdot}05$; NS, not significant.

Predictors of late-onset depression

In order to further investigate the relative importance of the MTHFR mutation, vascular risk factors and presence of psychosis to patients with late-onset depression, a logistic regression model of predictors of early-onset *versus* late-onset was constructed. Only presence of the 'at

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risk' MTHFR genotype remained a significant independent predictor (odds ratio (OR) = 3·8, 95% CI = 1·1–12·9). The presence of two or more vascular risk factors (OR = 2·9, 95% CI = 0·7–10·8) and the presence of psychosis (OR = 3·7, 95% CI = 0·9–12·7) were not significant within this limited sample.

DISCUSSION

This study has focused on associations between putative risk factors and behavioural features in older patients with depression. While a variety of subtyping systems have been proposed for severe depressive disorders, in this clinical cohort the most pertinent associations were between depression with an age of onset after 50 years of age and: (*i*) presence of the mutation of the MTHFR gene; (*ii*) presence of more than two vascular risk factors; and, (*iii*) presence of psychotic features. The vascular risk factors can be subjected to primary prevention and/or secondary intervention strategies.

The adverse biochemical consequences of being heterozygous or homozygous for the MTHFR gene mutation include raised plasma levels of homocysteine which may, in turn, predispose affected persons to atherosclerotic and thromboembolic processes (Wilcken, 1998; Hankey & Eikelboom, 1999). Although the mechanism by which homocysteine might cause vascular damage is unclear, it is has been suggested to reflect the important role that the transfer of methionine methyl groups play in lipid metabolism and subsequent vascular damage (Pilgeram, 1996). Since mild to moderately elevated levels of homocysteine can be readily corrected by folate and/or vitamin B_6 and B_{12} supplementation (Boushey *et al.* 1995), it is possible that such supplementation could play a vital role in preventing the vascular pathologies giving rise to late-onset depressive disorders (Bottiglieri *et al.* 2000). Clearly, these implications warrant more intensive evaluation in a larger sample of older patients with depression and, prospectively, in those at risk of late-life depression.

The association between late-onset depression and vascular risk factors found in this study is consistent with an accumulation of clinical and epidemiological evidence linking late-onset depression with cerebrovascular disease (Hickie & Scott, 1998; Steffens *et al.* 1999). These studies suggest that the aetiological processes underpinning some late-onset depressive disorders may be closely tied to vascular pathologies which progressively disrupt fronto-subcortical paths (Hickie *et al.* 1995; 1997; Krishnan & McDonald, 1995; Steffens *et al.* 1999; de Groot *et al.* 2000). Since biochemical risk factors to vascular disease (e.g. hypertension, elevated cholesterol, diabetes, smoking) are open to active preventative strategies, identification and modification of these risks may play an important role in depression prevention and management.

Contrary to earlier studies (e.g. Krishnan *et al.* 1996), it appears unlikely that the ApoE4 isoform has any specific relationship with depressive disorders, late-life depression, late-onset depression and/or cognitive impairment in patients with severe depression. It is, however, important that the results of such gene association studies in small samples be interpreted cautiously. Clearly, they require replication in larger and more ethnically diverse populations. Of the other behavioural features examined (i.e. melancholic and psychotic subtypes), later age of onset, clinically-assessed psychomotor change, and presence of two or more vascular risk factors were associated with psychotic features. This implies that for a proportion of these patients (who are common in specialist psychiatry and psychogeriatric service environments), vascular pathologies may also be aetiologically relevant.

The interpretation of results from this small sample size and relatively large number of comparisons requires caution and, ultimately, replication in independent samples. This study suggests an important series of interactions between: (*i*) genotypes 'at-risk' for vascular, rather than neurodegenerative disease (i.e. MTHFR rather than ApoE4); (*ii*) late-onset of depression; (*iii*) other behavioural or biochemical vascular disease risk factors (which become progressively more relevant to older rather than younger patients); and, (*iv*) the development of depressions characterized by psychomotor slowing and/or psychotic features. Future aetiological and/or treatment studies in late-life depression should therefore examine important behavioural features, cognitive, vascular and genetic (namely MTHFR) risk factors.

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REFERENCES

Alexopoulos, G. S., Meyers, B. S., Young, R. C., Campbell, S., Silbersweig, D. & Charlson, M. (1997). 'Vascular depression' hypothesis. *Archives of General Psychiatry* **54**, 915–922.

Bench, C. J., Friston, K. J., Brown, R. G., Frackowiak, R. S. J. & Dolan, R. J. (1993). Regional cerebral blood flow in depression measured by positron emission tomography: the relationship with clinical dimensions. *Psychological Medicine* **23**, 579–590.

