ORIGINAL ARTICLE

The Nature and Determinants of Neuropsychological Functioning in Late-Life Depression

Meryl A. Butters, PhD; Ellen M. Whyte, MD; Robert D. Nebes, PhD; Amy E. Begley, MA; Mary Amanda Dew, PhD; Benoit H. Mulsant, MD; Michelle D. Zmuda, BS; Rishi Bhalla, PhD; Carolyn Cidis Meltzer, MD; Bruce G. Pollock, MD, PhD; Charles F. Reynolds III, MD; James T. Becker, PhD

Context: Cognitive impairment in late-life depression (LLD) is highly prevalent, disabling, poorly understood, and likely related to long-term outcome.

Objectives: To determine the characteristics and determinants of neuropsychological functioning LLD.

Design: Cross-sectional study of groups of LLD patients and control subjects.

Setting: Outpatient, university-based depression research clinic.

Participants: One hundred patients without dementia 60 years and older who met *DSM-IV* criteria for current episode of unipolar major depression (nonpsychotic) and 40 nondepressed, age- and education-equated control subjects.

Main Outcome Measures: A comprehensive neuropsychological battery.

Results: Relative to control subjects, LLD patients performed poorer in all cognitive domains. More than half exhibited significant impairment (performance below the 10th percentile of the control group). Information processing speed and visuospatial and executive abilities were the most broadly and frequently impaired. The neuropsychological impairments were mediated almost entirely by slowed information processing ($\beta = .45$-$.80$). Education ($\beta = .32$) and ventricular atrophy ($\beta = .28$) made additional modest contributions to variance in measures of language ability. Medical and vascular disease burden, apolipoprotein E genotype, and serum anticholinergicity did not contribute to variance in any cognitive domain.

Conclusions: Late-life depression is characterized by slowed information processing, which affects all realms of cognition. This supports the concept that frontostriatal dysfunction plays a key role in LLD. The putative role of some risk factors was validated (eg, advanced age, low education, depression severity), whereas others were not (eg, medical burden, age at onset of first depressive episode). Further studies of neuropsychological functioning in remitted LLD patients are needed to parse episode-related and persistent factors and to relate them to underlying neural dysfunction.

Arch Gen Psychiatry. 2004;61:587-595

From the Departments of Psychiatry (Drs Butters, Whyte, Nebes, Dew, Mulsant, Bhalla, Meltzer, Pollock, Reynolds, and Becker and Mss Begley and Zmuda), Radiology (Dr Meltzer), and Neurology (Drs Meltzer and Becker), University of Pittsburgh Medical Center, and the Geriatric Research Education Clinical Center of the Pittsburgh VA Healthcare System (Drs Whyte and Mulsant), Pittsburgh, Pa.

LATE-LIFE DEPRESSION (LLD) is a heterogeneous disorder that has become a major public health concern as the population has aged. Late-life depression is associated with significant morbidity and mortality and is both underrecognized and undertreated.[1]

Cognitive impairment in LLD is substantial and disabling. The cognitive response to antidepressant treatment is variable, and impairments persist even after effective treatment of depression.[2,3] There is a substantially increased risk of developing a progressive dementia during the 2 to 4 years following a depressive episode.[4,5]

Of the studies describing cognitive functioning in LLD, only a few[6-9] have included both a comprehensive assessment of cognitive domains and a healthy control group. Although the findings across these studies differ somewhat, they suggest that impairments exist in visuospatial ability, memory, speed of information processing, and executive functioning, with the executive deficits being particularly related to late age at onset of first lifetime depressive episode (late-onset).[9,10] Factors that are associated with neuropsychological impairment in LLD patients include more severe depressive symptoms,[6,11,12] more severe anxiety,[13] and/or vegetative symptoms.[14] White matter hyperintensities are associated with psychomotor slowing[15] and executive function impairment, particularly in LLD patients with late-onset depression.[9,16] In fact, 2 influential models of the cognitive ef-

©2004 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 08/30/2016

fects of depression emphasize the role of subcortical-frontal lobe circuit dysfunction,[17-19] which would account for particular deficits in information processing speed and executive functions.

A variety of other risk factors may play a role in the likelihood that LLD patients will exhibit cognitive impairment. For example, older age may be associated with cognitive impairment in LLD,[20-22] although this is not always the case.[23,24] Some studies[25-28] have found no relationship between late-onset depression and greater risk for cognitive impairment during the index episode, although several studies[16,29-31] have found that they are related. Moreover, even if impairment were initially reversed with successful treatment of depression, there may be an increased risk for subsequently developing progressive dementia.[4] Several recent studies[5,32-35] have found an association between late-onset depression and Alzheimer disease. Some studies,[36,37] but not all,[22,38,39] have found an increase in cognitive dysfunction in LLD with increasing medical burden. The apolipoprotein E (*APOE*) ϵ4 allele has been found to be related to poorer cognitive functioning in geriatric depression patients in one[40] but not all studies.[41-43] Finally, there is evidence suggesting that serum anticholinergic burden negatively affects cognitive functioning, especially memory ability, in LLD.[44,45] Many of these non–depression-related factors also place so-called normal, elderly patients (ie, nonpsychiatric groups) at risk for cognitive dysfunction[46-48] and even for dementia.[49]

To our knowledge, no single study has provided a comprehensive analysis that includes predictors and outcomes related to neuropsychological functioning in LLD. That is, although some studies have evaluated a single cognitive domain or a single risk factor, none have examined both risk factors and cognitive functioning in a comprehensive manner. Moreover, we were particularly interested in examining the relationship among neuropsychological domains to determine whether there might be a parsimonious mediating cognitive factor. Specifically, we hypothesized that information processing speed, which plays a critical role in the effects of normal cognitive aging[50] and depression-related alterations in cognition,[51] would mediate the association between biological and clinical risk factors and other cognitive domains.

