Cognitive Function in Late Life Depression: Relationships to Depression Severity, Cerebrovascular Risk Factors and Processing Speed

Yvette I. Sheline, Deanna M. Barch, Keith Garcia, Kenneth Gersing, Carl Pieper, Kathleen Welsh-Bohmer, David C. Steffens, and P. Murali Doraiswamy

Background: *A number of studies have examined clinical factors linked to worse neuropsychological performance in late life depression (LLD). To understand the influence of LLD on cognition, it is important to determine if deficits in a number of cognitive domains are relatively independent, or mediated by depression- related deficits in a basic domain such as processing speed.*

Methods: *Patients who met DSM-IV criteria for major depression (*n = *155) were administered a comprehensive neuropsychological battery of tasks grouped into episodic memory, language, working memory, executive function, and processing speed domains. Multiple regression analyses were conducted to determine contributions of predictor variables to cognitive domains.*

Results: *Age, depression severity, education, race and vascular risk factors all made significant and independent contributions to one or more domains of cognitive function, with all five making independent contributions to processing speed. Age of onset made no independent contribution, after accounting for age and vascular risk factors. Of the five cognitive domains investigated, changes in processing speed were found to most fully mediate the influence of predictor variables on all other cognitive domains.*

Conclusions: *While slowed processing speed appears to be the most core cognitive deficit in LLD, it was closely followed by executive function as a core cognitive deficit. Future research is needed to help clarify mechanisms leading to LLD- related changes in processing speed, including the potential role of white matter abnormalities.*

Key Words: Late life depression, neuropsychology, cognitive deficit, age of onset, vascular risk factors, factor scores

Depression in late life is an under-recognized disorder associated with significant morbidity, including deficits in a range of cognitive functions (Lebowitz et al 1997; Charney et al 2003). Individuals with late life depression (LLD) are identified in a wide array of clinical settings, using a variety of instruments to determine neuropsychological functioning. Cognitive function in LLD has been addressed in a number of studies, and with variation in subsamples and ascertainment these studies have yielded a broad range of findings (Kramer-Ginsberg et al 1999; Hart et al 1987; Boone et al 1995; Butters et al 2004). To interpret these findings there are several important questions that need to be asked: are there truly deficits in a number of cognitive domains that are relatively independent, or are neuropsychological deficits in several different domains (e.g., executive function, episodic memory, etc.) mediated by depression- related deficits in a basic domain such as processing speed; what are the important clinical correlates or predictors of cognitive dysfunction in LLD; and what are the contributions of medical comorbidity and vascular risk factors to cognitive dysfunction in LLD.

Among studies that have used a matched control group, several (Kramer-Ginsberg et al 1999; Hart et al 1987; Boone et al 1995) suggested the presence of disturbances across a range of cognitive domains in LLD. However, in recent work, Butters et al (2004) found that group differences between controls and individuals with LLD in a range of cognitive domains (e.g., executive function, episodic memory, language processing, and visual spatial function) were fully mediated by deficits in processing speed. These results extend other work also suggesting an important role for processing speed in LLD (Degl'Innocenti et al 1998; Nebes et al 2000) and in aging in general (Salthouse 2000). Such results begin to suggest that the primary cognitive deficit associated with LLD may be a reduction in processing speed, which in turn impairs cognitive function in many other domains. However, these results need replication and extension in additional samples that vary in important factors such as age and depression severity.

A number of studies have examined clinical factors that might be linked to worse neuropsychological performance in LLD, including depression severity, comorbid anxiety, vegetative symptoms, number of prior episodes, age and late age of depression onset. Studies that have implicated depression severity or recurrence in cognitive impairment include those of Boone et al (1995), Lichtenberg et al (1995) and Raskin (1986), all of which have shown that after controlling for the direct effect of demographic variables there was still an effect of depression severity on cognitive function. However, these studies did not examine whether depression severity was independently related to performance in several different cognitive domains, or whether the influence of depression severity on at least some cognitive domains was mediated by an influence on a basic function such as processing speed. In addition, a broad array of deficits correlated with the number of prior depression episodes in a study of 24 elderly depressed subjects (Beats et al 1996). However, the number of episodes was not corrected for age or age of onset, making interpretation of the results difficult.

Many studies (King et al 1991, 1993, 1995; Lyness et al 1994) but not all (Boone et al 1994) have found greater age to be associated with worse cognitive task performance among individuals with LLD, particularly as related to executive function tasks (Lyness et al 1994). Cognitive impairment in LLD has also been shown to be greater in late-onset depression (Salloway et al 1996; Steingart and Hermann 1991; van Ojen et al 1995; van Reekum et al 1999); however, other

From the Departments of Psychiatry (YIS, DMB, KGa), Neurology (YIS), Radiology (YIS, DMB), and Psychology (DMB), Washington University, St. Louis, Missouri; and the Departments of Psychiatry (KGe, CP, KW-B, DCS, PMD) and Medicine (Neurology) (KW-B), Duke University, Durham, North Carolina.

Address reprint requests to Yvette Sheline, M.D., Washington University School of Medicine, Department of Psychiatry, Box 8134, 660 South Euclid, St. Louis, MO, 63110; E-mail: yvette@npg.wustl.edu.

Received June 17, 2005; revised August 10, 2005; accepted September 30, 2005.

0006-3223/06/$32.00
doi:10.1016/j.biopsych.2005.09.019

studies (Brodaty et al 2001; Greenwald and Kramer-Ginsberg 1988) found no relationship between age of onset for depression after correcting for chronological age. Thus, a variety of studies have found different clinical characteristics to be associated with the severity of cognitive deficits, with few studies examining a broad array of clinical factors simultaneously.

