Psychological Medicine (2009), **39**, 725–733. © Cambridge University Press 2008
doi:10.1017/S0033291708004042 Printed in the United Kingdom

ORIGINAL ARTICLE

A comparison of neurocognitive impairment in younger and older adults with major depression

A. J. Thomas[1]*, P. Gallagher[2], L. J. Robinson[2], R. J. Porter[3], A. H. Young[2], I. N. Ferrier[2] and J. T. O'Brien[1]

[1] *Institute for Ageing and Health, Newcastle University, UK*
[2] *School of Neurology, Neurobiology and Psychiatry, Newcastle University, UK*
[3] *Department of Psychological Medicine, Christchurch School of Medicine, New Zealand*

Background. Neurocognitive impairment is a well-recognized feature of depression that has been reported in younger and older adults. Similar deficits occur with ageing and it is unclear whether the greater deficits in late-life depression are an ageing-related phenomenon or due to a difference in the nature of late-life depression itself. We hypothesized that ageing alone would not fully explain the increased neurocognitive impairment in late-life depression but that differences in the illness explain the greater decrements in memory and executive function.

Method. Comparison of the neuropsychological performance of younger (<60 years) and older (⩾60 years) adults with major depressive disorder (MDD) and healthy comparison subjects. Scores for each depression group were normalized against their respective age-matched control group and the primary comparisons were on four neurocognitive domains: (i) attention and executive function; (ii) verbal learning and memory; (iii) visuospatial learning and memory; and (iv) motor speed.

Results. We recruited 75 subjects with MDD [<60 years ($n=44$), ⩾60 years ($n=31$)] and 82 psychiatrically healthy comparison subjects [<60 years ($n=42$), ⩾60 years ($n=40$)]. The late-life depression group had greater impairment in verbal learning and memory and motor speed but not in executive function. The two depressed groups did not differ in depression severity, global cognitive function, intelligence or education.

Conclusions. Late-life depression is associated with more severe impairment in verbal learning and memory and motor speed than depression in earlier adult life and this is not due to ageing alone.

Received 22 January 2008; Revised 11 June 2008; Accepted 11 June 2008; First published online 30 July 2008

Key words: Depression, geriatric, late-life, neuropsychology, unipolar.

Introduction

The prevalence of major depressive disorder (MDD) is approximately 2–3% in adults of all ages and the depression symptom profile remains broadly similar, although older severely ill subjects may have a higher frequency of psychomotor changes and psychotic symptoms (Brodaty *et al*. 1991, 1997). However, one domain of depressive symptomatology that is usually understood to be more severely impaired in late-life depression is cognition. Studies have consistently shown that both younger (e.g. Elliott *et al*. 1997; Austin *et al*. 1999; Porter *et al*. 2003) and older (e.g. Kramer-Ginsberg *et al*. 1999; Butters *et al*. 2004*b*; O'Brien *et al*. 2004; Sheline *et al*. 2006) depressed adults have neuropsychological deficits in information processing, memory and executive function (Elliott *et al*. 1997; Austin *et al*. 1999; Butters *et al*. 2000; Porter *et al*. 2003; O'Brien *et al*. 2004; Sheline *et al*. 2006). These deficits persist after clinical recovery (Paradiso *et al*. 1997; Butters *et al*. 2000; O'Brien *et al*. 2004; Bhalla *et al*. 2006) and seem to be a core part of depressive illness itself (Austin *et al*. 2001). These neurocognitive impairments have also been associated with hyperintense lesions in the deep white matter (Lesser *et al*. 1996; Kramer-Ginsberg *et al*. 1999), indicating that they may be due to disruption of frontal–subcortical circuitry. Some reports have suggested that neuropsychological deficits are associated with a poor response to treatment (Simpson *et al*. 1998; Kalayam & Alexopoulos, 1999) but others disagree (Butters *et al*. 2004*a*).

A recent systematic review of the literature on late-life depression reported executive dysfunction to be characteristic of depression beginning in later life (late-onset depression, LOD) whereas episodic

* Address for correspondence: Dr A. J. Thomas, Wolfson Research Centre, Institute for Ageing and Health, Newcastle General Hospital, Newcastle upon Tyne NE4 6BE, UK.
(Email: a.j.thomas@ncl.ac.uk)

memory dysfunction is a feature of both LOD and early onset depression (EOD) (Herrmann *et al*. 2007). However, the studies reviewed compared only these subgroups (EOD and LOD) with each other and with elderly controls and did not examine directly whether the cognitive profile is different in younger and older depressed subjects or whether more severe impairment in late-life depression is due to differences in the nature of depression in older people or can be explained by the additive effects of ageing. Despite general suggestions of such differences in neurocognitive impairments in older and younger adults with depression, surprisingly few studies have investigated this issue directly (Porter *et al*. 2007). Lockwood *et al*. (2002) compared 20 younger depressed adults ($\leqslant$60 years) with 20 older depressed adults and with 20 younger and 20 older controls on measures of attention and executive function. Executive function was impaired in the late-life depression group compared to both the younger depressed subjects and the older controls, and there was a significant depression–age interaction, but this study did not assess memory. Tarbuck & Paykel (1995) reported a similar study examining the neuropsychological profile in subject groups below and above the age of 60 years and, in addition to age-associated effects in most tests, found tasks with greater complexity were disproportionately impaired in the older depressed group.