METHODS

PARTICIPANTS

We enrolled 140 patients 60 years and older with current unipolar major depression (nonpsychotic). All patients had sought treatment at the Western Psychiatric Institute and Clinic (Pittsburgh, Pa) and were enrolled in federally sponsored intervention studies conducted within the Intervention Research Center for Late-Life Mood Disorders at the University of Pittsburgh School of Medicine. Forty elderly control subjects with no psychiatric history were recruited using local advertisements. The data for the present study were collected during participants' baseline, pretreatment evaluation. Details on subject recruitment, retention, and evaluation have been described elsewhere.[2,52] Diagnosis was established by a *Structured Clinical Interview for Axis I DSM-IV Disorders* (*SCID-IV*)[53] interview administered by formally trained master's-level and doctoral-level clinicians and a consensus diagnostic conference attended by the raters and at least 3 research geriatric psychiatrists. Patients and control subjects were excluded if they had psychotic symptoms or major unstable medical illnesses (eg, metastatic cancer). However, chronic diseases (eg, diabetes mellitus, hypertension) did not constitute exclusion criteria if the subject was medically stable. To study a broad, representative sample of those with LLD, ethnicity, insurance status, concurrent medical and psychiatric conditions, and symptom profile did not constitute exclusion criteria. Additional exclusionary criteria for the present study included the following: neurologic disorders or injuries known to have significant direct effects on cognitive functioning (eg, traumatic brain injury, multiple sclerosis) (n=10), uncorrectable sensory handicap (eg, blindness) (n=2), a diagnosis of any type of dementia from the University of Pittsburgh's Alzheimer's Disease Research Center either before or following resolution of the index depressive episode (n=19), or a best (including pretreatment and posttreatment) Dementia Rating Scale (DRS)[54,55] score of 129 or lower (n=9). A DRS score of 129 is 3 SDs below the mean of our age- and education-equated control group. These exclusionary criteria reduced the original patient study group of 140 to 100 (composed of 4 inpatients and 96 outpatients). After complete description of whichever parent treatment study in which subjects were participating, written informed consent approved by the University of Pittsburgh's Institutional Review Board was obtained.

MEASURES

Subjects had a broad-based pretreatment assessment that included clinical, psychosocial, biologic, and neuropsychological measures. (The neuropsychological measures are listed in Table 2.) Many of the nonneuropsychological measures assessed potential risk factors for cognitive impairment either in general or in LLD in particular. These measures, grouped by domain, included demographics (age, education, sex), depression-related factors (score on the 17-item Hamilton Depression Rating Scale [HDRS],[56] age at onset of first lifetime depressive episode), medical burden (score on Cumulative Illness Rating Scale–Geriatrics [CIRS-G]),[57] vascular burden (CIRS-G combined heart and vascular scale scores, *APOE* allele type,[40-43] serum anticholinergic burden[58]), and structural brain abnormalities (cortical and ventricular atrophy and white matter hyperintensity burden[59]).

Structural magnetic resonance (MR) imaging was conducted within 2 to 3 weeks of the baseline evaluation. Each subject's imaging data were read independently by 2 raters (including E.M.W. and C.C.M.) based on the Cardiovascular Health Study protocol.[59] The variables assessed were ventricular atrophy, sulcal atrophy, and the total white matter hyperintensity burden on the T1-weighted, T2-weighted, and proton density images. As per the Cardiovascular Health Study protocol, each variable was assigned a numerical rating by comparing each subject's imaging data to predefined visual standards that represent progressive severity on a 10-point scale (0 through 9). If the 2 independent raters differed in their rating by 1 point, the final rating was the mean of the 2 values. A greater than 1-point difference between raters was considered a major disagreement and was adjudicated by consensus. Four raters were involved in assessing the MR imaging data; these raters achieved intraclass correlation coefficients of 0.71 for ventricular atrophy, 0.44 for sulcal atrophy, and 0.66 for white matter hyperintensities.

Age at onset was ascertained from multiple sources, including the *SCID-IV*, all available medical and psychiatric records, and caregiver interviews. Comprehensive neuropsychological assessment was performed by 2 examiners who were highly trained and closely supervised by the first author (M.A.B.). In most cases, patients were tested before antidepressant treatment was initiated. All of the control subjects and 86 of the 100 depressed patients

©2004 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 08/30/2016

were psychotropic drug free. Seven patients were taking low doses of nortriptyline hydrochloride, which had been initiated 1 to 3 days before the assessment. Six patients were taking paroxetine at the time of the assessment; 4 had their initial dose within 3 days and 2 had been taking paroxetine for many months and were in the process of tapering off the medication. One patient had been taking mirtazapine for several weeks before testing. Importantly, all patients met clinical research criteria (ie, *DSM-IV*) for current major depression.

