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Decreased working memory and processing speed mediate cognitive impairment in geriatric depression

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ABSTRACT

Background. While neuropsychological dysfunction is common in geriatric depression, not all aspects of cognition are equally affected. It has been suggested that depressed patients are impaired only in tasks that make heavy demands on processing resources and that a resource decrement therefore underlies the neuropsychological decrements seen in geriatric depression. The present study examined whether processing resources in the form of working memory and information processing speed are decreased in depression and whether a decrease in these resources actually mediates neuropsychological impairment.

Methods. Measures of processing resources were administered to elderly depressed patients prior to treatment and to age-matched controls. Patients whose depression remitted were retested as were the controls. Subjects also received neuropsychological tests of episodic memory and visuospatial performance.

Results. Depressed patients performed significantly worse on measures of both processing speed and working memory. While performance on these measures improved in patients whose depression remitted, the amount of improvement was no greater than that seen in the controls with repeat testing. Hierarchical regression analyses showed that depression explained a significant amount of variance on the neuropsychological tasks. However, if the variance associated with processing resources was removed first, depression no longer accounted for a significant amount of neuropsychological variance.

Conclusions. Processing resources are decreased in elderly depressed patients and this decrease in resources appears to mediate impairments in several areas of neuropsychological functioning including episodic memory and visuospatial performance. The resource decrement persists after remission of the depression and thus may be a trait marker of geriatric depression.

INTRODUCTION

While cognitive dysfunction is common among older persons suffering from a major depression, not all components of cognition are equally impaired (Boone *et al*. 1995; Lichtenberg *et al*. 1995; Veiel, 1997; Zakzanis *et al*. 1998). The pattern of preserved and impaired cognitive performance associated with depression has led some researchers to propose that decrements occur only in those cognitive operations that require substantial amounts of 'effortful' processing and not in operations that are carried out relatively 'automatically' (Hasher & Zacks, 1979; Roy-Byrne *et al*. 1986; Tancer *et al*. 1990; Hartlage *et al*. 1993; Zakzanis *et al*. 1998). Humans appear to have a relatively limited amount of general-purpose attentional resources that can be allocated at any given moment to ongoing mental activities. The efficiency with which effortful mental operations (e.g. learning, problem-solving) can be carried out is postulated to depend on availability of these attentional resources, whereas automatic operations (e.g. activation of word meaning; incidental encoding of certain types of information) are viewed as

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occurring independently of attentional resources (Hasher & Zacks, 1979). The various cognitive decrements found in older depressed patients may, therefore, result not from deficits in specific cognitive operations (e.g. memory encoding), but rather from a reduction in the quantity of general-purpose processing resources which act to facilitate the efficient functioning of a wide array of effortful mental operations.

Several possible mechanisms have been proposed for how depression might reduce processing resources in geriatric patients. One is that the absolute amount of processing resources actually remains unchanged, but some of depressed patients' resources are focused on negative thoughts and depression-relevant themes and thus are not available for task-relevant processing (Hartlage *et al.* 1993). Another possibility is that the total amount of processing resources is actually diminished due to biological factors associated with late-life depression, such as a dopaminergic dysfunction (Roy-Byrne *et al.* 1986) or neuropathology (Videbech, 1997).

Evidence that depression is associated with a reduction in processing resources comes from a fairly restricted set of studies. Much of this work has focused on the relative success that depressed patients have in encoding different types of information into episodic memory (Roy-Byrne *et al.* 1986; Hartlage *et al.* 1993). Depressed patients perform more poorly (in comparison to age matched normals) on tasks involving intentional encoding strategies (e.g. the use of semantic structure or associations) than on tasks in which information is encoded into memory incidentally (i.e. automatically). Less attention has been paid to actually measuring the processing resources themselves. Processing resources have typically been operationalized as working memory capacity and speed of information processing. Working memory is conceptualized as a limited-capacity mental workspace involving both the short-term storage of information and the simultaneous manipulation of the contents of this store by executive processes. It therefore is not just a passive store of information but rather the storage of information in the service of ongoing cognitive operations (e.g. the maintenance of intermediate results or the products of previous processing steps needed in upcoming cognitive operations). As such, working memory is postulated to play an important role in higher-level processes ranging from language comprehension to reasoning (Gathercole, 1994).

Processing speed is the maximum rate at which elementary cognitive operations can be executed. It can be viewed as a general-purpose resource in that the rate of processing limits performance on higher-level operations (Krail & Salthouse, 1994). There is often a race between the rate at which information can be processed and the rate at which it becomes obsolete or unavailable due to decay or displacement. If processing steps are carried out too slowly, the products of earlier operations may be lost or no longer relevant by the time later operations occur. The speed at which elementary mental operations are completed also determines the amount of simultaneously active information available for higher-level processes. Many higher-order processes (e.g. comprehension of language) require simultaneous access to multiple sources of information. If processing is too slow, not all information may be available at the time it is needed and therefore the subject may be forced to re-activate information or to repeat processing steps. It is important to note that the effect of processing speed is not restricted to timed tasks or to tasks with speeded components. Its effect on performance is based on the internal dynamics of the processing system, not just the time required to complete the task. A generalized slowing of information processing is commonly thought to be the source of many of the cognitive decrements associated with normal ageing (Hale & Jansen, 1994; Salthouse, 1996*a*). Even age decrements in working memory capacity have been suggested to arise partly from a slowing of cognitive processing (Salthouse, 1992*a*) in that in the dominant model of working memory, the amount of information that can be held in working memory is partly determined by the speed with which it can be refreshed through rehearsal (Baddeley, 1996).