Betard, C., Robitaille, Y., Gee, M., Tiberghien, D., Larrivee, D., Roy, P., Mortimer, J. A. & Gauvreau, D. (1994). ApoE allele frequencies in Alzheimer's disease, Lewy body dementia, Alzheimer's disease with cerebrovascular disease and vascular dementia. *Neuroreport* **5**, 1893–1896.

Bottiglieri, T., Laundy, M., Crellin, R., Toone, B. K., Carney, M. W. P. & Reynolds, E. H. (2000). Homocysteine, folate, methylation, and monoamine metabolism in depression. *Journal of Neurology, Neurosurgery and Psychiatry* **69**, 228–232.

Boushey, C. J., Beresford, S. A. A., Omenn, G. S. & Motulsky, A. G. (1995). A quantitative assessment of plasma homocysteine as a risk factor for vascular disease: probable benefits of increasing folic acid intakes. *Journal of the American Medical Association* **274**, 1049–1057.

Boyce, P. M. & Hickie, I. (1994). A brave new world in managing depression – or is it? *Australian Family Physician* **23**, 627–632.

Brodaty, H., Harris, L., Wilhelm, K., Hickie, I., Boyce, P., Mitchell, P., Parker, G. & Eyers, K. (1993). Lessons from a mood disorders unit. *Australian and New Zealand Journal of Psychiatry* **27**, 254–263.

Carroll, B. J. (1989). Diagnostic validity and laboratory studies: rules of the game. In *The Validity of Psychiatric Diagnosis* (ed. L. N. Robins and J. E. Barrett), pp. 229–245. Raven Press: New York.

de Groot, J. C., de Leeuw, F. E., Oudkerk, M., Hofman, A., Jolles, J. & Breteler, M. M. B. (2000). Cerebral white matter lesions and depressive symptoms in elderly adults. *Archives of General Psychiatry* **57**, 1071–1076.

Fava, M., Borus, J. S., Alpert, J. E., Nierenberg, A. A., Rosenbaum, J. F. & Bottiglieri, T. (1997). Folate, vitamin B_{12}, and homocysteine in major depressive disorder. *American Journal of Psychiatry* **154**, 426–428.

Flament, M. F., Lane, R. M., Zhu, R. & Ying, Z. (1999). Predictors of an acute antidepressant response to fluoxetine and sertraline. *International Clinical Psychopharmacology* **14**, 259–275.

Folstein, M. F., Folstein, S. E. & McHugh, P. R. (1975). 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research* **12**, 189–198.

Gallagher, P. M., Meleady, R., Shields, C., Tan, K. S., McMaster, D., Rozen, R., Evans, A., Graham, I. M. & Whitehead, A. S. (1996). Homocysteine and risk of premature coronary heart disease. Evidence for a common gene mutation. *Circulation* **94**, 2154–2158.

Hamilton, M. (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery and Psychiatry* **23**, 56–61.

Hankey, G. J. & Eikelboom, J. W. (1999). Homocysteine and vascular disease. *Lancet* **354**, 407–413.

Heidrich, A., Thome, J., Rosler, M. & Baumer, A. (1997). Apolipoprotein E-ϵ4 allele frequency in late-onset depression. *Biological Psychiatry* **41**, 912–913.

Henderson, A. S., Easteal, S., Jorm, A. F., Mackinnon, A. J., Korten, A. E., Christensen, H., Croft, L. & Jacomb, P. A. (1995). Apolipoprotein E allele epsilon 4, dementia, and cognitive decline in a population sample. *Lancet* **346**, 1387–1390.

Hickie, I. (1996). Issues in classification: III. Utilising behavioural constructs in melancholia research. In *Melancholia: A Disorder of Movement and Mood* (ed. G. Parker and D. Hadzi-Pavlovic), pp. 38–56. Cambridge University Press: New York.

Hickie, I. & Scott, E. (1998). Late-onset depressive disorders: a preventable variant of cerebrovascular disease? *Psychological Medicine* **28**, 1007–1013.

Hickie, I., Parsonage, B. & Parker, G. (1990). Prediction of response to electroconvulsive therapy: preliminary validation of a sign-based typology of depression. *British Journal of Psychiatry* **157**, 65–71.

Hickie, I., Scott, E., Mitchell, P., Wilhelm, K., Austin, M.-P. & Bennett, B. (1995). Subcortical hyperintensities on magnetic resonance imaging: clinical correlates and prognostic significance in patients with severe depression. *Biological Psychiatry* **37**, 151–160.

Hickie, I., Hickie, C., Scott, E. & Wilhelm, K. (1996*a*). Magnetic resonance imaging in primary and secondary depression. In *Melancholia: A Disorder of Movement and Mood* (ed. G. Parker and D. Hadzi-Pavlovic), pp. 252–266. Cambridge University Press: New York.