PROCEDURES AND STATISTICAL ANALYSIS

Descriptive Analyses

We compared depressed patients and control subjects on each of the risk factors, using either *t* tests or nonparametric tests, when appropriate.

Neuropsychological Functioning in LLD

To characterize neuropsychological functioning in LLD, we first combined the measures within each of 6 domains to yield a single score that reflected distinct areas of cognition (attention; information processing speed; and visuospatial, executive, language, and memory ability). Initially, we transformed raw scores for individual variables into *z* scores, using the distribution of the elderly control sample,[6,60,61] and these *z* scores were then averaged within each neuropsychological area to produce domain scores. Internal consistency (Cronbach α) exceeded .70 for all but 2 domains. The α was .67 for the memory domain and .30 for the attention domain, leading us to exclude the attention domain from further analyses.

We next performed a series of analyses comparing patient and control subjects' domain scores to characterize cognitive functioning in LLD. The descriptive analyses revealed that the patients' CIRS-G scores were significantly higher than controls. After verifying that there were no interactions between group and CIRS-G total score, we used multivariate analysis of covariance (MANCOVA) to model the main effect of group on the 5 cognitive domains controlling for CIRS-G scores. We performed *t* tests on each domain and on each of the individual measures (with Bonferroni-adjusted *P* values) to determine which measures accounted for differences between the groups.

To further delineate the cognitive patterns exhibited by both the depressed patients and control subjects, the number of domains in which each subject was impaired (defined as performance below the 10th percentile of the control group) was determined. The percentage of control subjects and LLD patients whose performance fell below the 10th percentile of the control group for each domain also was calculated.

Age at onset of first depressive episode has frequently been found to be an important factor in many aspects of LLD (eg, related to cognitive functioning, structural anatomy, response to pharmacotherapy). Therefore, based on convention, we divided our sample into those with early-onset depression (onset at <60 years of age, n=43) and late-onset depression (onset at ≥60 years of age, n=57) and performed *t* tests or χ^2 analyses (where appropriate) comparing them on demographic, clinical, and biologic variables. MANCOVA (2 groups for 5 cognitive domains) comparing the groups' performance on the cognitive domains while controlling for age and serum anticholinergic burden was also performed.

Risk Factors for Cognitive Dysfunction

We examined the relationship among the domain scores and several potential risk factors for cognitive dysfunction in LLD patients. Univariate Pearson correlations among each of the potential risk factors and each of the 5 cognitive domains for the LLD group were calculated. We then performed a series of regression analyses using only those risk factors that had significant Pearson correlations ($P<.05$, $r=0.2$).

RESULTS

DESCRIPTIVE ANALYSES

There were no significant differences between the depressed patients and control subjects on age, sex, education, CIRS-G combined heart and vascular disease scores, frequency of *APOE*ϵ4, level of serum anticholinergic burden, or structural MR imaging measures of sulcal or ventricular atrophy (**Table 1**). Depressed patients reported more medical problems (CIRS-G) and also demonstrated higher burden of white matter hyperintensities (MR imaging) and overall poorer cognitive functioning (Mini-Mental State Examination[62] and the DRS).

NEUROPSYCHOLOGICAL FUNCTIONING IN LLD

MANCOVA revealed that CIRS-G was not a significant covariate ($F_{5,127}=0.92$, $P=.47$) and that depressed patients performed significantly worse than control subjects ($F_{5,127}=2.80$, $P=.02$). Two-sample *t* tests revealed that the controls and LLD patients differed in all 5 domains (**Table 2**). The information processing speed domain was the only one in which subjects differed significantly on all 3 component measures. Subjects differed on 2 of 3 tasks in the visuospatial domain, 2 of 4 tasks on the executive domain, only 1 task in the language domain, and no tasks in the memory domain. Table 2 presents the *z* score transformed data for the patients. By definition, the control group's mean *z* score is always 0. Depressed patients' and control subjects' raw scores on individual measures are presented in **Table 3**.

Table 4 shows the patterns of cognitive deficits exhibited by both depressed patients and control subjects. Only 39% of depressed patients performed within normal limits (greater than the 10th percentile of the control group in all domains). The overall distribution of cognitive performance differed between depressed patients and control subjects (Fisher exact $P=.01$); the depressed patients were impaired in more domains than were the control subjects (Wilcoxon exact $P<.001$). **Figure 1** depicts the percentage of subjects whose performance was impaired on each cognitive domain. Information processing speed was the most frequently impaired domain, followed by the visuospatial, memory, executive, and language domains. More depressed patients than control subjects were impaired in all domains (Fisher exact *P* values: visuospatial, $P=.01$; memory, $P=.01$; executive, $P=.02$; information processing speed, $P<.001$) except for language (Fisher exact $P=.10$).