The few studies that have directly tested working memory capacity in depressed patients (Channon *et al.* 1993; Lyness *et al.* 1994) have found depressed patients to perform poorly on some, but certainly not all, tasks thought to make substantial demands on working memory. By contrast, there is substantial literature demonstrating psychomotor slowing in de-

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pression (Sobin & Sackeim, 1997), although the degree to which this represents a slowing in the rate of cognitive processing as opposed to a more sensorimotor slowing is still not settled (Hart & Kwentus, 1987; Nebes *et al.* 1998). Certainly, to the extent that speed is considered a processing resource it would be the rate of information processing not the speed with which subjects can carry out motor responses that would be relevant.

Thus, it is still an open question whether working memory and information-processing speed are actually reduced in depression and, more importantly, whether any such reduction is responsible for other cognitive decrements seen in older depressed patients. There are a number of limitations to our present knowledge. First, the effects that depression has on working memory and on processing speed have not been examined at the same time in the same patients and so it is not clear whether just one or both types of processing resources are decreased with depression. A second issue is whether any decrement in processing resources in depressed patients persists after the depression remits. Some of the mechanisms postulated to produce a decrease in processing resources assume that it is a secondary effect of the depressed mood (e.g. resources are diverted to negative thoughts). If true, then one might expect the amount of available processing resources (i.e. working memory capacity and processing speed) to increase when the patients' depression remits. However, it is also possible that the decrement in processing resources is a stable trait arising from brain changes associated with late-life depression. Magnetic resonance imaging (MRI) studies have shown an increased prevalence of structural abnormalities in the brains of older depressed patients, including white matter hyperintensities and atrophy in the form of ventricular and sulcal enlargement (Videbech, 1997). There is evidence linking the severity of such structural abnormalities to deficits in depressed patients' performance on a variety of cognitive tasks (Lesser *et al.* 1996; Simpson *et al.* 1997). If such brain changes are the source of decreased processing resources in depressed patients, then the amount of available processing resources should remain unchanged following remission of the depression. Of course, any improvement in performance between the time patients are depressed and when they remit could reflect merely a practice effect. To demonstrate that remission of depression produces an improvement in processing resources beyond that attributable to practice requires that we compare any change in the performance of depressed patients over the course of treatment to that occurring in normal age-matched controls tested at the same intervals.

Finally, and most importantly, there is still little direct evidence that limitations in processing resources are actually responsible for depressed patients' difficulties on higher-level cognitive tasks. One way to investigate this issue is to use hierarchical regression to examine the amount of depression-related variance (i.e. the performance difference between depressed and normal-old subjects) present in cognitive tasks both before and after controlling for the variance associated with measures of processing speed or working memory. The rationale is that the degree to which the depression-related variance on a task is reduced by statistically controlling for working memory and processing speed reflects the importance of these resources in mediating the effect that depression has on that task. This approach equates the depressed and normal-old with respect to an index of processing resources in order to determine whether there is any direct effect of depression left after removing the effect of differences in processing resources. It should be noted that this procedure is concerned only with the variance associated with depression and not all sources of variance on the task. This approach has been used extensively in studies exploring the source of the cognitive decrements associated with normal ageing (Salthouse, 1992*a*, 1996*b*; Krail & Salthouse, 1994; Kirasic *et al.* 1996). These studies have shown that statistically controlling for working memory capacity and/or processing speed greatly attenuates age differences on a variety of higher-level cognitive tasks from episodic memory to problem solving. These results have been interpreted as strong evidence that processing resources are a major mediator of the deleterious effect that normal ageing has on cognition. In the present study, we used a similar approach to examine the role that possible limitations in processing resources have in producing the cognitive decrements found in the elderly depressed.

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It should be noted that the mere presence of a deficit in working memory or processing speed does not necessarily mean that these processing resources mediate co-existing performance decrements on higher-level cognitive operations. Sliwinski & Buschke (1997) found that while Alzheimer's disease patients show a substantial slowing (in comparison to the normal-old) on cognitive tasks, removing the influence of processing speed only minimally attenuated the Alzheimer-related variance on episodic-memory tasks. They interpreted this as evidence that the episodic memory impairment seen in Alzheimer's disease has a different mechanism from that causing the milder memory decrement associated with normal ageing.