Hickie, I., Mason, C., Parker, G. & Brodaty, H. (1996*b*). Prediction of ECT response: validation of a refined sign-based (CORE) system for defining melancholia. *British Journal of Psychiatry* **169**, 68–74.

Hickie, I., Scott, E., Wilhelm, K. & Brodaty, H. (1997). Subcortical hyperintensities on magnetic resonance imaging in patients with severe depression – a longitudinal evaluation. *Biological Psychiatry* **42**, 367–374.

Huppert, F. A. (1987). Cognitive function. In *The Health and Lifestyle Survey: Preliminary Report of a Nationwide Survey of the Physical and Mental Health, Attitudes and Lifestyle of a Random Sample of 9003 British Adults* (ed. B. D. Cox), pp. 43–50. Health Promotion Research Trust: London.

Jacques, P. F., Bostom, A. G., Williams, R. R., Ellison, R. C., Eckfeldt, J. H., Rosenberg, I. H., Selhub, J. & Rozen, R. (1996). Relation between folate status, a common mutation in methylene-tetrahydrofolate reductase, and plasma homocysteine concentrations. *Circulation* **93**, 7–9.

Kalmijn, S., Launer, L. J., Lindemans, J., Bots, M. L., Hofman, A. & Breteler, M. M. (1999). Total homocysteine and cognitive decline in a community-based sample of elderly subjects: the Rotterdam Study. *American Journal of Epidemiology* **150**, 283–289.

Krishnan, K. R. R. & McDonald, W. M. (1995). Arteriosclerotic depression. *Medical Hypotheses* **44**, 111–115.

Krishnan, K. R. R., Hays, J. C., Tupler, L. A., George, L. K. & Blazer, D. G. (1995). Clinical and phenomenological comparisons of late-onset and early-onset depression. *American Journal of Psychiatry* **152**, 785–788.

Krishnan, K. R. R., Tupler, L. A., Ritchie, Jr., J. C., McDonald, W. M., Knight, D. L., Nemeroff, C. B. & Carroll, B. J. (1996). Apolipoprotein E-ϵ4 frequency in geriatric depression. *Biological Psychiatry* **40**, 69–71.

Lalouschek, W., Aull, S., Serles, W., Schnider, P., Mannhalter, C., Lang, T., Deecke, L. & Zeiler, K. (1999). Genetic and nongenetic factors influencing plasma homocysteine levels in patients with ischemic cerebrovascular disease and in healthy control subjects. *Journal of Laboratory and Clinical Medicine* **133**, 575–582.

Leboyer, M., Leboyer, M., Bellivier, F., Jouvent, R., Nosten-Bertrand, M., Mallet, J. & Pauls, D. (1998). Psychiatric genetics: search for phenotypes. *Trends in Neurosciences* **21**, 102–105.

Lesser, I. M., Boone, K. B., Mehringer, C. M., Wohl, M. A., Miller, B. L. & Berman, N. G. (1996). Cognition and white matter hyperintensities in older depressed patients. *American Journal of Psychiatry* **153**, 1280–1287.

Lyness, J. M., Caine, E. D., Cox, C., King, D. A., Conwell, Y. &

Olivares, T. (1998). Cerebrovascular risk factors and later-life major depression. Testing a small-vessel brain disease model. *American Journal of Geriatric Psychiatry* **6**, 5–13.

Markus, H. S., Ali, N., Swaminathan, R., Sankaralingam, A., Molloy, J. & Powell, J. (1997). A common polymorphism in the methylenetetrahydrofolate reductase gene, homocysteine, and ischemic cerebrovascular disease. *Stroke* **28**, 1739–1743.

Mitchell, P. (1996). Validity of the CORE: I. A neuroendocrinological strategy. In *Melancholia: A Disorder of Movement and Mood* (ed. G. Parker and D. Hadzi-Pavlovic), pp. 138–148. Cambridge University Press: New York.

Moustapha, A. & Robinson, K. (1998). High plasma homocysteine: a risk factor for vascular disease in the elderly. *Coronary Artery Disease* **9**, 725–730.

Ohara, K., Nagai, M., Suzuki, Y., Yoshida, K., Tsukamoto, T. & Ohara, K. (1999). Apolipoprotein E $\epsilon 4$ allele and Japanese late-onset depressive disorders. *Biological Psychiatry* **45**, 308–312.

Parker, G. & Brotchie, H. (1992). Psychomotor change as a feature of depressive disorders: an historical overview. *Australian and New Zealand Journal of Psychiatry* **26**, 146–155.

Parker, G., Hadzi-Pavlovic, D. & Boyce, P. (1989). Endogenous depression as a construct: a quantitative analysis of the literature and a study of clinical judgements. *Australian and New Zealand Journal of Psychiatry* **23**, 357–368.