Comparison of early- and late-onset LLD patients revealed that the late-onset subgroup was significantly older at the time of neuropsychological evaluation

©2004 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 08/30/2016

Table 1. Characteristics of the Study Participants

Characteristic	Controls (n = 40)	Patients With LLD (n = 100)	Test Statistics
Age, mean (SD), y	69.9 (7.2)	70.8 (6.6)	$t_{138} = -0.70$, $P = .49$
Male, No. (%)	18 (45)	31 (31)	$\chi^2_1 = 2.46$, $P = .12$
Education, mean (SD), y	13.6 (2.9)	13.3 (2.6)	$t_{138} = 0.56$, $P = .58$
White, %	87.5	92.0	Fisher exact test = 0.52
CIRS-G score, mean (SD)*	4.7 (3.0)	8.3 (3.5)	$t_{132} = -6.00$, $P<.001$
CIRS-G heart and vascular score, mean (SD)	1.4 (1.5)	1.6 (1.5)	$t_{131} = -0.77$, $P = .45$
APOE4 carrier, No. (%)	7/33 (21)	21/78 (27)	$\chi^2_1 = 0.40$, $P = .53$
Detectable serum anticholinergic level (>0.25 pmol/mL), No. (%)	20/36 (56)	56/87 (64)	$\chi^2_1 = 84$, $P = .36$
Structural MR imaging CHS ratings, mean (SD)†			
Sulcal atrophy	4.8 (1.4)	5.1 (1.3)	$t_{73} = -0.83$, $P = .41$
Ventricular atrophy	3.3 (1.9)	3.6 (1.4)	$t_{73} = -0.64$, $P = .52$
White matter hyperintensity burden	1.4 (1.0)	2.5 (1.4)	$t_{72} = -2.98$, $P<.004$
Mini-Mental State Examination score	29.1 (1.1)	28.3 (1.7)	$t_{109} = 3.28$, $P<.002$
Dementia Rating Scale score	139.4 (3.5)	136.7 (5.7)	$t_{116} = 3.45$, $P<.001$
HDRS (17-item) score	2.4 (2.0)	21.6 (4.1)	$t_{81.7} = -33.73$, $P<.001$
Age of first depression episode, mean (SD), y	. . .	57.7 (17.9)	
Late onset (age ≥60 y), No. %	. . .	57 (57)	
Single episode, No. %	. . .	51 (51)	

Abbreviations: CHS, Cardiovascular Health Study; CIRS-G, Cumulative Illness Rating Scale–Geriatrics; HDRS, Hamilton Depression Rating Scale; LLD, late-life depression; MR, magnetic resonance.

*Square root transformation was used in the analyses. Means and standard deviations are reported in the original units.

†Reduced sample (17 controls, 58 patients with LLD). The only difference between subjects who did and did not undergo MR imaging was that controls who underwent MR imaging had more mean (SD) years of education (14.82 [2.74] vs 12.61 [2.61]; $t_{38} = 2.60$, $P = .01$) than those who did not. There were no other significant differences between subjects who did and did not undergo MR imaging in age, sex, CIRS-G, HDRS, age at onset, and the 5 cognitive domain scores at $\alpha<.05$.

Table 2. Results of *t* Tests Comparing Elderly Control Subjects' and LLD Patients' *z* Score Performance on Cognitive Domains and Individual Neuropsychological Tests*

Variable	Mean (SD)	*t* Statistic	*df*	Cohen d Effect Size	Bonferroni Adjusted *P* Value	Unadjusted *P* Value
Information Processing Speed domain	−1.31 (1.78)	5.98	136	0.95		<.001
Digit-Symbol[63]	−0.82 (1.01)	4.36	137	0.82	<.001	
Grooved Pegboard[64]	−2.12 (3.25)	5.80	130	0.88	<.001	
Trails A[65]	−0.99 (1.77)	4.15	122	0.69	<.001	
Visuospatial domain	−0.78 (1.06)	4.17	138	0.82		<.001
Simple drawings[66]	−0.82 (1.53)	3.73	109	0.63	.005	
Block Design[63]	−0.86 (1.10)	4.26	137	0.82	<.001	
Clock drawing[67]	−0.60 (1.10)	2.95	136	0.57	.06	
Executive domain	−0.85 (1.53)	4.72	138	0.73		<.001
EXIT[68]	−0.58 (1.34)	2.73	94.8	0.49	.13	
Trails B[65]	−1.42 (2.95)	4.24	136	0.65	<.001	
Stroop[69]	−0.61 (1.96)	2.35	123	0.39	.34	
WCST errors[70]	−0.68 (1.57)	3.07	111	0.52	.05	
Language domain	−0.41 (0.86)	2.69	138	0.52		.008
Boston Naming Test[71]	−0.79 (1.72)	3.38	120	0.56	.02	
Letter fluency (F, A, S)[72]	−0.24 (0.94)	1.34	138	0.25	>.99	
Animal fluency[72]	−0.39 (0.87)	2.32	138	0.42	.37	
Spot-the-Word[73]	−0.23 (1.14)	1.13	138	0.22	>.99	
Memory domain†	−0.47 (0.81)	3.07	138	0.58		.003
Logical Memory[74]	−0.35 (1.15)	1.70	138	0.32	>.99	
Modified Rey-Osterrieth[75,76]‡	−0.54 (1.11)	2.67	136	0.51	.14	
CVLT[77]	−0.50 (0.94)	2.79	137	0.52	.10	

Abbreviations: CVLT, California Verbal Learning Test; EXIT, Executive Interview; LLD, late-life depression; WCST, Wisconsin Card Sorting Test.

*Results are given for the patients with LLD (n = 100).