A number of studies have also linked medical illness burden, especially cerebrovascular risk factors, to the presence of LLD. The relationship of comorbid illness and cognitive dysfunction is complex and differing results across studies have depended in part upon the measures used to assess illness. Some studies have not found overall medical burden to be related to neuropsychological functioning (King et al 1995; Caine et al 1993; Lyness et al 1998; Taylor et al 2004) whereas others have found the overall medical burden (La Rue et al 1992) as evidenced by the Cumulative Illness Rating Scale geriatric version (CIRS) (Miller et al 1992) to be related to functional status. In a recent study of older LLD patients (mean age 83) that matched late onset and early onset depressed subjects for age (Rapp et al 2005), late onset depression (LOD) subjects had significantly more comorbid cerebrovascular illness and more impairment in executive function. In contrast, those with a recurrent illness that started at an earlier age had more impairment in episodic memory. The study had relatively few subjects, however (20 per group), and relatively low mean MMSE scores (23.8 for recurrent depression and 22.4 for LOD), compared with other similar studies.

While many studies have examined one or a few cognitive domains in relationship to late life depression, few studies have examined a comprehensive range of neuropsychological functions. Examining multiple aspects of neuropsychological functioning simultaneously is critical given the possibility that deficits in one or more basic aspects of cognitive functions (e.g., processing speed) could mediate depression related deficits in other cognitive domains, as suggested by the Butters et al (2004) study. In the current study we were able to gather a large sample of subjects studied at two different sites—Washington University in St. Louis and Duke University in Raleigh/Durham. The sample was not only large in size but also geographically diverse– (East coast vs mid-west; both sites with urban and rural participants), and diverse in comorbid illness, particularly cardiovascular illness severity. In addition, we gathered a sufficiently large sample to conduct multivariate analyses in which we simultaneously examined an array of clinical factors– age, age of onset, education, vascular risk factor index from the Framingham Study and depression severity to examine these effects on neuropsychological functioning. We were interested in addressing the following questions: 1) are depression severity, age, education, race or vascular burden associated with performance in cognitive domains such as working memory, executive function, episodic memory, language processing or processing speed among individuals with LLD; 2) are the contributions of depression severity, age, education, race or vascular burden to cognitive performance independent of each other; 3) is age of onset, after correction for chronological age, associated with worse performance in any cognitive domain; and 4) are the influences of predictor variables on cognitive domains fully or partially mediated by an effect on a more basic cognitive function such as processing speed.

Methods and Materials

Subjects

Patients who met DSM-IV criteria for major depression (n = 155) by Structured Clinical Interview for Axis I DSM-IV Disorders (SCID-IV) administered by a research psychiatrist (YIS, PMD, KGa or KGe) were recruited for an ongoing National Institute of Mental Health (NIMH) study "Treatment Outcome in Vascular Depression." Patients were recruited through advertising and physician referral to Washington University Medical Center (n = 87) and Duke University Medical Center (n = 68). All patients were enrolled in a 12 week treatment trial with sertraline. All patients were screened to rule out severe or unstable medical disorders (e.g. myocardial infarction [MI] within past 3 months, end stage cancer, decompensated cardiac failure), known primary neurological disorders including dementia, delirium, diagnosed stroke within the past 3 months, Parkinson's Disease, brain tumors, multiple sclerosis, seizure disorder, conditions or drugs that may cause depression (e.g. systemic steroids, pancreatic cancer, uncorrected hypothyroidism), Mini Mental Status Examination score <21 (Folstein et al 1983), history of other Axis I disorders prior to their depression diagnosed by SCID-IV, current suicidal risk, current episode that failed to respond to adequate trials of two prior antidepressants for at least 6 weeks at therapeutic doses, use of psychotropic prescription or non-prescription drugs or herbals (e.g. hypericum) within three weeks or 5 half lives, except for limited use of certain hypnotics or in exceptions when the patients' depression was worsening. Of 277 phone screens at WU and 374 at Duke there were 120 clinic screens at Washington University (WU) and 105 at Duke. The exclusionary criteria further reduced the patient study group to the combined 174 patients. For these patients there was partial missing data on 19 subjects, leaving 155 complete data sets for analysis. Written informed consent approved by the relevant Institutional Review Board was obtained for all subjects.

Measures

Data were obtained from evaluations performed by research staff of the clinical research study and included medical, psychiatric, demographic, MRI and neuropsychological measures. Demographic variables (see Table 1) were age, education, gender, race, depression symptom severity (scored on the Montgomery-Asberg Depression Rating Scale– MADRS), age of depression onset and vascular burden as defined by the Framingham Study (Wolf et al 1991). The Framingham Study uses a stroke risk prediction assessment tool that includes the following risk factors to predict 10-year risk of stroke in both men and women: age, systolic blood pressure, the use of antihypertensive therapy, diabetes mellitus, cigarette smoking, cardiovascular disease (coronary heart disease, cardiac failure, or intermittent claudication), atrial fibrillation, and left ventricular hypertrophy by electrocardiogram.

Table 1. Demographic Data

	WU n = 87 Mean (STD)	Duke n = 68 Mean (STD)	Total Sample n = 155 Mean (STD)
Age	68.87 (7.49)	68.55 (7.07)	68.72 (7.28)
Education	13.87 (2.95)	14.23 (3.31)	14.04 (3.12)
Gender (M, F)	32, 60	43, 39	75, 99
Race (White, Black, Asian)	78, 8, 1	64, 4	142, 12, 1
MADRS Score	27.05 (4.52)	25.18 (4.28)	26.17 (4.50)
Age of Depression Onset	53.46 (18.08)	55.70 (15.83)	54.51 (17.05)
Vascular Burden	12.20 (4.80)	11.35 (4.31)	11.80 (4.58)

WU, Washington University; MADRS, Montgomery Asberg Depression Rating Scale.