In view of the limited information from direct comparisons using the same instruments in younger and older depressed subjects, we investigated whether attention, memory and executive function are differentially impaired in older adults with depression compared with younger depressed subjects. We hypothesized that, following standardization of scores to their respective, similar-aged control groups, older depressed adults would have more severe deficits in both memory and executive function.

Method

Younger (<60 years) and older ($\geqslant$60 years) adults who fulfilled diagnostic criteria for DSM-IV major depression were recruited from primary and secondary care facilities in the Tyne and Wear region in the North of England. These subjects have been reported previously in separate studies and were drawn from community- and hospital-based clinics (Porter *et al*. 2003; O'Brien *et al*. 2004). They all received a full neuropsychiatric assessment including physical examination, blood screen and cognitive assessment (including the mini-mental state examination, MMSE; Folstein *et al*. 1975). Comprehensive demographic and clinical information was collected, including education, social class, family history, psychiatric and medical history, and medication history. Subjects were excluded if they had ever met criteria for other mental illnesses, including manic episodes and dementia, if their MMSE score was <24, if they had received electroconvulsive therapy in the past 3 months or if they had a history of alcohol or substance abuse. Psychiatrically healthy comparison subjects were recruited from spouses and friends of depressed subjects and of other patients attending the same units and by local advertising. They were thus drawn from the same socio-economic background as the depressed subjects. Comparison subjects received the same neuropsychiatric assessment and were subject to the same exclusion criteria as the depressed subjects but additionally had no history of psychiatric illness. The severity of depression in study subjects was assessed using the Montgomery–Åsberg Depression Rating Scale (MADRS; Montgomery & Åsberg, 1979). The study was approved by the relevant local research ethics committees and, after full explanation of the study, all subjects gave written informed consent to participate.

Neuropsychological assessment

A combination of pen-and-paper and computerized tasks from the Cambridge Automated Neuropsychological Test Battery (CANTAB) was administered to all study subjects. In addition, the pre-morbid IQ of all subjects was estimated using the National Adult Reading Test (NART; Nelson, 1982). CANTAB tests were administered according to the manual protocols using a PC with a colour touch-sensitive screen. These tests have been used previously in both older (Abas *et al*. 1990; Beats *et al*. 1996; O'Brien *et al*. 2004) and younger (O'Brien *et al*. 1993; Porter *et al*. 2003) subjects and have been described in detail elsewhere. The test battery was designed to assess attention, memory and executive function and the individual tests administered are described briefly below.

Controlled Oral Word Association Test (*Benton's FAS; Benton & Hampsher, 1976*). This is a standard test of verbal fluency in which subjects generate words beginning with 'F', 'A' and 'S', following a prescribed set of rules. Subjects are given 60 s with each letter and the total number correct and errors (perseverative and rule breaks) are recorded.

Spatial Working Memory (*CANTAB*). This is a self-ordered search task that requires subjects to locate counters hidden in boxes and avoid repetitious searching of locations. Thus, subjects need to develop a search strategy and this forms a test of executive ability. Between- and within-search errors are

https://doi.org/10.1017/S0033291708004042 Published online by Cambridge University Press

recorded along with a strategy score, based on the use of a systematic searching strategy.

Vigil Continuous Performance Test (*Vigil CPT; Cegalis & Bowen, 1991*). In this continuous performance test, subjects view serially presented random letters over 8 min and must respond only to the sequence of an 'A' followed by a 'K'. Response latency and errors of omission and commission are recorded.

Rey Auditory Verbal Learning Test (*RAVLT; Rey, 1964*). This is a test of immediate and delayed verbal learning. Subjects are presented with a list of 15 words a total of five times, with immediate recall tested after each occasion (list A1–A5). A distracter list (list B) is then presented, again with an immediate recall test. Without further presentation, recall of list A is then tested immediately and again after a filled delay of 30 min (list A7). Finally, recognition of both lists is tested from among a series of distracters. For each measure, the number of words correct is recorded.

Pattern recognition (*CANTAB*). Subjects learn a series of 12 complex patterns before being presented with pairs of patterns and are required to identify the familiar one. Two sets are presented and total percentage correct and response latency are recorded.

Spatial recognition (*CANTAB*). Subjects are required to learn the on-screen spatial position of five serially presented squares, with a subsequent forced-choice recognition between two locations. Four trials are completed and total percentage correct and response latency are recorded.

Statistical analysis

Prior to analysis, neurocognitive data for the subject groups were converted to standardized z scores based on the mean and standard deviation of their respective control groups. Composite scores were then calculated by summing the z scores for the primary outcome measures from each of four neurocognitive domains (see Appendix for details): (i) attention and executive function; (ii) verbal learning and memory; (iii) visuospatial learning and memory; (iv) motor speed (see Appendix for outcome measures contributing to each domain). Missing data, due to subject fatigue during testing, resulted in incomplete composite scores in one or more domains for seven subjects (three younger, four older). These data points were replaced with the mean of each group to enable analysis of the full dataset. To satisfy the assumptions permitting parametric analysis, the data were first square root transformed (to make all data points positive values, this was done following the addition of a constant). Data from the four neurocognitive domains were then analysed using a general linear model (GLM) multivariate analysis of variance (MANOVA) with group (older depressed or younger depressed) and sex as fixed factors. To control the type 1 error rate, only those domains that were found to be significant in the multivariate analysis were examined in more detail, on an individual test basis.