†All memory test scores reflect delayed free recall performance.

‡The original figure with several details removed to make it more appropriate for clinical geriatric populations.

($t_{98}=-4.52$, $P<.001$), had a higher percentage of males ($\chi^2_1=5.42$, $P=.02$), and had higher levels of serum anticholinergic burden ($\chi^2_1=4.05$, $P=.04$). MANCOVA comparing the groups' performance on the cognitive domains detected no significant differences between the groups.

©2004 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 08/30/2016

RISK FACTORS FOR COGNITIVE DYSFUNCTION

We examined univariate correlations and identified those with $P<.05$. Age and education were significantly associated with nearly all cognitive domains. The HDRS total score, number of medications, and age at onset of first depressive episode were each significantly correlated with 1 or 2 cognitive domains. Each of the 3 MR imaging variables was significantly correlated with 2 to 4 cognitive domains. Of note, each of the risk factors noted thus far was significantly correlated with information processing speed. Sex, CIRS-G total score, CIRS-G vascular scale, *APOE* allele type, and serum anticholinergic burden were not significantly correlated with any of the cognitive domains.

To understand associations among the factors that affect cognitive function in depressed patients without dementia, we used multiple regression analyses. Consistent with our initial hypothesis, the correlations between information processing speed and the various risk factor variables (and other neuropsychological domains) were uniformly high and significant. This observation supported our hypothesis that information processing speed is a mediating factor in the cognitive functioning of the elderly, depressed patients and is consistent with current models of cognitive aging.[50] To examine these relationships further, we regressed the language, visuospatial, memory, and executive domain scores on information processing speed and those risk factors that were significantly correlated ($P<.05$, $r=.20$) with the domain scores (ie, age, education, HDRS score, age at onset of first depressive episode, and all 3 MR imaging measures). All of the predictor variables were entered simultaneously, and only those that significantly increased the explained variance (after controlling for all other variables) were retained. With one exception, information processing speed was the sole significant predictor of each of the other neuropsychological domain scores; this is represented in **Figure 2** by paths from speed to each of the other domains (with the associated β weights). We then regressed the speed domain score on age, education, and HDRS score, and each had a significant, independent association with speed. Education was the only predictor variable that had an independent association with one of the domain scores after accounting for the association with speed. Thus, the language domain score, but not the other domain variables, was significantly associated with both speed and level of education.

When we repeated the analysis using the MR imaging variables from the patients who had undergone scanning, the path weights were virtually identical. We first regressed the domain scores on speed and ventricular atrophy (and the other predictor variables), and the extent of ventricular enlargement was significantly associated only with the language domain. When the MR imaging variables were regressed on the other predictors, only age was associated with the degree of ventricular enlargement. Age did not independently predict any domain scores, acting only through the mediation of ventricular atrophy and speed.

Table 3. Comparison of Elderly Subjects' and LLD Patients' Raw Score Performance on Individual Neuropsychological Tests*

Variable	Controls (n = 40)	Patients With LLD (n = 100)
Information Processing Speed domain		
Digit-Symbol	49.60 (11.82)	39.85 (11.98)
Grooved Pegboard	85.11 (14.86)	116.56 (48.35)
Trails A†	1.49 (0.50)	1.98 (0.88)
Visuospatial domain		
Simple drawings	16.65 (1.21)	15.66 (1.85)
Block Design	35.97 (9.47)	27.81 (10.41)
Clock drawing‡	8.60 (1.13)	7.93 (1.25)
Executive domain		
EXIT	6.67 (3.11)	8.47 (4.16)
Trails B†	3.65 (1.55)	5.75 (5.30)
Stroop§	2.79 (0.74)	3.23 (1.44)
WCST errors	11.95 (9.46)	18.42 (14.86)
Language domain		
Boston Naming Test	55.70 (3.55)	52.90 (6.11)
Letter fluency (F, A, S)	38.03 (12.81)	34.95 (12.00)
Animal fluency	18.30 (5.14)	16.28 (4.45)
Spot-the-Word	9.30 (4.65)	10.38 (5.30)
Memory domain		
Logical Memory	23.63 (7.45)	20.99 (8.57)
Modified Rey-Osterreith‖	16.36 (4.65)	13.85 (5.16)
CVLT	10.30 (3.42)	8.59 (3.22)

Abbreviations: CVLT, California Verbal Learning Test; EXIT, Executive Interview; LLD, late-life depression; WCST, Wisconsin Card Sorting Test.

*Data are given as mean (SD) of conventional scoring method except where indicated.

†Represents the mean number of seconds per completed connection.

‡Score based on Rouleau et al.[19]

§Score represents the ratio of number correct on color trial divided by number correct on color-word interference trial.

‖Maximum score is 24.

Table 4. Percentage of Participants Exhibiting Cognitive Deficits (Defined as 10th Percentile Below Comparison Group)

No. of Deficits	Controls, % (n = 40)	Patients With LLD, % (n = 100)
0	67.5	39
1	20	16
2	7.5	18
3	5	13
4	0	5
5	0	9
Total	**100**	**100**

Abbreviation: LLD, late-life depression.