Age at onset was ascertained from the SCID-IV and all available medical and psychiatric records. The neuropsychological testing was performed by a highly trained examiner who was closely supervised by a Ph.D. level psychologist (DMB and KW-B). Patients were tested prior to the initiation of antidepressant medication and were psychotropic free.

Neuropsychological Test Performance in LLD

All participants were administered a large battery of neuropsychological tests that covered cognitive domains relevant to understanding late-life depression. We grouped the cognitive tasks into the following rationally motivated domains based on the prior literature regarding the cognitive processes tapped by each of the tasks. To combine the tasks, we created *Z* scores for the primary dependent measure of interest across all participants and then summed the *Z*-scores. Variables in which good performance was represented by lower values (e.g., Trails) rather than higher values were reverse scored to insure that higher *Z*-scores represented better performance for all variables. Cronbach's alpha (a measure of internal consistency) was computed for each domain.

Language Processing. This domain included the Shipley Vocabulary Test (number correct), the Boston Naming Test (number correct), and the Word reading condition of the Stroop (number completed). Cronbach's alpha for this domain was .62. The Shipley is sometimes used in addition to years of education as a measure of educational access, particularly in samples that have wide variability in education. However, this sample had a relatively small standard deviation (3 years) for education, and if we removed the Shipley Vocabulary Test from the language processing factor, Cronbach's alpha worsened. Thus, we decided to retain the Shipley as a component of the language processing factor.

Processing Speed. This domain included Symbol-digit modality (number completed), the color naming condition of the Stroop task (number completed), and Trails A (reverse scored time to completion). The alpha for this domain was .81.

Working Memory. This domain included digit span forward (number of trials correctly completed), digit span backwards (number of trials correctly completed), and ascending digits (number of trials correctly completed). The alpha for this domain was .69. Although some would contend that all executive function can be explained in terms of working memory, there is evidence that they encompass separate functions (see Kane and Engle, 2002 for a review).

Episodic Memory. This domain included word list learning (total correct), logical memory (total correct immediate), constructional praxis (memory performance), and the Benton Visual Retention Test (total correct). The alpha for this domain was .73.

Executive Function. This domain included verbal fluency (total phonological and semantic), Trails B (reverse scored time to completion), the color-word interference condition of the Stroop (number completed), the Initiation-Perseveration subscales of the Mattis, and categories completed from the Wisconsin Card Sorting Test. The Alpha for this domain was .75. While verbal fluency is sometimes considered a measure of language, it is a widely used and well validated measure of executive function (Henry and Crawford 2005).

Results

Demographic variables used as predictor variables of cognitive function were age, education, gender, race, depression symptom severity on MADRS, age of depression onset and vascular burden as defined by the Framingham Study (Wolf et al 1991). The number, mean and standard deviation of these variables are shown in Table 1.

We began our analysis by examining the relationships among the different domains of cognitive function. As shown in Table 2, all of the cognitive domains are highly and significantly intercor-

Table 2. Distribution of, and Correlations Among, Cognitive Domains

	Processing Speed[a]	Language Processing[b]	Working Memory[c]	Episodic Memory[d]	Executive Function[e]
Processing Speed M = .25 (SD = 2.1) Range: −5.8–5.0	—	.59[f]	.41[f]	.62[f]	.77[f]
Language Processing M = .15 (SD = 2.1) Range: −9.7–4.1	—	—	.42[f]	.55[f]	.67[f]
Working Memory M = .04 (SD = 2.3) Range: −6.0–5.4	—	—	—	.37[f]	.60[f]
Episodic Memory M = .21 (SD = 2.8) Range: −12–5.8	—	—	—	—	.68[f]
Executive Function M = .19 (SD = 3.4) Range: −10.4–6.5	—	—	—	—	—

[a]Language processing includes the variables from Shipley Vocabulary Test, Boston Naming, and Stroop-Word.
[b]Working memory includes the variables forward, backwards and ascending from digit span.
[c]Episodic memory includes the variables from word list learning, logical memory, constructional praxis and Benton Visual Retention Test.
[d]Executive function includes the variables from verbal fluency, Trails B, Stroop-Color Word interference, Initiation-Perseveration subscale of the Mattis Dementia Rating Scale and Wisconsin Card Sorting Task.
[e]Processing speed includes the variables from finger tapping, symbol-digit modality, Stroop-Color naming, and Trails A.
[f]$p < .001$. $df = 155$.

Table 3. Correlations Between Cognitive Performance and Age, Depression, Race and Vascular Risk

	Age	MADRS	Cardiovascular Risk	Education Level	Race
Processing Speed	−.49[b]	−.20[a]	−.40[b]	.21[a]	−.19[a]
Language Processing	−.32[b]	−.22[a]	.11	.36[b]	−.26[b]
Working Memory	−.15[a]	−.19[a]	.06	.17[a]	−.15
Episodic Memory	−.45[b]	−.14[a]	−.19[a]	.43[b]	−.06
Executive Function	−.44[b]	−.21[a]	−.27[b]	.38[b]	−.19[a]

MADRS, Montgomery Asberg Depression Rating Scale.
[a] $p < .05$. $df = 155$.
[b] $p < .01$. $df = 155$.

related. We also examined the correlations among predictor variables – age, depression score, race and vascular burden scores. MADRS scores were not correlated with either age, $r = .07$, $p > .37$, race $r = .03$, $p > .74$ or vascular burden, $r = -.01$, $p > .91$. However, age and vascular burden scores were strongly and significantly correlated, $r = .55$, $p < .001$.

We have organized our results according to the questions we posed at the end of the introduction.

1) Are Depression Severity, Age, Race or Vascular Burden Associated with Performance in Cognitive Domains?