Results

We recruited 75 depressed subjects (<60 years ($n=44$), ⩾60 years ($n=31$)] and 82 psychiatrically healthy comparison subjects (<60 years ($n=42$), ⩾60 years ($n=40$)]. Their demographic and clinical characteristics are summarized in Table 1. At assessment, of the 31 older subjects with depression, 25 were on antidepressant monotherapy [16 selective serotonin reuptake inhibitors (SSRIs), four venlafaxine, three monoamine oxidase inhibitors (MAOIs), one tricyclic antidepressant (TCA) and one mianserin], two were on combination therapy (fluoxetine and mirtazapine; dothiepin and mirtazpine) and four were not on antidepressant treatment. Of the younger depressed subjects, none were on antidepressant treatment at the time of testing, and this median time to referral and commencement of antidepressant treatment is in keeping with other studies (e.g. Hornblow *et al*. 1990).

Analysis of the composite z scores indicated that there was no (relative) difference in MMSE scores ($t=0.384$, df$=72$, $p=0.702$), NART scores ($t=0.923$, df$=72$, $p=0.359$) or years of education ($t=0.849$, df$=73$, $p=0.399$) between younger and older depressed patients, normalized against their respective control groups. There was also no difference in depression severity (as assessed by the MADRS) between the older and younger depressed groups ($t=0.81$, df$=71$, $p=0.935$).

Primary neurocognitive analysis

A single MANOVA was performed on the four neurocognitive domains. Significant main effects of group (MANOVA main effect: $F=2.501$, df$=4,68$, $p=0.05$) and sex (MANOVA main effect: $F=4.891$, df$=4,68$, $p=0.002$) were observed, with older patients performing worse than younger patients and male subjects performing worse than female subjects. There was no significant sex by group interaction ($F=0.504$, df$=4,68$, $p=0.733$). Examination of the four neurocognitive domains after excluding patients on anticholinergic medications indicated that the significant between-group differences in the verbal memory and

https://doi.org/10.1017/S0033291708004042 Published online by Cambridge University Press

Table 1. *Demographics and illness characteristics*

	Depressed		Controls		
	Younger	Older	Younger	Older	Contrasts[a]
Sex, F:M, *n* (%)	29:15 (66:34)	24:7 (77:23)	27:15 (64:36)	30:10 (75:25)	–
Age (years)	32.9 (10.6)	72.4 (6.7)	30.9 (9.7)	73.3 (6.7)	(YD = YC) < (OD = OC)
NART	107.9 (10.7)	105.6 (11.3)	109.8 (6.8)	111.2 (11.0)	N.S.
Education (years)	13.3 (2.4)	9.8 (2.2)	14.3 (1.7)	10.4 (2.1)	(YD < YC) > (OD = OC)
MMSE	29.5 (1.0)	26.9 (2.1)	29.7 (0.5)	27.8 (1.9)	(OD < (OC) = YC = YD)
MADRS	28.9 (5.5)	29.0 (6.1)	N.A.	N.A.	–
Duration of current episode (months)	12.5 (23.5)	7.0 (9.5)	N.A.	N.A.	–
Median (months)	6	3.7			
Age of onset (years)	29.2 (9.0)	58.7 (17.7)	N.A.	N.A.	YD < OD
Median (years)	29.0	67.0			

F, female; M, male; NART, National Adult Reading Test; MADRS, Montgomery–Åsberg Depression Rating Scale; YD, younger depressed; OD, older depressed; YC, younger controls; OC, older controls; N.S., not significant; N.A., not available.

Data are mean (standard deviation) unless specified otherwise.

[a] Contrasts performed only if overall ANOVA was significant.

motor domains remained significant. All other domains remained non-significant (data not shown).

Examination of the between-subject effects for each of the four individual neurocognitive domains revealed that the main effect of group resulted from significant differences in the verbal learning and memory [composite score (higher scores represent worse performance): younger mean = 2.51, S.D. = 0.65; older mean = 2.80, S.D. = 0.58; $F = 5.922$, df = 1, 71, $p = 0.017$] and motor speed (composite score: younger mean = 2.53, S.D. = 0.74; older mean = 2.95, S.D. = 0.76; $F = 5.927$, df = 1, 71, $p = 0.017$) domains, with no difference in attention and executive function (composite score: younger mean = 3.08, S.D. = 1.11; older mean = 3.08, S.D. = 1.12; $F = 0.001$, df = 1, 71, $p = 0.980$) or visuospatial learning and memory (composite score: younger mean = 2.49, S.D. = 0.36; older mean = 2.48, S.D. = 0.35; $F = 0.139$, df = 1, 71, $p = 0.711$). The main effect of sex resulted from females outperforming males within the verbal learning domain only ($F = 15.874$, df = 1, 71, $p < 0.001$).