In the present study we examined the performance of patients with late-life depression on measures of working memory and processing speed, both when the patients were depressed and after successful treatment. The study had three goals. The first was to investigate whether late-life depression is associated with a decrease (in comparison to the normal-old) on measures of working memory and processing speed. The second was to examine whether depressed patients' performance on measures of processing resources normalized when their depression remitted. The final and most important goal of this project was to determine whether there was any evidence that a decrease in working memory and/or processing speed mediated depression-related deficits on a variety of complex neuropsychological tasks. This latter analysis examined whether the higher-order cognitive impairments seen in depressed older patients have the same source as the milder decrements of normal ageing or whether they are due to a qualitatively different mechanism, as appears to be the case in Alzheimer's disease (Sliwinski & Buschke, 1997).

METHOD

Subjects

The 39 depressed geriatric patients in this study were all participants in a double-blind randomized treatment trial comparing nortriptyline and paroxetine conducted by the Mental Health Clinical Research Center for the Study of Late-Life Mood Disorders at the University of Pittsburgh. This treatment trial recruited patients from the two geriatric in-patient units and the out-patient Late-Life Depression Research Clinic of Western Psychiatric Institute and Clinic, a teaching hospital of the University of Pittsburgh Medical Center. All patients suffered from a major depressive disorder (non-bipolar and non-psychotic). After the patient had signed an informed consent, a geropsychiatric team carried out a comprehensive evaluation that included a psychiatric, social and medical history, a physical examination and a battery of laboratory tests (Mulsant *et al.* 1994). Each patient was given, among other measures, the Structured Clinical Interview for *DSM-IV* Disorders (First *et al.* 1994), the 17-item version of the Hamilton Rating Scale for Depression (HRSD; Hamilton, 1967), the Mini-Mental State Examination (MMSE; Folstein *et al.* 1975) and the Dementia Rating Scale (DRS; Mattis, 1988). Based on all information available, Axis I and Axis II diagnoses were established during a consensus conference according to *DSM-IV* (American Psychiatric Association, 1994) criteria. For entry into the treatment study a patient's baseline HRSD score had to be > 15. Exclusion criteria included a history of other major psychiatric or neurological disorders (e.g. psychosis, alcoholism, stroke, Parkinson's disease). During a 12 week acute-treatment phase, patients were reassessed weekly with the HRSD and other scales and their antidepressant dosage was adjusted based on operationalized guidelines (Mulsant *et al.* 1999). Remission from depression was defined as a HRSD score of $\leqslant 10$ for 3 consecutive weeks. Patients who did not respond during the 12-week acute-treatment phase, or who experienced unacceptable side effects were switched openly to the other antidepressant (Rescue phase).

Data are reported from all the depressed patients in the treatment study for whom complete cognitive and neuropsychological results were available. We did, however, exclude patients who carried a diagnosis of Alzheimer's disease or other dementing illness or whose score on the DRS was $> 1{\cdot}5$ standard deviations below the normative mean (i.e. below 128; Mattis, 1988). Obviously, without long-term follow-up we cannot be certain that our sample did not include patients with an incipient dementia, but we did exclude patients who were

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Table 1. *Baseline characteristics (mean and standard deviation) for the total depressed sample, the subgroup of patients whose depression remitted and the normal old controls*

	N	Age Mean (S.D.)	Education Mean (S.D.)	HRSD Mean (S.D.)	DRS Mean (S.D.)
All depressed patients	39	70·8 (7·1)	12·7 (2·2)	23·3 (4·5)	137·4 (3·8)
Depressed remitters	20	72·0 (6·8)	12·2 (2·0)	22·3 (4·0)	136·6 (4·4)
Normal old controls	19	70·4 (7·9)	13·2 (2·3)	2·1 (1·5)	138·4 (3·7)

HRSD, Hamilton Rating Scale for Depression; DRS, Dementia Rating Scale.

currently demented. The mean age, education and baseline HRSD, MMSE and DRS of the depressed patients are found in Table 1.

Of the 39 depressed patients in this study, 20 were cases of recurrent depression, while 19 were in their first episode of depression. Fifteen had an early-onset of depression, with a first episode of depression occurring at or before age 59 (mean = 42·7, S.D. = 10·7), while 24 had a late-onset of depression, with a first episode occurring at age 60 or later (mean = 68·9, S.D. = 6·5). Twenty-one of the 39 patients experienced a remission of their depression with treatment, of whom 20 were available for retesting. Of these, 16 responded to the antidepressant to which they had been initially randomized (five to nortriptyline and 11 to paroxetine), while the remaining four patients failed to respond to the initial antidepressant but did remit in the Rescue phase when they were switched openly to the other antidepressant (one responding to nortriptyline and three to paroxetine).

We also tested a group of 19 normal elderly controls recruited from the community to match the patients in age and education. These individuals went through the same diagnostic procedures as the depressed patients (SCID, HRSD, etc.) and were tested at the same intervals. The control subjects did not differ from the total sample of 39 depressed patients (see Table 1) in either age ($t(56) = 0{\cdot}22$) or education ($t(56) = 0{\cdot}74$), neither did these controls differ in age ($t(37) = 0{\cdot}68$) or education ($t(37) = 0{\cdot}16$) from the subgroup of 20 depressed patients who remitted.