As shown in Table 3, age was significantly negatively correlated with performance across all cognitive domains, though the smallest association was with working memory. In addition, MADRS scores were significantly negatively correlated with performance in all cognitive domains. Vascular burden showed significant negative correlations with processing speed, memory and executive function. Race showed significant negative correlations with processing speed, language, executive function and a trend with working memory. As one would expect, education was significantly positively correlated with all cognitive domains, with the strongest associations to language, episodic memory and executive function. To determine if age, depression severity, education or vascular burden were significantly more strongly correlated with one cognitive domain versus another, we used the techniques for comparing correlated correlation coefficients developed by Meng et al (1992). These analyses indicated that age was significantly more strongly correlated with processing speed than with language function or working memory ($ps < .05$) In addition, age was significantly more strongly correlated with language function than with working memory ($p < .05$), as well as significantly more strongly correlated with episodic memory than with language function or working memory ($ps < .05$). Lastly, age was also significantly more strongly correlated with executive function than with language or working memory ($ps < .05$). For depression severity, there were no significant differences among any of the cognitive domains in strength of correlations with MADRS scores. Vascular burden was significantly more strongly correlated with processing speed than any of the other cognitive domains (all $ps < .01$), and significantly more strongly correlated with executive function than with language or episodic memory. Education was significantly more strongly correlated with processing speed than with language function, episodic memory or executive function ($ps < .01$). In addition, education was significantly more strongly correlated with episodic memory and executive function than with working memory ($ps < .01$).

2) Are the Contributions of Predictor Variables to Cognitive Performance Independent of Each Other?

As shown in Table 3, age, MADRS depression scores, education, race and vascular burden were correlated with performance in the majority of cognitive domains. However, age and depression severity were not correlated with each other, and vascular burden and depression severity were not correlated with each other. Further, none of these factors was correlated with education or race. This pattern suggests that these factors may make independent contributions to cognitive performance. To confirm this, we developed a series of regression models in which age, MADRS depression scores, vascular burden, race and education were used to predict cognitive performance. As shown in Table 4, age, depression severity, vascular burden, race and education all made independent contributions to processing speed. Age, depression severity, race and education made independent contributions to language function. For working memory, depression severity made a significant independent contribution, with a trend for education. For episodic memory, age and education made significant contributions. For executive function, age, depression severity, race and education but not vascular burden all made independent contributions.

3) Is Age of Onset, After Correction for Chronological Age, Associated with Worse Performance in Any Cognitive Domain?

We next examined the relationship of age of onset to the other predictor variables and to cognitive function. Age of onset was significantly correlated with age, $r = .42$, $p < .01$ and vascular burden, $r = .25$, $p < .01$, and showed a trend level relationship to depression severity, $r = -.14$, $p = .08$. Age of onset was not significantly correlated with education, $r = -.06$, $p > .05$. In addition, age of onset was significantly negatively correlated with performance in all of the cognitive domains, rs $-.18$ to $-.21$, $ps < .05$, other than working memory, $r = -.06$, $p > .05$. However, a series of hierarchical regressions indicated that age of onset did not make any significant independent contributions to performance in any of the cognitive domains when variance associated with age and vascular burden was taken into account. Thus, the relationship of age of onset to cognitive function was fully mediated by age and vascular burden.

4) Are the Influences of Predictor Variables on Cognitive Domains Fully or Partially Mediated by an Effect on a More Basic Cognitive Function such as Processing Speed?

To examine this possibility, we performed a series of hierarchical regressions to predict cognitive domain performance (one each for language, working memory, episodic memory, and

Table 4. Independent Contributions of Age, Depression, Vascular Burden, Education and Race to Cognitive Function

	Processing Speed	Language Processing	Working Memory	Episodic Memory	Executive Function
Age	$\beta = -.37$	$\beta = -.31$	$\beta = -.13$	$\beta = -.43$	$\beta = -.35$
	$t = -4.5$	$t = -3.7$	$t = -1.4$	$t = -5.4$	$t = -4.4$
	$p < .001$	$p < .001$	$p > .10$	$p < .001$	$p < .001$
Depression	$\beta = -.15$	$\beta = -.16$	$\beta = -.16$	$\beta = -.07$	$\beta = -.15$
	$t = -2.2$	$t = -2.2$	$t = -2.1$	$t = -0.96$	$t = -2.3$
	$p < .05$	$p < .05$	$p < .05$	$p > .3$	$p < .05$
Vascular Burden	$\beta = -.15$	$\beta = .08$	$\beta = -.02$	$\beta = .06$	$\beta = -.06$
	$t = -1.9$	$t = 0.9$	$t = -0.21$	$t = 0.8$	$t = -.8$
	$p = .06$	$p < .4$	$p > .8$	$p > .4$	$p > .4$
Education	$\beta = .14$	$\beta = .31$	$\beta = .14$	$\beta = .37$	$\beta = .32$
	$t = -2.0$	$t = 4.4$	$t = 1.7$	$t = 5.5$	$t = 4.7$
	$p < .05$	$p < .001$	$p > .09$	$p < .001$	$p < .001$
Race	$\beta = -.17$	$\beta = -.24$	$\beta = -.14$	$\beta = -.04$	$\beta = -.16$
	$t = -2.5$	$t = -3.5$	$t = -1.7$	$t = -.59$	$t = -2.5$
	$p = .01$	$p = .001$	$p > .08$	$p > .5$	$p < .02$

executive function) in which processing speed and education level were entered in step one, and either age, MADRS score, race or vascular burden score was entered in step two. If changes in other cognitive domains are mediated through processing speed, then age, depression severity, race or vascular burden should no longer be a significant predictor once we account for processing speed-related variance. Age continued to significantly predict episodic memory performance even after accounting for variance associated with processing speed, $\beta = -.18$, $t(154) = -2.8$, $p < .01$. However, age did not continue to predict language function, working memory or executive function after accounting for variance associated with processing speed. Thus, there were age-related changes in episodic memory that were not mediated by age-related changes in processing-speed. Race continued to significantly predict language function even after accounting for variance associated with processing speed, $\beta = -.15$, $t(154) = -2.5$, $p = .02$. MADRS depression scores no longer predicted performance in language function, working memory, episodic memory or executive function after variance associated with processing speed was taken into account. Vascular burden scores no longer predicted performance in episodic memory or executive function once variance associated with processing speed was taken into account. The relationships among the predictor variables and between the predictor and cognitive variables are illustrated in Figure 1.