Parker, G., Hadzi-Pavlovic, D., Boyce, P., Wilhelm, K., Brodaty, H., Mitchell, P., Hickie, I. & Eyers, K. (1990). Classifying depression by mental state signs. *British Journal of Psychiatry* **157**, 55–65.

Parker, G., Hadzi-Pavlovic, D., Mitchell, P., Hickie, I., Wilhelm, K., Brodaty, H., Boyce, P. & Roy, K. (1991). Psychosocial risk factors distinguishing melancholic and non-melancholic depression: a comparison of six systems. *Psychiatry Research* **39**, 211–226.

Parker, G., Hadzi-Pavlovic, D., Wilhelm, K., Hickie, I., Brodaty, H., Boyce, P., Mitchell, P. & Eyers, K. (1994). Defining melancholia: properties of a refined sign-based measure. *British Journal of Psychiatry* **164**, 316–326.

Parker, G., Hadzi-Pavlovic, D., Austin, M.-P., Mitchell, P., Wilhelm, K., Hickie, I., Boyce, P. & Eyers, K. (1995). Subtyping depression, I. Is psychomotor disturbance necessary and sufficient to the definition of melancholia? *Psychological Medicine* **25**, 815–824.

Parker, G., Hadzi-Pavlovic, D. & Boyce, P. (1996*a*). Issues in classification: II. Classifying melancholia. In *Melancholia: A Disorder of Movement and Mood* (ed. G. Parker and D. Hadzi-Pavlovic), pp. 20–37. Cambridge University Press: New York.

Parker, G., Hickie, I. & Mason, C. (1996*b*). Validity of the CORE: III. Outcome and treatment prediction. In *Melancholia: A Disorder of Movement and Mood* (ed. G. Parker and D. Hadzi-Pavlovic), pp. 160–171. Cambridge University Press: New York.

Pilgeram, L. (1996). Perspective: a mechanism underlying homocysteinemia and increased risk of coronary artery and cerebrovascular disease. *Circulation* **94**, 2990.

Rao, R. (2000). Cerebrovascular disease and late life depression: an age old association revisited. *International Journal of Geriatric Psychiatry* **15**, 419–433.

Salloway, S., Malloy, P., Kohn, R., Gillard, E., Duffy, J., Rogg, J., Tung, G., Richardson, E., Thomas, C. & Westlake, R. (1996). MRI and neuropsychological differences in early- and late-life-onset geriatric depression. *Neurology* **46**, 1567–1574.

Schmand, B., Hooijer, C., Jonker, C., Lindeboom, J. & Havekes, L. M. (1998). Apolipoprotein E phenotype is not related to late-life depression in a population-based sample. *Social Psychiatry and Psychiatric Epidemiology* **33**, 21–26.

Simpson, S. W., Jackson, A., Baldwin, R. C. & Burns, A. (1997). Subcortical hyperintensities in late-life depression: acute response to treatment and neuropsychological impairment. *International Psychogeriatrics* **9**, 257–275.

Skoog, I., Hesse, C., Aevarsson, O., Landahl, S., Wahlstrom, J., Fredman, P. & Blennow, K. (1998). A population study of apoE genotype at the age of 85: relation to dementia, cerebrovascular disease, and mortality. *Journal of Neurology, Neurosurgery and Psychiatry* **64**, 37–43.

Steffens, D. C. & Krishnan, K. R. R. (1998). Structural neuroimaging and mood disorders: Recent findings, implications for classification, and future directions. *Biological Psychiatry* **43**, 705–712.

Steffens, D. C., Helms, M. J., Krishnan, K. R. R. & Burke, G. L. (1999). Cerebrovascular disease and depression symptoms in the cardiovascular health study. *Stroke* **30**, 2159–2166.

Wang, X. L., McCredie, R. M. & Wilcken, D. E. L. (1995). Polymorphisms of the apolipoprotein E gene and severity of coronary artery disease defined by angiography. *Arteriosclerosis, Thrombosis and Vascular Biology* **15**, 1030–1034.

Widlöcher, D. J. (1983). Psychomotor retardation: clinical, theoretical, and psychometric aspects. *Psychiatric Clinics of North America* **6**, 27–40.

Wilcken, D. E. L. (1998). Homocysteine and vascular disease. *Medical Journal of Australia* **168**, 431–432.

Wilcken, D. E. L., Wang, X. L., Sim, A. S. & McCredie, R. M. (1996). Distribution in healthy and coronary populations of the methylenetetrahydrofolate reductase (MTHFR) C sub 677 T mutation. *Arteriosclerosis, Thrombosis and Vascular Biology* **16**, 878–882.