Working-memory and processing-speed measures

There are no pure measures of working memory or processing speed, although there are tasks that make especially high demands on these resources and thus are good markers for these constructs. We chose our working-memory and processing speed measures based on the extensive normal-ageing literature investigating how processing resources affect cognitive performance. Our measure of working memory was the *N* back test (Dobbs & Rule, 1989) in which subjects listen to a string of digits presented at the rate of one digit per second. As they hear each digit, they are to say the digit that occurred *N* back in the string. In the first condition, $N = 0$ which means that the subjects are to repeat the digit they just heard. In the next condition, $N = 1$, they are to say the digit immediately prior to the digit they just heard. For example, if given the digit string '5, 2, 7, 1, 9 …', they would say nothing after the first digit; after hearing '2' they would say '5'; after hearing '7', they would say '2', etc. If this particular digit string was presented in the $N = 2$ condition, they would say nothing after the first two items, then after they heard '7', they would say '5'; after they heard '1', they would say '2', etc. Thus, the $N = 1$ and following conditions ($N = 2$, 3, 4 and 5) require subjects to add the most recent digit to their memory, keep the digit string in order, retrieve the appropriate item from earlier in the string and then drop it from memory after they have given it as a response. Subjects were given two digit strings for each condition, with each string having ten digits that required a response (e.g. for $N = 1$ the string would be 11 items long since the subject did not respond to the first digit, while for $N = 2$ the string would be 12 digits long, etc.). Each string was presented until the subject made an error. Their score on that string was then the number of correct responses they gave before making an error. Thus, the maximum possible correct on each string was 10 and since there were two strings for each of the six conditions ($N = 0$, 1, 2, 3, 4 and 5), the total possible score was 120. Normal ageing is associated with a substantial

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decrement on this task (Dobbs & Rule, 1989) and, like other working memory tasks, the *N* back test activates dorsolateral prefrontal cortex (Braver *et al.* 1997).

Our measure of processing speed was derived from the Digit Symbol Substitution Test (DSST), a subtest of the Wechsler Adult Intelligence Test – Revised (Wechsler, 1981). The DSST has a code table at the top of the page in which the digits 1 through 9 are arranged in numerical order. Beneath each digit in the table is a different symbol. Below the code table are rows of double boxes, one box above the other. In the top of each double box is a digit while the bottom box is empty. The subject has 90 s to write in each bottom box the symbol paired with that digit in the code table. The subjects' performance was expressed as mean time-per-correct response (90 s/number of correct responses). While the DSST has been shown to be an excellent measure of information-processing speed (Salthouse, 1992*b*) it does have a problem in that the speed with which subjects can write also contributes to task performance. To reduce the contribution of this motor component of the task, we used an approach devised by Storandt (1976). This involves giving a companion task that has the same general format as the DSST except that the digits above the response boxes are replaced by the symbols associated with those digits in the coding key, and the subject has only to copy the symbols. Since the sensorimotor requirements of this Copy task and the DSST are similar, by subtracting the mean time-per-item on the Copy task from that on the DSST it is possible to obtain a purer measure of the time it takes an individual to perform the more cognitive aspects of the DSST. Storandt (1976) called the difference in mean time-per-item between the DSST and the Copy test Coding Time and we used this as our measure of processing speed.

Neuropsychological battery

As part of their baseline workup for the antidepressant treatment study, the depressed patients and controls had been administered a large battery of standardized neuropsychological tests that examined a variety of cognitive domains. Preliminary examination of the results from this battery showed that a number of these measures showed robust differences between the depressed patients and the normal old including: (*a*) the MMSE; (*b*) the Block Design subtest from the WAIS III (Wechsler, 1997*a*); (*c*) the Logical Memory subtest – immediate recall, from the Wechsler Memory Scale III (Wechsler, 1997*b*); (*d*) immediate recall summed across five presentations of List A from the California Verbal Learning Test (Delis *et al.* 1987); and (*e*) immediate recall of the Rey-Osterreith Complex Figure (Osterrieth, 1944). These particular measures were therefore used in analyses examining whether differences in processing resources between the depressed and normal old subjects could explain the depression-associated decrements present in these tests of higher-level neuropsychological function.

Procedure

Results for the depressed patients on the tests of processing resources are from a baseline testing session, which took place before initiation of antidepressant therapy, and from a session at the end of acute treatment (only for the 20 patients who remitted). The test session at the end of acute treatment typically occurred 12 weeks after baseline, except for those patients who were switched to the Rescue phase where the interval was longer (16–20 weeks) because they restarted treatment with the other medication after failing to respond to the antidepressant to which they were originally randomized. When tested at the end of the acute-treatment phase, patients were in remission from their depression (i.e. their HDRS score had $\leqslant 10$ for 3 consecutive weeks) and were still taking an antidepressant. The data for the control subjects are from a baseline and a 12-week testing session. Results for the large neuropsychological test battery were available only from baseline testing on both patients and controls.