Given the strong positive correlation between processing speed and executive function, it was important to determine the ability of executive function to mediate the association between predictor variables and the cognitive domains. We repeated these mediator analyses using each of the other cognitive domains and found that second to processing speed, executive function had a strong mediator relationship with the remaining cognitive domains. The result of the mediator analysis for executive function was as follows: A series of hierarchical regressions were performed to predict cognitive domain performance (one each for language, working memory, episodic memory, and processing speed) in which executive function and education level were entered in step one, and either age, MADRS score, vascular burden score, or race was entered in step two. In this case, unless they made independent contributions to cogni-

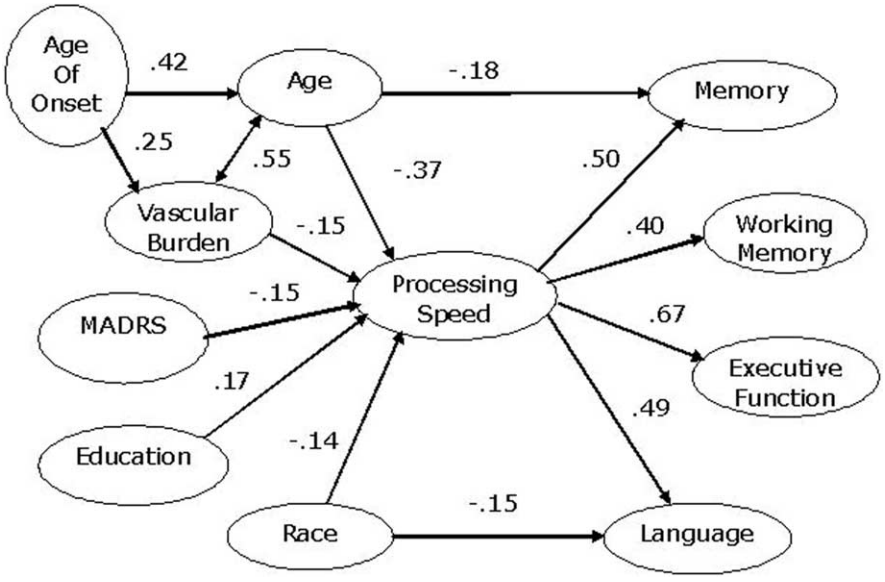

Figure 1. Relationships among the predictor variables and between the predictor and cognitive variables derived from the multiple regression analyses. The numerical values represent standardized beta weights.

Table 5. Comparison of the Predictor/Processing Speed Relationship and the Predictor/Executive Function Relationship as Mediators

Does processing speed fully mediate the relationship between each predictor variable and the other cognitive domains?

	Executive Function	Working Memory	Memory	Language
Age	Yes	Yes	No	Yes
MADRS	Yes	Yes	Yes	Yes
Vascular Burden	Yes	Yes	Yes	Yes
Race	Yes	Yes	Yes	No

Does executive function fully mediate the relationship between each predictor variable and the other cognitive domains?

	Processing Speed	Working Memory	Memory	Language
Age	No	No	No	Yes
MADRS	Yes	Yes	Yes	Yes
Vascular Burden	No	Yes	Yes	Yes
Race	Yes	Yes	Yes	No

MADRS, Montgomery Asberg Depression Rating Scale.

tive function, predictor variables should no longer be significant once we account for executive function-related variance. Age continued to significantly predict processing speed, $\beta = -.18$, $t(154) = -3.2$, $p = .002$, working memory performance, $\beta = .15$, $t(154) = 2.0$, $p = .04$, and episodic memory, $\beta = -.20$, $t(154) = -3.1$, $p = .002$, after accounting for variance associated with executive function. Race continued to significantly predict language function after accounting for variance associated with executive function, $\beta = -.15$, $t(154) = -2.4$, $p = .02$. In addition, vascular burden continued to significantly predict processing speed after accounting for variance associated with executive function, $\beta = -1.7$, $t(154) = -3.2$, $p = .002$. In summary, we found that second to processing speed, executive function also mediated the association between the predictor variables and the other cognitive domains; however, it mediated 11/16 potential relationships compared with 14/16 relationships mediated by processing speed. A comparison between the predictor variable/processing speed relationship and the predictor variable/executive function relationship as mediators is shown in Table 5.

Discussion

In this study we investigated neuropsychological functioning in LLD using a comprehensive battery of neuropsychological tests in a sample of 155 patients in two different geographical locations. Our goal was to examine a range of cognitive functioning in LLD. The factors that were created– processing speed, memory, executive function, working memory and language—all had high Cronbach's alpha, indicating high internal consistency among the measures. These factors are similar to those created by Butters et al (2004) with the difference that instead of a visual/spatial domain we included a working memory domain. We only had one visual/spatial measure and therefore could not create a visual/spatial domain score that would have psychometric properties similar to the other domain scores. We found that cognitive performance across all of the cognitive domains was strongly intercorrelated in this sample of clinically depressed individuals, results which echo the findings of Butters et al, who found neuropsychological impairment across a broad array of functions in their LLD sample. Like Butters et al (2004), we also found a central role for processing speed in predicting the other cognitive domains, however while our data are similar to Butters et al, some important differences should be pointed out. We conducted multiple mediator analyses testing each cognitive domain as a mediator of the other domains to compare their ability to mediate cognitive function. We found that while processing speed was the best mediator for cognitive performance (see Table 5), executive function could also be modeled as an excellent though less complete mediator. Further, unlike Butters et al, we found an important role for vascular risk factors in cognitive performance. Finally, we found race to be an independent predictor of cognitive function, as discussed below.