Analyses of individual tests from within these significant domains are presented below (see also Table 2).

Verbal learning and memory

Older depressed patients were impaired to a greater extent on several indices of the RAVLT, including total trials A1–A5 ($t = 2.968$, df = 71, $p = 0.004$), list A6 ($t = 2.735$, df = 71, $p = 0.008$) and A7 delayed recall ($t = 2.264$, df = 71, $p = 0.027$). There was no significant difference in interference list B ($t = 0.714$, df = 71, $p = 0.477$) or list A delayed recognition ($t = 0.388$, df = 71, $p = 0.699$) or the percentage retention at A7 from the maximum list recall A1 to A5 ($t = 1.397$, df = 71, $p = 0.170$). To examine the rate of learning of the initial word list (A1–A5), a repeated-measures ANOVA with 'group' as the between-subjects factor and 'word list' as the within-subjects factor was performed. In addition to confirming the main effect of group ($F = 7.857$, df = 1, 71, $p = 0.007$), there was also a group by word list interaction ($F = 2.549$, df = 4, 284, $p = 0.049$), with the relative magnitude of the difference between younger and older patients becoming larger with successive presentations (see Fig. 1).

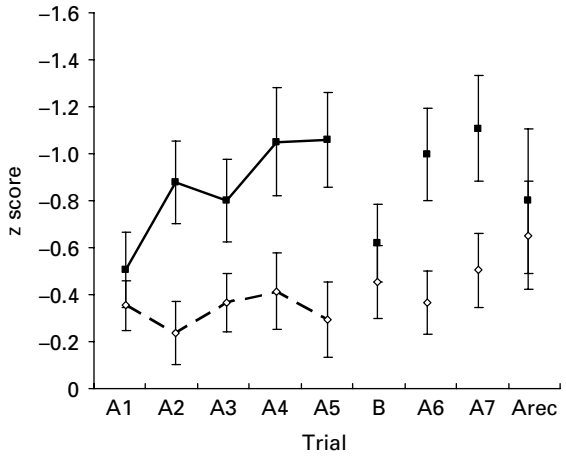

Fig. 1. Rey Auditory Verbal Learning Test (RAVLT) *z* scores for younger (- - ◇ - -) and older (– ■ –) patients.

https://doi.org/10.1017/S0033291708004042 Published online by Cambridge University Press

Table 2. *Neurocognitive test results for the younger and older patient groups (all data are mean z scores[a] and S.D. unless specified otherwise)*

	Younger		Older		
	Mean	S.D.	Mean	S.D.	Effect size[b] (*d*)
Verbal fluency					
Correct (total)	−0.46	0.83	−0.67	1.20	−0.21
Perseverations	0.15	0.73	−0.03	0.85	−0.23
Rule breaks	0.07	0.96	−0.14	0.93	−0.22
Spatial working memory					
Between-search errors	−0.87	1.29	−0.44	0.76	0.39
Within-search errors	0.10	0.77	−0.02	1.09	−0.13
Strategy score	−0.68	1.06	−0.17	0.78	0.52
Vigil CPT					
Omission errors	−2.64	5.75	−4.35	7.73	−0.26
Commission errors	−1.62	3.39	−0.35	1.06	0.46
Latency (ms)	−0.36	1.54	−1.22	1.67	−0.52
RAVLT					
List A1	−0.40	0.73	−0.55	0.89	−0.19
A1–A5 (total)	−0.45	0.92	−1.14	1.06	−0.67
List B	−0.50	1.05	−0.67	0.91	−0.17
List A7 recall	−0.55	1.08	−1.17	1.25	−0.53
List A7 retention (% of maximum at A1–A5)	−0.51	1.18	−1.10	2.07	−0.43
List A7 recognition	−0.70	1.55	−0.85	1.69	−0.09
Pattern recognition					
Correct (%)	−0.65	1.26	−0.76	1.17	−0.09
Latency (ms)	−1.06	1.79	−1.64	2.14	−0.30
Spatial recognition					
Correct (%)	−0.65	1.10	−0.51	0.92	0.14
Latency (ms)	−0.56	1.51	−1.33	2.52	−0.38

CPT, Continuous Performance Test; RAVLT, Rey Auditory Verbal Learning Test; S.D., standard deviation.

[a] Signs have been modified so that negative scores always represent worse performance with respect to the control group.

[b] Cohen's *d*: negative scores indicate worse performance in the older patient group compared to the younger patient group.

Motor speed

Older patients exhibited slowed reaction times on the Vigil test ($t=2.235$, df = 69, $p=0.029$) whereas the differences in latencies on the pattern ($t=1.257$, df = 72, $p=0.213$) and spatial ($t=1.633$, df = 71, $p=0.107$) recognition tests failed to reach significance.