One factor complicating our evaluation of change in cognitive performance with recovery from depression is the presence of two different antidepressant treatments – nortriptyline and paroxetine. Nortriptyline produces substantial anticholinergic effects in depressed geriatric patients (Pollock *et al.* 1998) as well as some cognitive decrements (Meyers *et al.* 1991; Young *et al.* 1991). By contrast, paroxetine has a minimal anticholinergic effect (Pollock *et al.* 1998) and does not appear to produce major

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cognitive dysfunction (Hawley *et al*. 1997; Nebes *et al*. 1999). Since the deleterious effects of nortriptyline on cognition are commonly thought to result from the drug's anticholinergic effects (Meyers *et al*. 1991), we measured the total anticholinergicity present in the subjects' blood both at baseline and at retest following recovery. This allowed us to determine whether an increase in serum anticholinergicity associated with antidepressant treatment acted to reduce processing resources thus potentially masking a cognitive improvement associated with remission of the depression. A blood sample (10 ml) was drawn at each testing session to determine patients' serum anticholinergicity (SA). The serum was stored at −20 °C until assayed. We applied a radioreceptor binding assay developed by Tune & Coyle (1980) that uses the specific binding of tritiated quinuclidinyl benzilate (3H-QNB) for rat muscarinic brain receptors from the striatum and forebrain to quantify the concentration of anticholinergic drugs in the serum. Anticholinergic drugs competitively inhibit binding of 3H-QNB to rat muscarinic receptors. Atropine was used for displacement at various concentrations and the results are reported in picomoles of atropine equivalents (Pollock *et al*. 1998).

RESULTS

Effect of depression on processing resources

We compared the baseline performance of the total depressed sample ($N = 39$) to that of the normal controls on our two measures of processing resources using t tests (df = 56). In order to control for inhomogeneity of variance, the Coding Time data first underwent a log 10 transformation. The means (untransformed) for the two tasks are shown in Table 2. In both tasks the depressed patients performed significantly worse (df = 56) than did the normal old (Coding Time, $t = 3{\cdot}15$, $P < 0{\cdot}003$; N back, $t = 2{\cdot}99$, $P < 0{\cdot}005$). We then repeated these t tests (df = 37) using the baseline data from only those 20 depressed patients who later remitted. The remitters also performed significantly worse at baseline than did the normal old on both processing resource measures (Coding Time, $t = 2{\cdot}74$, $P < 0.01$; N back, $t = 2.90$, $P < 0{\cdot}007$).

Table 2. *Means* (*and standard deviations*) *on the processing-speed* (*Coding Time*) *and working-memory* (N *back*) *measures for the total depressed sample*, *the subgroup of patients whose depression remitted and the normal old controls*

	Coding Time Mean (S.D.)	*N* back Mean (S.D.)
All depressed	1·26 (0·6)	48·77 (17·1)
Depressed remitters		
Baseline results	1·32 (0·7)	46·25 (17·3)
Follow-up results	1·23 (0·7)	56·10 (20·8)
Normal old controls		
Baseline results	0·86 (0·3)	64·37 (21·6)
Follow-up results	0·77 (0·2)	69·63 (13·9)

Coding Time represents mean time (in seconds) per correct response on the DSST minus that on the symbol-copy test. For *N* back, the score is the number correct out of a maximum of 100.

Various patient characteristics have been shown to influence the severity of cognitive impairment in late-life depression including the severity of the depression and the age at onset of the first episode of depression. We therefore examined whether baseline performance in the total depressed sample varied as a function of these factors. Baseline HRSD prior to treatment did not correlate significantly with either Coding Time ($r = 0{\cdot}27$) or N back ($r = -0{\cdot}17$). When patients with an early onset of depression (age 59 and younger) were compared to those with a late onset of depression ($\geqslant 60$) using a t test (df = 37), there was no difference in performance on either Coding Time ($t = 0{\cdot}68$) or N back ($t = 0{\cdot}37$).

Change in processing resources with treatment

We next examined whether performance on the measures of processing resources improved with remission from depression. We compared the baseline performance of the 20 depressed patients with their performance at the end of acute treatment when their depression had remitted. Looking first at change in the severity of the patients' depression, the mean score of the 20 responders on HRSD at baseline was 22·3 (S.D. = 4·5); by the end of acute treatment it had decreased to 6·2 (S.D. = 3·0). To determine whether this decrease in the depression severity was associated with an improvement in the patients' processing resources, we had to account for any practice effect arising from taking the tests multiple times. We therefore used a repeated measures MANOVA to compare the change in performance from baseline to follow-up in the depressed patients to that in the elderly controls.