COMMENT

Compared with an age- and education-equated control group, largely unmedicated, depressed, elderly patients without dementia performed more poorly on all cognitive domains measured. The depth and breadth of impairment were substantially greater than previously suspected. More than half of LLD patients exhibited clinically and statistically significant cognitive impairment. The most frequently impaired cognitive domains were information processing speed, visuospatial, memory, and ex-

©2004 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 08/30/2016

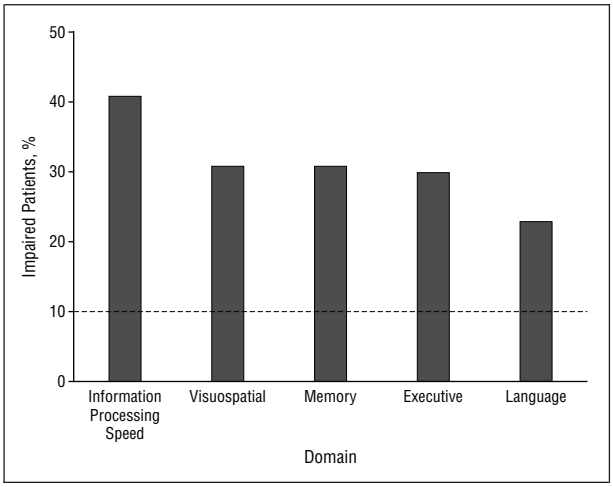

Figure 1. Performance on cognitive domains by patients with late-life depression. Impairment is defined as performance below the 10th percentile of the control subjects (see reference line).

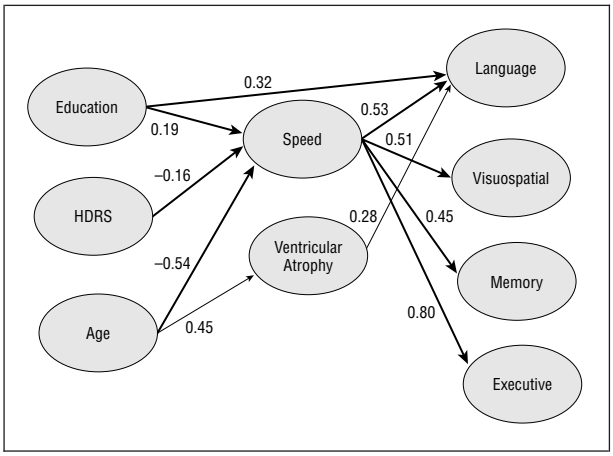

Figure 2. Relationships among cognitive domains and predictor variables. Thin arrows represent significant results from multiple regression analyses performed on the depressed subsample that underwent magnetic resonance imaging (n=58). Bold arrows represent significant results from multiple regression analyses performed on both the subsample and the full sample of depressed patients. HDRS indicates Hamilton Depression Rating Scale.

ecutive abilities. The depressed patients' impairments in the information processing speed and visuospatial domains were due to poor performance across nearly all of the individual measures that contributed to each of these broad domains. By contrast, the impairment in executive functioning was restricted to 2 tasks that specifically measure set-shifting ability.

These findings on neuropsychological functioning in LLD are in general agreement with the existing literature. Both Boone et al[6] and Lesser et al[9] found that, compared with control subjects, mixed-age groups of mildly to moderately depressed patients were impaired in nonverbal intelligence, visual memory, and executive ability. The depressed patients in the study by Lesser et al were also impaired in constructional ability and information processing speed, as were the most depressed patients in the sample studied by Boone et al. In a group of 10 elderly, depressed patients, Hart et al[7] found deficits compared with control subjects in measures of verbal and visual memory, construction, executive ability, and information processing speed. Finally, Kramer-Ginsberg et al[8] found that compared with a control group, a group of 41 elderly, depressed patients exhibited deficits in memory, visuospatial ability, and information processing speed.

In the present study, relative to control subjects, LLD patients showed impairment in all 5 of the domains measured along with a strikingly wide range of overall cognitive ability. Some patients exhibited virtually no measurable impairment, whereas others were impaired across multiple cognitive domains. In comparison with earlier studies, the relatively large size of our depressed group and their relatively advanced age and severe depressive symptoms enabled us to better characterize the cognitive heterogeneity of the disorder.

It is striking that the broad array of neuropsychological deficits was explained almost entirely by a fundamental deficit in information processing speed (Figure 2). Other combinations of predictor variables (eg, with executive function as a mediator) did not result in such parsimonious relationships among predictors and outcomes. Thus, factors slowing information processing speed affect a range of cognitive functions in LLD patients.

The finding that cognitive dysfunction is largely accounted for by information processing speed is in accord with our previous work in geriatric depression.[51] Thirty-eight of the 100 depressed patients in the present study also participated in the study by Nebes et al[51]; however, the overlap in measures was limited to 2 tests (Block Design and Digit Symbol subtests of the Wechsler Adult Intelligence Scale III). The present results also fit within the framework proposed by Salthouse[50] that the cognitive effects of normal aging are almost entirely accounted for by slowing of information processing. It is also noteworthy that prior work from our group[3] has shown that this slowing of information processing persists even after depressed patients have responded to antidepressant treatment. Although there was some improvement in the performance of the depressed patients during treatment, the magnitude of this improvement was no greater than that produced in older control subjects by practice alone. Thus, the cognitive slowing that appears to be central to neuropsychological impairment of our depressed patients may well be a trait feature of geriatric depression.