Exploratory analyses

To examine the effect of age of onset of depression (AOD) on neurocognitive domains, the older patient group was divided into subjects with AOD $\geqslant$60 years ($n=19$) and AOD <60 years ($n=12$). The primary MANOVA was then repeated with the group recoded as younger patients *versus* AOD $\geqslant$60 years *versus* AOD <60 years (sex was removed as a factor because of the small sample sizes). The MANOVA main effect of group differed at a trend level ($F=2.457$, df = 8, 70, $p=0.053$). This was the result of trends in the verbal domain ($F=2.637$, df = 2, 72, $p=0.078$) and motor speed domain ($F=2.815$, df = 2, 72, $p=0.067$), with the later age of onset group performing worse than the younger group. At the time of testing the AOD $\geqslant$60 years group was slightly older than the AOD <60 years group, although this difference in age did not reach statistical significance (AOD $\geqslant$60 years: age = 74.1 years; AOD <60 years: age = 69.6 years; $t=1.904$, df = 29, $p=0.067$).

Discussion

In this comparison of the neurocognitive performance of older and younger adults with major depression we found a robust difference in verbal learning and memory and a subtle effect in motor speed, with older

https://doi.org/10.1017/S0033291708004042 Published online by Cambridge University Press

depressed subjects being significantly more impaired than younger depressed subjects. Those with a late onset of depression were similarly more impaired than depressed subjects with an early age of onset, although this was only at a trend level of significance and may reflect a type 2 error. We did not identify any differences in visuospatial learning or attention and executive function between the groups. Our main hypotheses were therefore only partly supported, as we had hypothesized differences in executive function as well as in verbal learning and memory.

To our knowledge this study is the largest comparison of neuropsychological performance between older and younger adults with depression and the first to specifically examine verbal and visuospatial learning and memory. Although the study may have been more robust with larger numbers of subjects, especially in our exploratory analyses, the main findings are highly significant (or non-significant) and not therefore likely to have been altered with larger groups. The groups were well matched on potentially important confounding variables: global cognitive function (measured using the MMSE), severity of depression (as assessed by the MADRS) and in premorbid intelligence (tested using the NART). Study subjects were drawn from community and hospital clinics and there may have been differences in the recruitment pattern of patients, reflecting the underlying differences in the nature of the service provision for the different age groups. However, the two patient groups were very similar in MADRS and NART scores, suggesting that if any differences were present they were subtle and unlikely to have affected our findings.

The younger depressed subjects spent a little less time in education than their controls but as their NART scores were well matched this is not likely to be a clinically important difference. The main difference, apart from age, was in antidepressant treatment. We do not think this is likely to have affected our findings because most of the antidepressants used were SSRIs. Studies in healthy volunteers on the cognitive effects of SSRIs (e.g. Hasbroucq *et al*. 1997; Furlan *et al*. 2001; Siepmann *et al*. 2003) involving both younger (Siepmann *et al*. 2003) and older subjects (Furlan *et al*. 2001) have reported either no change or an improvement in measures of memory and attention. Similarly, a study of older people with mild cognitive impairment, but no depression, reported improvement in global cognition and memory on fluoxetine (Mowla *et al*. 2007).

In an investigation by Lockwood *et al*. (2002), executive impairment was reported in late-life depression; specifically, they identified differences in response initiation and inhibition and in set shifting but, as in our study, they did not find differences in attention compared with younger depressed subjects. They also took age 60 as the cut-off for younger *versus* older groups, had similar aged groups, a similar age difference (of about 40 years) between groups, and their subjects, like ours, had severe depression. In another similar previous investigation, Tarbuck & Paykel (1995) examined two groups of depressed in-patients, again using a cut-off of 60 years of age. The groups were well matched for gender, number of previous episodes, NART-estimated IQ and severity of depressive symptoms, and were assessed on a comprehensive battery of tests during the depressive episode and upon recovery. Overall, significant effects of age were observed on the majority of tests administered, both when depressed and after recovery, with tasks assessing complexity being disproportionately impaired in the older depressed group. This absence of a difference in executive function is especially surprising because not only was it identified in these studies but also, compared with EOD, LOD has usually been associated with such a pattern of impairment (Herrmann *et al*. 2007). We used a conservative approach to analysis and because our MANOVA on the executive composite domain did not identify any differences we did not conduct further analyses. Our surprising finding here suggests that there may be important heterogeneity among even those with more severe late-life depression or it may simply reflect the heterogeneity of measures used to assess executive function, which is a broad construct, encompassing several related domains.

We had hypothesized that we would find more widespread differences between the older and younger depressed groups. Our findings support the view that, with the exception of verbal learning and motor speed (although the latter was only for the Vigil test of reaction time), the more severe impairments in older people with depression are primarily due to ageing rather than to differences in the nature of depressive illness in later life because ageing itself produces a similar pattern of neurocognitive impairment to depression (Austin *et al*. 2001). That the most robust difference was in verbal learning and memory raises the question of whether this is due to a subgroup of the older depressed subjects having early Alzheimer's disease. None of our older subjects met standard criteria for dementia because any such potential subjects were excluded from the study. We have been able to follow-up many of the study subjects for up to 4 years and none have developed dementia, suggesting that incipient Alzheimer's disease in some of our subjects is not the explanation of the larger verbal memory impairment we identified in the older depressed group. Our findings of greater verbal declarative

memory impairment in older depressed subjects may reflect a greater hippocampal volume reduction in this group (Steffens *et al*. 2000). Although it should be noted that, as can be seen in Fig. 1, the *z* score difference remains level across successive presentations in the younger depressed group while increasing over successive presentations in the older group. This suggests that the rate of learning in the younger group is constant relative to their controls, but is reduced in the older group. In addition, despite reduced delayed recall in older relative to younger depressed subjects, the percentage retention index did not differ significantly, suggesting that impaired delayed recall in the older group was the result of poorer initial learning or encoding. The pathophysiology of this remains to be determined, although both cortisol toxicity and damage due to vascular disease have been proposed, as discussed below.