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If remission is associated with an improvement in processing resources that is more than just a practice effect, then we would expect to see a greater improvement in the performance of the depressed patients than in that of the controls. The MANOVA resulted in a significant effect of group: $F(2, 36) = 6{\cdot}05$, $P < 0{\cdot}01$ and time-of-testing: $F(2, 36) = 9{\cdot}09$, $P < 0{\cdot}001$. There was, however, no interaction between group and time-of-testing: $F(2, 36) = 0{\cdot}67$. The MANOVA was followed by univariate ANOVAs which looked at the two resource measures separately. They showed a significant main effect of group for both Coding Time ($F(1, 37) = 9{\cdot}36$, $P < 0{\cdot}005$) and N back ($F(1, 37) = 7.91$, $P < 0{\cdot}008$) with the normal old performing significantly better than the depressed on both measures. The effect of time-of-testing was also significant for both Coding Time ($F(1, 37) = 5{\cdot}80$, $P < 0{\cdot}03$) and N back ($F(1, 37) = 13{\cdot}97$, $P < 0{\cdot}001$) with performance improving from baseline to follow-up in both measures. However, there were no significant interactions between group and time-of-testing for either Coding Time ($F(1, 37) = 0{\cdot}05$) or N back ($F(1, 37) = 1{\cdot}29$). That is, the depressed patients and normal controls showed similar improvement between the baseline and follow-up testing sessions on both measures of processing resources. We next examined whether the magnitude of the decrease in HRSD shown by patients between baseline and follow-up correlated with the change in their performance between sessions. Change in HRSD did not correlate significantly with change in either Coding Time ($r = 0{\cdot}01$) or N back ($r = 0{\cdot}05$). Thus, overall, there was no evidence that recovery from depression produced an improvement in performance on measures of processing resources.

The lack of a differentially greater improvement in the performance of the depressed with respect to the normal old could mean that the improvement in processing speed and working memory seen in the depressed patients with treatment was not due to the change in their mood state, but rather, to practice and increased familiarity with the tasks. The continued superiority of the controls at follow-up suggests that the decrement in the depressed patients' processing resources persists even after their depression has lifted. That is, a decrement in processing resources is a trait effect of late-life depression. There is, however, another possibility. Some of the depressed patients had been treated with an antidepressant having anticholinergic effects (i.e. nortriptyline). Rusted *et al.* (1991) have argued that anticholinergic medications impair processing resources, especially working memory. Thus, it is possible that the anticholinergic effect of the antidepressants may have masked or offset the improvement in processing resources produced by remission of the depression. This seems unlikely, however, since the mean serum anticholinergic level rose only slightly from baseline to the end of the acute treatment phase (0·35 pmole to 0·50 pmole). However, to directly examine whether a change in serum anticholinergic levels in some of the depressed patients may have masked an improvement in their processing resources, we performed an ANCOVA covarying for the effect of serum anticholinergicity at baseline and follow-up. Serum anticholinergicity was not a significant covariate for either Coding Time ($F(1, 18) = 3{\cdot}56$) or N back ($F(1, 18) = 0{\cdot}24$). Thus, it does not appear that increased serum anticholinergicity with antidepressant treatment was responsible for the lack of a differentially greater improvement in processing resources with recovery from depression.

Mediation of higher-level cognition by processing resources

We next ran hierarchical regressions to determine the amount of depression-related variance present on the MMSE, the Block Design test, and the immediate recall measures from the Rey-Ostereith Figure, CVLT, and Logical Memory. The first regression examined the amount of depression-related variance present in a task when depression was the only predictor, while the second analysis entered one of the two resource measures into the regression before depression, thereby removing the variance due to that resource before examining the influence of depression. The amount by which the depression-related variance on a neuropsychological task is attenuated by controlling for differences in a particular processing resource demonstrates the degree to which that processing resource mediates the decrement produced by depression. For example, Table 3 shows that

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Table 3. *Results of hierarchical regression analyses examining the effects of depression, and the processing-speed and working-memory measures on neuropsychological task performance*

	R^2	Incr. R^2	F		R^2	Incr. R^2	F
Block design				Rey Immediate			
Depression	0·112	—	7·09*	Depression	0·078	—	4·63*
Speed	0·130	—	8·38**	Speed	0·047	—	2·68
Depression	0·175	0·045	3·00	Depression	0·091	0·044	2·67
Working mem.	0·254	—	19·09**	Working mem.	0·152	—	9·84**
Depression	0·280	0·034	1·94	Depression	0·173	0·021	1·39
Speed	0·130	—	8·38**	Speed	0·047	—	2·68
Working mem.	0·283	0·153	11·71**	Working mem.	0·156	0·109	6·98*
Depression	0·297	0·014	1·05	Depression	0·174	0·018	1·15
Logical memory				MMSE			
Depression	0·069	—	4·13*	Depression	0·088	—	5·39*
Speed	0·117	—	7·42**	Speed	0·203	—	14·24**
Depression	0·137	0·020	1·25	Depression	0·220	0·017	1·23
Working mem.	0·271	—	20·86**	Working mem.	0·131	—	8·42**
Depression	0·277	0·006	0·42	Depression	0·161	0·030	2·00
Speed	0·117	—	7·42**	Speed	0·203	—	14·24**
Working mem.	0·291	0·174	13·53**	Working mem.	0·241	0·038	2·74
Depression	0·293	0·002	0·10	Depression	0·248	0·007	0·53
CVLT 1-5							
Depression	0·121	—	7·59**				
Speed	0·279	—	21·29**				
Depression	0·305	0·026	1·98				
Working mem.	0·131	—	8·32**				
Depression	0·186	0·055	3·60				
Speed	0·279	—	21·29**				
Working mem.	0·308	0·029	2·24				
Depression	0·322	0·014	1·15				