We examined the relationship of predictor variables including age, age of onset, education, race, depression severity and cerebrovascular risk factors to cognitive function in LLD. We found that age, depression severity, race and education all made significant and independent contributions to one or more domains of cognitive function, with all four making independent contributions to processing speed. Further, in the current study, we found that vascular risk factors were correlated with worse performance in processing speed, executive function and episodic memory. In addition, vascular risk factors made a contribution to processing speed independent of age, education and depression severity. This result contrasts with the findings of Butters et al (2004), who did not find that comorbid illness in general was associated with performance in any cognitive domain, though they examined only cumulative illness ratings and not vascular risk scores. However, our results are consistent with the results of several other studies in the literature. In one group of subjects with vascular risk factors and white matter hyperintensities, Gupta et al (1988) reported impairment on 13 of 17 neuropsychological instruments evaluating executive control, recent memory, constructional praxis, and speeded psychomotor integration. Alexopoulos et al (1997) found significant impairments in fluency and naming in LLD patients with vascular illness, defined as a score of 1–4 on the vascular subscale of the Cumulative Illness Rating Scale for Geriatrics (CIRS-G). In a pooled analysis of elderly subjects in two antidepressant trials ($n = 444$) we found a correlation between baseline cognitive impairment and higher systolic hypertension (Doraiswamy et al 2003). Cerebrovascular risk factors in normal elderly have also been associated with cognitive impairment (Waldstein and Katzel 2004). Similarly Ylikoski et al (2000) found that while overall health status was not related to cognition in 113 elderly subjects, those with hypertension and cardiac disease had cognitive impairment in Stroop, Trails A and verbal fluency, tests falling under our domains of processing speed and executive function. Thus, our results are in agreement with literature suggesting that vascular risk factors, perhaps more so than overall medical burden have a specific role in producing cognitive impairment.

As described above, the current study also found that age, depression severity and race were associated with poor performance in many different cognitive domains. For age, changes in processing speed fully mediated age-related influences on working memory, language function, and executive function. However, age continued to have a significant influence on episodic memory, even after age related changes in processing speed were taken into account. For race, even after accounting for processing speed, there continued to be an independent contribution to language. Other studies (Mehta et al 2004) have also identified effects of race on cognitive function after accounting for demographic variables including health and socioeconomic

indicators. The independent effect of this variable (β-weight in our study was similar. In contrast, changes in processing speed were found to fully mediate the influence of depression severity on all other cognitive domains. In addition, changes in processing speed fully mediated the influence of vascular risk factors on executive function and episodic memory.

The central role of processing speed in predicting impairment in other cognitive domains is noteworthy both for the strength and breadth of the association with other cognitive domains but also for the fact that this result clearly replicates the findings of Butters et al (2004). The Butters study (2004), with a sample of 100 LLD subjects found this same striking role of processing speed in mediating depression related changes in other cognitive domains. In contrast, other researchers such as Alexopoulos et al (2000) and Lockwood et al (2002) emphasized executive dysfunction as the most basic deficit in LLD. The differences between the results of the studies emphasizing processing speed versus those emphasizing other cognitive deficits such as executive dysfunction may primarily reflect differences in analysis strategy. Like Alexopoulos et al, we found zero-order associations between various predictor variables and executive function in LLD as well as between predictor variables and processing speed. However, in the current study we found that the relationship between predictor variables and executive function was more fully mediated by changes in processing speed than an alternative model using executive dysfunction as the mediator. Many prior studies did not conduct mediator analyses that would have allowed the determination of whether depression-related changes in cognitive function were mediated by depression-related changes in other cognitive domains such as processing speed or executive function.

The biological implication of slowed processing speed is important in understanding the pathophysiology of LLD. Both executive dysfunction and slow information processing may operate through fronto-striatal disconnection. A large literature describes changes in white matter, especially increased numbers of white matter hyperintensities in late life depression (Fujikawa et al 1993; Coffey et al 1990; Krishnan et al 1988; Figiel et al 1991). Disruptions in white matter integrity would be expected to slow processing speed in all affected domains. Recent studies using diffusion tensor imaging have found preliminary evidence for disruption of prefrontal pathways in patients with LLD (Taylor et al 2004; Alexopoulos et al 2002). Further study is needed to understand the relationship between cognitive deficits and structural changes in white matter in late life depression.

Examining other factors potentially predicting cognitive performance, we did not find an independent contribution to cognitive function for age of onset once chronological age was taken into account, although we did not examine LOD subjects separately. Some studies have identified impairments in neuropsychological functioning related to late onset of depression (Steingart and Hermann 1991; van Ojen et al 1995; van Reekum et al 1999). However these studies did not examine the relationship of age of onset, age and vascular risk factors in a multivariate analysis and thus there may have been an apparent effect of age of onset which would have been subsumed under the effect of age and vascular burden, had that analysis been conducted.

There are several factors that limit the ability to generalize the findings of the current study to late life depressed patients in general. The subjects were all participants in an antidepressant treatment study, and therefore had to meet eligibility criteria. While a broad array of medical illnesses met inclusionary criteria, subjects with acute or severe physical illness were excluded. Our study also does not apply to late life depressed subjects with a Mini-Mental Status Exam score of less than 21, excluding those with mild cognitive impairment or dementia. Also, we did not include a nondepressed comparison sample. While the performance of LLD subjects in this study is similar to previous studies we cannot therefore discuss the degree of cognitive impairment relative to a comparison sample and do not know if these findings are applicable only to LLD or are part of a greater continuum, anchored by normal controls.