An important difference, likely to be relevant, between the younger and older depressed groups is that the former were physically healthy whereas the latter had co-morbidity typical of older people with depression, especially vascular disease. Although the cognitive impairment profile typical of cerebrovascular disease is of executive dysfunction and impaired attention (O'Brien, 2006), prominent impairments in memory are recognized and reported (Jokinen *et al*. 2006) and in some studies impairments in verbal memory and psychomotor speed have been most prominent (Nyenhuis *et al*. 2004). Thus, cerebrovascular disease may explain part of this increased impairment in late-life depression. An alternative explanation for the difference in late-life depression is the greater dysfunction in the hypothalamic–pituitary–adrenal (HPA) axis, associated with memory impairment, compared with depression in earlier life (Rubin *et al*. 1987; O'Brien *et al*. 1996). Given the robust evidence for age-related HPA axis dysfunction and memory impairments in age-related cerebrovascular disease, then both are likely to be contributors to our findings.

The difference we identified between older and younger depressed subjects on motor speed resulted from the older subjects having slower reaction times on the Vigil CPT. We do not think this is due to age-related physical impairment because each group was compared to its age-matched control group, or to depression severity and more severe psychomotor retardation in the older group because the younger and older depressed subjects showed similar levels of depression severity on the MADRS (see Table 1). However, it is possible that a similar burden of depression may have a greater impact on cognition in the older depressed group because of a loss of cognitive reserve in this group due to the combined effect of other factors, such as a higher burden of cerebrovascular disease and a longer exposure to HPA axis-related hypercortisolaemia. Furthermore, recent reports (Butters *et al*. 2004*b*; Sheline *et al*. 2006) on the neurocognition of late-life depression have indicated that information processing speed may be the core deficit in late-life depression, underpinning the range of other deficits. Impaired reaction time appears to be tapping into this same domain (information processing speed) and this may therefore not only be key to cognitive impairment in late-life depression but also a deficit that is different (more severe) in late-life compared with early life depression. However, as our study was designed before these findings were reported, we are not able to examine this important issue more closely. Furthermore, in a recent follow-up study of the younger patients and controls we found evidence that baseline psychomotor impairment was the only domain that differed between patients who remitted and those who did not at <6 months (Gallagher *et al*. 2007). Although this is only a preliminary finding, it may suggest that psychomotor impairment in younger depressed patients may be predictive of individuals who may develop a more chronic or recurrent illness. In the context of the present findings, it was also of interest that there was evidence of a significantly greater improvement in verbal declarative memory in patients who remitted compared to those who did not (Gallagher *et al*. 2007).

The sex difference we identified, due to women performing better than men on verbal learning, has been reported previously (Herlitz *et al*. 1997, 1999; Lewin *et al*. 2001) and, as in our study, appears to be a feature common to mid-life and late-life depression (Herlitz *et al*. 1997) that persists up to 90 years of age (de Frias *et al*. 2006).

Although age of depression onset is an important issue, we did not design our study to investigate this and the interpretation of our exploratory analyses needs to take this into account. The issue has been investigated previously by other groups and a recent review of the literature on late-life depression identified executive dysfunction to be typical of LOD compared with EOD (Herrmann *et al*. 2007). However, our finding that LOD subjects may have greater impairments in learning and memory is consistent with some previous reports (e.g. Salloway *et al*. 1996) and with our main findings supporting the view that late-life depression may be different cognitively from depression in younger adults.

In conclusion, we have addressed the specific question of whether depression in older people, compared with depression in younger adults, is associated with more severe cognitive impairments after correcting for age-related changes. We have reported

https://doi.org/10.1017/S0033291708004042 Published online by Cambridge University Press

evidence here suggesting that the illness itself accounts for some of the difference in the poorer cognitive performance in late-life depression. We believe that our approach, normalizing depression groups against age-matched comparison groups, combined with the relatively large numbers for such a study and the detailed neuropsychological assessment used, makes our findings robust and relevant.

Appendix: Neurocognitive tests included in each domain

(i) Attention and executive function	FAS: total correct SWM: between-search errors Vigil: omission and commission errors
(ii) Verbal learning and memory	RAVLT: total trials 1–5 RAVLT: trial A7 delayed recall RAVLT: list A delayed recognition
(iii) Visuospatial learning and memory	PRM: correct SRM: correct
(iv) Motor speed	Vigil: latency PRM: latency for correct responses SRM: latency for correct responses

FAS, Benton's FAS; SWM, Spatial Working Memory; RAVLT, Rey Auditory Verbal Learning Test; PRM, Pattern Recognition Memory; SRM, Spatial Recognition Memory.