* $P < 0·05$; ** $P < 0·01$.

depression was associated with 11·2% of the variance (R^2) on the Block Design task, while processing speed accounted for 13% of the variance when each factor was considered alone. However, 17·5% of the variance was accounted for when speed was entered into the regression before depression. Thus, the increment in R^2 associated with depression after first controlling for processing speed was only 4·5% (i.e. 17·5% minus 13%). Similarly, 25·4% of the variance on the Block Design test was associated with working memory alone, which increased to 28·0% when depression was entered after working memory, for an increment in the R^2 of only 3·4%. Thus, after controlling for the variance associated with either speed or working memory, depression accounted for practically none of the variance on the Block Design task. Another way to look at this, is to express the amount of depression-related variance that remains after controlling for the effect of a particular resource as a percentage of amount of depression-related variance that existed before controlling for the effect of the resource. For example, depression explained 11·2% of the total variance on Block Design when it was the sole predictor, but only 4·5% if the effect of processing speed was removed first. Thus, removal of the variance associated with processing speed reduced the depression-related variance by 60% (i.e. 11·2–4·5/11·2). For the Logical Memory recall, this reduction was 71%, for CVLT recall, 79%, for recall of the Rey figure, 44% and for the MMSE, 81%. Comparable figures for the reduction in the depression-related variance when the variance associated with removal of the effect of working-memory are 70%, 91%, 55%, 73% and 66%.

Thus, when considered alone, depression explained a significant amount (between 7% and 12%) of the total variance on these five neuropsychological measures, but when the variance associated with either working memory or processing speed was removed first, the effect of depression was reduced substantially. In fact, looking at the F values associated with the increment in R^2, the effect of depression on these neuropsychological measures was no longer significant after controlling for the effect of either processing resource.

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Processing speed and working memory are not totally independent types of processing resources. In the most well specified model of working memory (Baddeley, 1996), processing speed plays an important role in determining working-memory capacity. Processing speed has actually been shown to mediate much of the effect that normal ageing has on working-memory (Salthouse, 1991; Kirasic *et al.* 1996). Therefore, we next examined whether working memory still explained any unique variance on the neuropsychological tasks if the effect of processing speed was removed first. We entered processing speed into the regression equation before working memory (see Table 3), which greatly attenuated the effect of working memory. For example in the Block Design task, when considered alone working memory explained 25·4% of the variance. However, if the effect of processing speed was first removed, the increment in R^2 for working memory was 15·3%, a decrease in the amount of variance explained by working memory of 40%. For the Logical Memory task this reduction was 36%, for the CVLT, 78%, for the Rey Figure, 28%; and for the MMSE, 71%. However, except for the CVLT and MMSE, the effect of working memory remained significant even after the effect of processing speed was removed. So while a substantial amount of the effect that working memory had on episodic memory and visuospatial performance (from 15% to 78%) was explained by underlying differences in processing speed, working memory still explained significant unique variance on three of the five tasks.

DISCUSSION

The main findings from this study were first, that patients suffering from a late-life depression were substantially impaired (in comparison to matched normal old controls) on measures of processing resources in the form of working memory and processing speed. Secondly, while processing speed and working memory performance improved when the patients' depression remitted, the magnitude of this improvement was no greater than that seen in normal old controls tested at the same time points. That is, there was no evidence that remission of the patients' depression produced any greater improvement in their processing resources than did merely performing the task multiple times. Thirdly, depressed patients were impaired (compared to the normal old) on neuropsychological measures of visuospatial abilities, verbal and visuospatial episodic memory and a measure of general cognitive performance (the MMSE). However, if the variance associated with either working memory or processing speed was removed, depression no longer had a significant effect. That is, differences between the depressed patients and normal controls in processing speed and working memory appear to mediate most of the depression-related variance on these particular tests of episodic memory and visuospatial performance. Finally, while processing speed accounted for much of the depression-related variance in working memory performance itself, after the influence of speed was removed, working memory continued to explain a significant amount of the variance.