Examination of a broad array of potential risk factors revealed that a few exerted their influence on cognitive function by altering speed of information processing. Nearly all of the effects that the various risk factors had on language, memory, visuospatial, and executive ability were accounted for by alterations in information processing speed. The strength and direction of the independent associations among age, education, and depression symptoms, and processing speed are all straightforward. Patients who were older or who had more severe depressive symptoms were cognitively slower. By contrast, education was a protective factor—greater educational achievement was associated with faster information processing speed. Education level was also independently associated with the language domain score, which is heavily dependent on semantic knowledge.

Some risk factors had no effect on cognitive performance in the present analyses. We found, as have oth-

©2004 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 08/30/2016

ers,[22,38,39] no association between overall medical burden and cognitive ability. Therefore, the source of the cognitive dysfunction associated with LLD seems not to be related to the excess medical burden that characterizes many elderly, depressed individuals. Perhaps most notably, in our study group, we detected no effect of *APOE* allele type on the variance in cognitive ability. Several investigators,[42,43] including ourselves,[41] have found that the presence of the *APOE*ϵ4 allele does not influence overall cognitive functioning in the context of LLD. The present study extends this work, particularly by specifying that the *APOE*ϵ4 allele does not influence any particular cognitive domain, especially memory functioning, in LLD. This point is important because impairment in memory functioning is the hallmark of early Alzheimer disease. The lack of influence on memory ability suggests that LLD patients' increased risk of Alzheimer disease is mediated by some other, non–APOE-related factor.

Our group has previously found that even minimal serum anticholinergic activity has a negative effect on cognitive ability in both a community sample[44] and older, depressed patients without dementia.[45] Mulsant et al[44] studied a community sample that included individuals with dementia, whereas the present study excluded patients with even mild dementia on an a priori basis. It is possible that patients with preclinical or mild Alzheimer disease are the most vulnerable to deleterious anticholinergic effects, which would explain why Mulsant et al detected the relationship, whereas this study did not. The present study group was larger, but otherwise its subjects had similar characteristics to those studied by Nebes et al.[45] Nonetheless, since the study by Nebes et al[45] was conducted 5 years earlier in the same research clinic as the present study, it is possible that clinicians became more vigilant in reducing anticholinergic burden in patients identified clinically as being at risk for cognitive impairment.

In a secondary analysis, we examined how the MR image–derived variables affected cognitive outcomes. Although fewer subjects were entered into the multiple regression equations, β weights associated with the patterns of associations between non–MR image variables did not change substantially; neither cortical atrophy nor white matter hyperintensity scores were associated with any outcomes, whereas ventricular atrophy was linked to information processing speed and language domain scores. This finding is in accord with the general finding that structural neuroimaging abnormalities are associated with cognitive impairment in LLD.[37,78,79] However, the lack of influence of white matter hyperintensities on any domain of cognitive ability contrasts with more recent studies.[6,8,9,15,16,80] The reason for this discrepancy is not clear. Our finding that white matter hyperintensities are not related to cognitive functioning is indirectly supported by the only neuropathologic study of LLD to date, in which O'Brien et al[81] found no relationship between cognitive functioning in LLD and either vascular or Alzheimer-type neuropathologic characteristics. This issue bears further study, especially in subjects with late-onset depression.

The general pattern of neuropsychological functioning found in this study along with the model emanating from the risk factor analyses is relevant to the predominant cognitive theories of LLD.[17-19] Massman et al[19] compared middle-aged patients with depression and patients with cortical and subcortical dementia syndromes. They concluded that among cognitively impaired depressed patients, the pattern of dysfunction resembles that associated with disorders that disrupt the frontostriatal pathways (eg, Huntington disease, Parkinson disease). Recent studies revealing evidence that disruption of prefrontal systems or their modulating subcortical pathways may play an important role in LLD have led to suggestions that in many older, depressed patients subcortical cerebrovascular disease disrupts frontostriatal circuits, producing dysfunction in executive abilities.[17,18] This executive dysfunction is seen as a major component of the various cognitive impairments associated with LLD.[10]

The present finding that LLD patients as a group are characterized by impairments in information processing speed, visuospatial ability, and executive function supports the subcortical-frontal circuit dysfunction model of LLD. However, our findings diverge from the emphasis on executive dysfunction as the primary deficit characterizing LLD in studies by Alexopoulos et al.[17,18] Rather, the present findings, similar to those of Degl'Innocenti et al[82] and Nebes et al,[51] suggest that poor performance on measures of executive dysfunction (even more so than other cognitive domains) is largely accounted for by slowed information processing speed. The conflicting views on the nature of the fundamental deficit notwithstanding, there is growing evidence that both executive dysfunction and information processing speed may be mediated by the striatum.[83,84]

The present study represents an enhancement in methodologic rigor over previous studies by (1) using minimal exclusionary criteria to maximize the heterogeneity among LLD patients, thus permitting evaluation of a range of potential risk factors for cognitive impairment; (2) using a large, exclusively geriatric, mostly outpatient group to maximize the generalizability of findings; (3) including elderly control subjects to account for normal age-related cognitive changes; and (4) using a comprehensive neuropsychological battery to assess a range of cognitive functions. Nevertheless, there are a number of limitations to this study. One is the difficulty we had in measuring subjects' attention. Attention is a multifaceted concept, and it is possible that we did not measure the aspects most relevant to depression, reflected in the very low Cronbach α of the attention measures. Another limitation is that the control group of normal, elderly individuals was relatively small and had less medical disease burden than did the depressed group. Although several analyses demonstrated that the difference in disease burden had no effect on the results, a control group more closely equated to the LLD patients in terms of medical burden would be ideal. In addition, the exploratory nature of our multiple regression analyses limited our ability to determine the extent of multicollinearity among our variables. Finally, although this study had a substantially larger patient group than most in the literature, larger sample sizes, including late-onset depression, in both the depressed and control groups would permit more extensive modeling of the relationship between risk factors and cognitive dysfunction in LLD.