In summary, in a large sample of patients with LLD we have found that depression severity, age, education, race and vascular burden are associated with performance in a range of cognitive domains including working memory, executive function, episodic memory, language processing and processing speed– with the exception of trends for vascular risk factors with language and working memory. Importantly, the influences of all our predictor variables on cognitive domains were fully or partially mediated by the effect of processing speed, which appears to be a core cognitive deficit in LLD. Future research is needed to help clarify the mechanisms that lead to LLD related changes in processing speed, including the potential role of white matter abnormalities in this process. Further, once prospective data are analyzed we will be able to examine how changes in processing speed are related to changes in other domains and clinical outcome following treatment.

We gratefully acknowledge the assistance of Brigitte Mittler and Karee Powers with neuropsychological testing; of Patty Flynn, RN, BSN; Pat Deppen, RN, MA; and Cammie Hellegers in coordinating the study, and of Brigitte Mittler and Tony Durbin for their technical assistance in preparation of the manuscript.

YIS, DMB and KGa are supported by a Collaborative R01 for Clinical Studies of Mental Disorders Grant Number MH60697. PMD, KGe, KW-B, and CP are supported by a Collaborative R01 for Clinical Studies of Mental Disorders Grant Number MH62158. YIS also receives support from National Institute of Mental Health (NIMH) K24 65421 and DCS receives support from NIMH K24 70027. KW-B also receives support from National Institute on Aging (NIA) 05128 and NIA 11380. Additionally, this work was supported by a grant (RR00036) to the Washington University School of Medicine General Clinical Research Center.

PMD has received grants and consulting fees from antidepressant manufacturers. He does not own stock in these companies.

Alexopoulos GS, Kiosses DN, Choi SJ, Murphy CF, Lim KO (2002): Frontal white matter microstructure and treatment response of late-life depression: a preliminary study. *Am J Psychiatry* 159:1929–1932.

Alexopoulos GS, Meyers BS, Young RC, Campbell S, Silbersweig D, Charlson M (1997): 'Vascular depression' hypothesis. *Arch Gen Psychiatry* 54:915–922.

Alexopoulos GS, Meyers BS, Young RC, Kalayam B, Kakuma T, Gabrielle M, et al (2000): Executive dysfunction and long-term outcomes of geriatric depression. *Arch Gen Psychiatry* 57:285–290.

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

Boone KB, Lesser IM, Miller BL, Wohl M, Berman N, Lee A, Palmer B (1994): Cognitive functioning in a mildly to moderately depressed geriatric sample: relationship to chronological age. *J Neuropsychiatry Clin Neurosci* 6:267–272.

Boone KB, Lesser IM, Miller BL, Wohl M, Berman N, Lee A, et al (1995): Cognitive functioning in older depressed outpatients: relationship of presence and severity of depression to neuropsychological test scores. *Neuropsychology* 9:390–398.

Brodaty H, Luscombe G, Parker G, Wilhelm K, Hickie I, Austin MP, Mitchell P (2001): Early and late onset depression in old age: different aetiologies, same phenomenology. *J Affect Disord* 66:225–236.

Butters MA, Whyte EM, Nebes RD, Begley AE, Dew MA, Mulsant BH, et al (2004): The nature and determinants of neuropsychological functioning in late-life depression. *Arch Gen Psychiatry* 61:587–595.

Caine ED, Lyness JM, King DA (1993): Reconsidering depression in the elderly. *Am J Geriatr Psychiatry* 1:4–20.

Charney DS, Reynolds CF, Lewis L, Lebowitz BD, Sunderland T, Alexopoulos GS, et al (2003): Depression and Bipolar Support Alliance consensus statement on the unmet needs in diagnosis and treatment of mood disorders in late life. *Arch Gen Psychiatry* 60:664–672.

Coffey CE, Figiel GS, Djang WT, Weiner RD (1990): Subcortical hyperintensity on magnetic imaging: a comparison of normal and depressed elderly subjects. *Am J Psychiatry* 147:187–189.

Degl'Innocenti A, Agren H, Backman L (1998): Executive deficits in major depression. *Acta Psychiatr Scand* 97:182–188.

Doraiswamy PM, Krishnan KR, Oxman T, Jenkyn LR, Coffey D, Burt T, Clary CM (2003): Does antidepressant therapy improve cognition in elderly depressed patients? *J Geront* 58A:1137–1144.

Figiel GS, Krishnan KR, Doraiswamy PM, Rao VP, Nemeroff CB, Boyko OB (1991): Subcortical hyperintensities on brain Magnetic Resonance Imaging: a comparison between late age onset and early onset elderly depressed subjects. *Neurobiol Aging* 26:245–247.

Folstein MF, Robins LN, Helzer JE (1983): The Mini-Mental State Examination. *Arch Gen Psychiatry* 40:812.

Fujikawa T, Yamawaki S, Touhouda Y (1993): Incidence of silent cerebral infarction in patients with major depression. *Stroke* 24:1631–1634.

Greenwald BS, Kramer-Ginsberg E (1988): Age at onset in geriatric depression: relationship to clinical variables. *J Affect Disord* 15:61–68.

Gupta SR, Naheedy MH, Young JC, Ghobrial M, Rubino FA, Hindo W (1988): Periventricular white matter changes and dementia. Clinical neuropsychological, radiological and pathological correlation. *Arch Neurol* 45: 637–641.

Hart RP, Kwentus JA, Taylor JR, Harkins SW (1987): Rate of forgetting in dementia and depression. *J Consult Clin Psychol* 55:101–105.