Our finding that processing resources are reduced in depressed patients and that this reduction appears to mediate depression related decrements on a variety of cognitive tasks (especially episodic memory) is consistent with the literature (Hasher & Zacks, 1979; Roy-Byrne *et al.* 1986; Tancer *et al.* 1990; Hartlage *et al.* 1993; Zakzanis *et al.* 1998) suggesting that depression is associated with cognitive decrements only in tasks that make substantial demands upon processing resources. That is, these results would suggest that rather than depressed patients having focal deficits on a variety of cognitive abilities, the likelihood that they will be impaired on a particular task is a function of the degree to which that task is dependent upon processing speed and working memory for its efficient performance.

The role that processing resources play in determining cognitive performance in depression is very similar to that seen in normal ageing. Processing speed and working memory mediate most of the age-related variance on a wide variety of cognitive areas from declarative memory to language comprehension to problem solving. While processing speed often accounts for most (80–100%) of age-related variance in higher level cognitive tasks, working memory can be a significant mediator of cognitive performance even after the effect of processing speed is removed. Working memory appears to

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be an especially important mediator of performance on tests of episodic memory and more complex problem solving like Block Design (Salthouse, 1991, 1992*a*; Kirasic *et al*. 1996).

The present results are, however, very different from those associated with Alzheimer's disease. Sliwinski & Bushke (1997) found that even though AD patients were substantially slower than the normal old, differences in processing resources did not mediate AD patients' performance on episodic memory tasks. That is, the memory deficits found in AD appear to have a different underlying mechanism from that producing the milder memory decrements seen in normal ageing. By contrast, performance of non-demented depressed patients on episodic memory and visuospatial tasks seems to be mediated by the same mechanism as that producing the milder impairments seen in normal ageing – that is, decreased processing resources. Of course, we had intentionally excluded patients who either carried a diagnosis of dementia or whose performance on the DRS was so poor as to suggest a dementing illness. Thus, even though our depressed patients were cognitively impaired in comparison to the normal old, the source of these deficits may be different from that seen in depressed patients with a so called pseudodementia, who often go on to develop Alzheimer's disease (Alexopolous *et al*. 1993).

Even after our patients' depression had remitted, they still showed a decrement (compared to normals) on measures of both working memory and processing speed. This is consistent with a number of recent studies of late-life depression. Paradiso *et al*. (1997) showed that patients in remission from their depression performed worse than normals on the DSST. Abas *et al*. (1990) and Beats *et al*. (1996) both found that depressed elderly patients showed response slowing on psychological tasks even after they had recovered from their depression and that the magnitude of this persistent slowing was positively correlated with MRI measures of brain atrophy. They concluded that a general cognitive slowing may be a trait marker of geriatric depression, due perhaps to neuropathology in elderly depressed individuals. Thus, the present results suggest that impaired cognition may be a persistent characteristic of patients with late-life depression even if they are not showing signs of a dementing illness. It should however be remembered that although our patients' depression had remitted at the point when they were retested, their recovery cannot be considered stable since their HRSD had been $\leqslant 10$ for only 3 weeks. It is thus, possible that if we had retested these individuals several months later their cognitive performance would have normalized. It should also be noted that while all the control subjects were retested 12 weeks after baseline, some of the patients were retested up to 20 weeks after baseline, because they did not respond to the first antidepressant. This time difference could have acted to counter any disproportionate gain in performance on the resource measures by the depressed patients. Unfortunately, the patients who did not remit were not available for retest and thus, we were not able to directly examine the effect of practice in depressed patients who remained depressed.

A number of researchers have postulated that patients suffering from a major depression have a frontal-striatal dysfunction which produces deficits in 'executive' functions (Beats *et al*. 1996; Videbech, 1997; Veiel, 1997; Royall, 1999). Working memory is often considered one of the 'executive' functions mediated predominantly by the frontal lobes. Our working-memory (*N* back test) has been linked to frontal lobe function in functional imaging studies and found to strongly activate dorsolateral prefrontal cortex in normal individuals (Braver *et al*. 1997). Thus, the present results can be seen as consistent with the presence of an executive dysfunction in major depression. However, it should be noted that we also found processing speed mediated much of the depression-related variance in working memory, although some unique variance did remain after the effect of cognitive speed had been removed. Thus, it is possible that the mechanism responsible for much of executive dysfunction seen in depressed patients may be a slowing in the rate of information processing, a possibility that has also recently been raised by Degl'Inocednti *et al*. (1998). The neuroanatomical basis for such a cognitive slowing is not clear, although subcortical white matter hyperintensities have been associated with a slowing on cognitive tasks in both normal elderly individuals (Ylikoski *et al*. 1993) and depressed patients (Lesser *et al*. 1996).

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Overall, the present results show that processing resources in the form of working memory and processing speed are decreased in non-demented patients suffering from a late-life depression. This resource decrement persists after remission of the depression, making it unlikely that it reflects a misallocation of resources to negative thoughts or depression-relevant themes as has been suggested. Instead it appears more likely that the resource decrement is produced by changes in the brains of the older patients associated with a late-life depression. Finally, the decrease in processing resources appears to mediate and perhaps account for most of the cognitive decrements that depressed geriatric patients have in more complex tasks including those evaluating episodic memory and visuospatial performance.

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