Declaration of Interest

None.

References

Abas MA, Sahakian BJ, Levy R (1990). Neuropsychological deficits and CT scan changes in elderly depressives. *Psychological Medicine* **20**, 507–520.

Austin MP, Mitchell P, Goodwin GM (2001). Cognitive deficits in depression: possible implications for functional neuropathology. *British Journal of Psychiatry* **178**, 200–206.

Austin MP, Mitchell P, Wilhelm K, Parker G, Hickie I, Brodaty H, Chan J, Eyers K, Milic M, Hadzi-Pavlovic D (1999). Cognitive function in depression: a distinct pattern of frontal impairment in melancholia? *Psychological Medicine* **29**, 73–85.

Beats BC, Sahakian BJ, Levy R (1996). Cognitive performance in tests sensitive to frontal lobe dysfunction in the elderly depressed. *Psychological Medicine* **26**, 591–603.

Benton AL, Hampsher K (1976). *Multilingual Aphasia Examination*. University of Iowa: Iowa City.

Bhalla RK, Butters MA, Mulsant BH, Begley AE, Zmuda MD, Schoderbek B, Pollock BG, Reynolds 3rd CF, Becker JT (2006). Persistence of neuropsychologic deficits in the remitted state of late-life depression. *American Journal of Geriatric Psychiatry* **14**, 419–427.

Brodaty H, Luscombe G, Parker G, Wilhelm K, Hickie I, Austin MP, Mitchell P (1997). Increased rate of psychosis and psychomotor change in depression with age. *Psychological Medicine* **27**, 1205–1213.

Brodaty H, Peters K, Boyce P, Hickie I, Parker G, Mitchell P, Wilhelm K (1991). Age and depression. *Journal of Affective Disorders* **23**, 137–149.

Butters MA, Becker JT, Nebes RD, Zmuda MD, Mulsant BH, Pollock BG, Reynolds 3rd CF (2000). Changes in cognitive functioning following treatment of late-life depression. *American Journal of Psychiatry* **157**, 1949–1954.

Butters MA, Bhalla RK, Mulsant BH, Mazumdar S, Houck PR, Begley AE, Dew MA, Pollock BG, Nebes RD, Becker JT, Reynolds 3rd CF (2004*a*). Executive functioning, illness course, and relapse/recurrence in continuation and maintenance treatment of late-life depression: is there a relationship? *American Journal of Geriatric Psychiatry* **12**, 387–394.

Butters MA, Whyte EM, Nebes RD, Begley AE, Dew MA, Mulsant BH, Zmuda MD, Bhalla R, Meltzer CC, Pollock BG, Reynolds 3rd CF, Becker JT (2004*b*). The nature and determinants of neuropsychological functioning in late-life depression. *Archives of General Psychiatry* **61**, 587–595.

Cegalis J, Bowen J (1991). *Vigil: Software for the Assessment of Attention*. Forthought: Nashua, NA.

de Frias CM, Nilsson L-G, Herlitz A (2006). Sex differences in cognition are stable over a 10-year period in adulthood and old age. *Aging, Neuropsychology, and Cognition* **13**, 574–587.

Elliott R, Baker SC, Rogers RD, O'Leary DA, Paykel ES, Frith CD, Dolan RJ, Sahakian BJ (1997). Prefrontal dysfunction in depressed patients performing a complex planning task: a study using positron emission tomography. *Psychological Medicine* **27**, 931–942.

Folstein MF, Folstein SE, McHugh PR (1975). 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research* **12**, 189–198.

Furlan PM, Kallan MJ, Ten Have T, Pollock BG, Katz I, Lucki I (2001). Cognitive and psychomotor effects of paroxetine and sertraline on healthy elderly volunteers. *American Journal of Geriatric Psychiatry* **9**, 429–438.

Gallagher P, Robinson LJ, Gray JM, Porter RJ, Young AH (2007). Neurocognitive function following remission in major depressive disorder: potential objective marker of response? *Australian and New Zealand Journal of Psychiatry* **41**, 54–61.

Hasbroucq T, Rihet P, Blin O, Possamai CA (1997). Serotonin and human information processing: fluvoxamine can improve reaction time performance. *Neuroscience Letters* **229**, 204–208.

Herlitz A, Airaksinen E, Nordstrom E (1999). Sex differences in episodic memory: the impact of verbal and visuospatial ability. *Neuropsychology* **13**, 590–597.

Herlitz A, Nilsson LG, Backman L (1997). Gender differences in episodic memory. *Memory and Cognition* **25**, 801–811.

Herrmann LL, Goodwin GM, Ebmeier KP (2007). The cognitive neuropsychology of depression in the elderly. *Psychological Medicine* **37**, 1693–1702.

Hornblow AR, Bushnell JA, Wells JE, Joyce PR, Oakley-Browne MA (1990). Christchurch Psychiatric Epidemiology Study: use of mental health services. *New Zealand Medical Journal* **103**, 415–417.