Henry J, Crawford JR (2005): A meta-analytic review of verbal fluency deficits in depression. *J Clin Exp Neuropsychol* 27:78–101.

Kane MJ, Engle RW (2002): The role of prefrontal cortex in working-memory capacity, executive attention, and general fluid intelligence: An individual-differences perspective. *Psychonomic Bull Rev* 9:637–671.

King DA, Caine ED, Conwell Y, Cox C (1991): The neuropsychology of depression in the elderly: a comparative study of normal aging and Alzheimer's disease. *J Neuropsychiatry Clin Neurosci* 3:163–168.

King DA, Caine ED, Cox C (1993): Influence of depression and age on selected cognitive functions. *Clin Neuropsychol* 7:443–453.

King DA, Cox C, Lyness JM, Caine ED (1995): Neuropsychological effects of depression and age in an elderly sample: a confirmatory study. *Neuropsychology* 9:399–408.

Kramer-Ginsberg E, Greenwald BS, Krishnan KR, Christiansen B, Hu B, Ashtari M, et al (1999): Neuropsychological functioning and MRI signal hyperintensities in geriatric depression. *Am J Psychiatry* 156:438–444.

Krishnan KR, Goli V, Ellinwood EH, France RD, Blazer DG, Nemeroff CB (1988): Leukoencephalopathy in patients diagnosed as major depressive. *Biol Psychiatry* 23:519–522.

La Rue A, Goodman S, Spar JE (1992): Risk factors for memory impairment in geriatric depression. *Neuropsychiatry Neuropsychol Behav Neurol* 5:178–184.

Lebowitz BD, Pearson JL, Schneider LS, Reynolds CF, Alexopoulos GS, Bruce ML, et al (1997): Diagnosis and treatment of depression in late life. Consensus statement update. *JAMA* 278:1186–1190.

Lichtenberg PA, Ross T, Millis SR, Manning CA (1995): The relationship between depression and cognition in older adults: a cross-validation study. *J Gerontol B Psych Sci Soc Sci* 50:P25–P32.

Lockwood KA, Alexopoulos GS, van Gorp WG (2002): Executive dysfunction in geriatric depression. *Am J Psychiatry* 159:1119–1126.

Lyness JM, Caine ED, Cox C, King DA, Conwell Y, Olivares T (1998): Cerebrovascular risk factors and later-life major depression. Testing a small-vessel brain disease model. *Am J Geriatr Psychiatry* 6:5–13.

Lyness SA, Eaton Em, Schneider LS (1994): Cognitive performance in older and middle-aged depressed outpatients and controls. *J Gerontol B Psych Sci Soc Sci* 49:P129–P136.

Mehta KM, Simonsick EM, Rooks R, Newman AB, Pope SK, Rubin SM, et al (2004): Black and white differences in cognitive function test scores: What explains the difference? *J Am Geriatr Sco* 52:2120–2127.

Meng X, Rosenthal R, Rubin DB (1992): Comparing correlated correlation coefficients. *Psychological Bulletin* 111:172–175.

Miller MD, Paradis CF, Houck PR, Mazumdar S, Stack JA, Rifai AH, et al (1992): Rating chronic medical illness burden in geropsychiatric practice and research: application of the Cumulative Illness Rating Scale. *Psychiatry Res* 41:237–248.

Nebes RD, Butters MA, Mulsant BH, Pollock BG, Zmuda M, Houck PR, Reynolds CF (2000): Decreased working memory and processing speed mediate cognitive impairment in geriatric depression. *Psychol Med* 30:679–691.

Rapp MA, Dahlman K, Sano M, Grossman HT, Haroutunian V, Gorman JM (2005): Neuropsychological differences between late-onset and recurrent geriatric major depression. *Am J Psychiatry* 162:691–698.

Raskin A (1986): Partialing out the effects of depression and age on cognitive functions: experimental data and methodological issues. In: Poon LW, editor. *Handbook for Clinical Memory Assessment of Older Adults.* Washington, DC: American Psychological Association, pp 244–256.

Salloway S, Malloy P, Kohn R, Gillard E, Duffy J, Rogg J, et al (1996): MRI and neuropsychological deficits in early- and late-life-onset geriatric depression. *Neurology* 46:1567–1574.

Salthouse TA (2000): Aging and measures of processing speed. *Biol Psychology* 54:35–40.

Steingart A, Hermann N (1991): Major depressive disorder in the elderly: the relationship between age of onset and cognitive impairment. *Int J Geriatr Psychiatry* 6:593–598.

Taylor WD, MacFall JR, Payne ME, McQuoid DR, Provenzale JM, Steffens DC, Krishnan KR (2004): Late-life depression and microstructural abnormalities in dorsolateral prefrontal cortex white matter. *Am J Psychiatry* 161: 1293–1296.

van Ojen R, Hooijer C, Bezemer D, Jonker C, Lindelboom J, van Tilburg W (1995): Late-life depressive disorder in the community, I: the relationship between MMSE score and depression in subjects with and without psychiatric history. *Br J Psychiatry* 156:311–315.

van Reekum R, Simard M, Clarke D, Binns MA, Conn D (1999): Late-life depression as a possible predictor of dementia: cross-sectional and short-term follow-up results. *Am J Geriatr Psychiatry* 7:151–159.

Waldstein SR, Katzel LI (2004): Gender differences in the relation of hypertension to cognitive function in older adults. *Neurol Res* 26:502–506.

Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB (1991): Probability of stroke: A risk profile from the Framingham Study. *Stroke* 22:312–318.

Ylikoski R, Ylikoski A, Raininko R, Keskivaara P, Sulkava R, Tilvis R, Erkinjuntti T (2000): Cardiovascular diseases, health status, brain imaging findings and neuropsychological functioning in neurologically healthy elderly individuals. *Arch Gerontol Geriatr* 30:115–130.