Jokinen H, Kalska H, Mantyla R, Pohjasvaara T, Ylikoski R, Hietanen M, Salonen O, Kaste M, Erkinjuntti T (2006). Cognitive profile of subcortical ischaemic vascular disease. *Journal of Neurology, Neurosurgery and Psychiatry* **77**, 28–33.

Kalayam B, Alexopoulos GS (1999). Prefrontal dysfunction and treatment response in geriatric depression. *Archives of General Psychiatry* **56**, 713–718.

Kramer-Ginsberg E, Greenwald BS, Krishnan KR, Christiansen B, Hu J, Ashtari M, Patel M, Pollack S (1999). Neuropsychological functioning and MRI signal hyperintensities in geriatric depression. *American Journal of Psychiatry* **156**, 438–444.

Lesser IM, Boone KB, Mehringer CM, Wohl MA, Miller BL, Berman NG (1996). Cognition and white matter hyperintensities in older depressed patients. *American Journal of Psychiatry* **153**, 1280–1287.

Lewin C, Wolgers G, Herlitz A (2001). Sex differences favoring women in verbal but not in visuospatial episodic memory. *Neuropsychology* **15**, 165–173.

Lockwood KA, Alexopoulos GS, van Gorp WG (2002). Executive dysfunction in geriatric depression. *American Journal of Psychiatry* **159**, 1119–1126.

Montgomery SA, Åsberg M (1979). A new depression scale designed to be sensitive to change. *British Journal of Psychiatry* **134**, 382–389.

Mowla A, Mosavinasab M, Pani A (2007). Does fluoxetine have any effect on the cognition of patients with mild cognitive impairment? A double-blind, placebo-controlled, clinical trial. *Journal of Clinical Psychopharmacology* **27**, 67–70.

Nelson HE (1982). *National Adult Reading Test, NART*. Nelson Publishing Company: Windsor.

Nyenhuis DL, Gorelick PB, Geenen EJ, Smith CA, Gencheva E, Freels S, deToledo-Morrell L (2004). The pattern of neuropsychological deficits in Vascular Cognitive Impairment-No Dementia (Vascular CIND). *Clinical Neuropsychologist* **18**, 41–49.

O'Brien JT (2006). Vascular cognitive impairment. *American Journal of Geriatric Psychiatry* **14**, 724–733.

O'Brien JT, Ames D, Schweitzer I, Colman P, Desmond P, Tress B (1996). Clinical and magnetic resonance imaging correlates of hypothalamic-pituitary-adrenal axis function in depression and Alzheimer's disease. *British Journal of Psychiatry* **168**, 679–687.

O'Brien JT, Lloyd A, McKeith I, Gholkar A, Ferrier N (2004). A longitudinal study of hippocampal volume, cortisol levels, and cognition in older depressed subjects. *American Journal of Psychiatry* **161**, 2081–2090.

O'Brien JT, Sahakian BJ, Checkley SA (1993). Cognitive impairments in patients with seasonal affective disorder. *British Journal of Psychiatry* **163**, 338–343.

Paradiso S, Lamberty GJ, Garvey MJ, Robinson RG (1997). Cognitive impairment in the euthymic phase of chronic unipolar depression. *Journal of Nervous and Mental Disease* **185**, 748–754.

Porter RJ, Bourke C, Gallagher P (2007). Neuropsychological impairment in major depression: its nature, origin and clinical significance. *Australia and New Zealand Journal of Psychiatry* **41**, 115–128.

Porter RJ, Gallagher P, Thompson JM, Young AH (2003). Neurocognitive impairment in drug-free patients with major depressive disorder. *British Journal of Psychiatry* **182**, 214–220.

Rey A (1964). *Clinical Examination in Psychology*. University of Paris: Paris

Rubin RT, Poland RE, Lesser IM, Martin DJ, Blodgett AL, Winston RA (1987). Neuroendocrine aspects of primary endogenous depression. III. Cortisol secretion in relation to diagnosis and symptom patterns. *Psychological Medicine* **17**, 609–619.

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

Sheline YI, Barch DM, Garcia K, Gersing K, Pieper C, Welsh-Bohmer K, Steffens DC, Doraiswamy PM (2006). Cognitive function in late life depression: relationships to depression severity, cerebrovascular risk factors and processing speed. *Biological Psychiatry* **60**, 58–65.

Siepmann M, Grossmann J, Muck-Weymann M, Kirch W (2003). Effects of sertraline on autonomic and cognitive functions in healthy volunteers. *Psychopharmacology* **168**, 293–298.

Simpson S, Baldwin RC, Jackson A, Burns AS (1998). Is subcortical disease associated with a poor response to antidepressants? Neurological, neuropsychological and neuroradiological findings in late life depression. *Psychological Medicine* **28**, 1015–1026.

Steffens DC, Byrum CE, McQuoid DR, Greenberg DL, Payne ME, Blitchington TF, MacFall JR, Krishnan KR (2000). Hippocampal volume in geriatric depression. *Biological Psychiatry* **48**, 301–309.

Tarbuck AF, Paykel ES (1995). Effects of major depression on the cognitive function of younger and older subjects. *Psychological Medicine* **25**, 285–295.