©2004 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 08/30/2016

CONCLUSIONS

Clearly, LLD is a multifactorial disorder with multiple clinically meaningful phenotypes and trajectories.[9,15,85-87] This study provides the most extensive characterization to date of the range, type, and depth of cognitive impairments in elderly patients who are in an episode of major depression. In addition, the association between a broad range of risk factors and domain-specific cognitive functioning was demonstrated. The data show that cognitive impairment in LLD is prevalent and broad based, involving half of a clinical study group and encompassing a broad range of deficits, notably speed of information processing, visuospatial ability, and executive function. Most of the variance in the cognitive domains measured in this study was attributable to information processing speed and was not related to the burden of chronic medical illness, *APOE*ϵ4 allele distribution, or even serum anticholinergic burden. Further study is needed to clarify the persistence of deficits after successful treatment, their relationship to Mild Cognitive Impairment and subsequent diagnosis of dementia, and the extent to which their progression can be slowed (or halted) with currently available therapies, including dopaminergic and cholinesterase inhibitor therapies.

Submitted for publication September 19, 2003; final revision received December 24, 2003; accepted January 20, 2004.

This research was supported by US Public Health Service grants MH01684, MH01077, MH65416, MH52247, MH43832, MH37869, and AG05133.

Some of the data in this article were presented at the Eighth International Conference on Alzheimer's Disease and Related Disorders; July 21, 2002; Stockholm, Sweden.

We thank Sati Mazumdar, PhD, and Patricia Houck, MS, for invaluable statistical advice; Melanie Fukui, MD, and Joelle Scanlon, PhD, for rating the MR imaging scans; and the staff of the Mental Health Intervention Research Center for Late-Life Mood Disorders for their help recruiting and evaluating participants in this study.

REFERENCES

1. Charney DS, Reynolds CF, Lewis L, Lebowitz BD, Sunderland T, Alexopoulos GS, Blazer DG, Katz IR, Meyers BS, Arean PA, Borson S, Brown C, Bruce ML, Callahan CM, Charlson ME, Conwell Y, Cuthbert BN, Devanand DP, Gibson MJ, Gottlieb GL, Krishnan KR, Laden SK, Lyketsos CG, Mulsant BH, Niederehe G, Olin JT, Oslin DW, Pearson J, Persky T, Pollock BG, Raetzman S, Reynolds M, Salzman C, Schulz R, Schwenk TL, Scolnick E, Unutzer J, Weissman MM, Young RC, Depression and Bipolar Support Alliance. Depression and bipolar support alliance consensus statement on the unmet needs in diagnosis and treatment of mood disorders in late life. *Arch Gen Psychiatry*. 2003;60:664-672.
2. Butters MA, Becker JT, Nebes RD, Zmuda M, Mulsant BH, Pollock BG, Reynolds CF. Changes in cognitive functioning following treatment of late-life depression. *Am J Psychiatry*. 2000;157:1949-1954.
3. Nebes RD, Pollock BG, Houck PR, Butters MA, Mulsant BH, Zmuda MD, Reynolds CF. Persistence of cognitive impairment in geriatric patients following antidepressant treatment: a randomized, double-blind clinical trial with nortriptyline and paroxetine. *J Psychiatr Res*. 2003;37:99-108.
4. Alexopoulos GS, Meyers BS, Young RC, Mattis S, Kakuma T. The course of geriatric depression with "reversible dementia": a controlled study. *Am J Psychiatry*. 1993;150:1693-1699.
5. Steffens DC, Plassman BL, Helms MJ, Welsh-Bohmer KA, Saunders AM, Breitner JC. A twin study of late-onset depression and apolipoprotein E epsilon 4 as risk factors for Alzheimer's disease. *Biol Psychiatry*. 1997;41:851-856.
6. Boone KB, Lesser IM, Miller BL, Wohl M, Berman N, Lee ABP, Palmer B, Back C. Cognitive functioning in older depressed outpatients: relationships of presence and severity of depression to neuropsychological test scores. *Neuropsychology*. 1995;9:390-398.
7. Hart RP, Kwentus JA, Taylor JR, Harkins SW. Rate of forgetting in dementia and depression. *J Consult Clin Psychol*. 1987;55:101-105.
8. Kramer-Ginsberg E, Greenwald BS, Krishnan KR, Christiansen B, Hu B, Ashtari M, Patel M, Pollack S. Neuropsychological functioning and MRI signal hyperintensities in geriatric depression. *Am J Psychiatry*. 1999;156:438-444.
9. Lesser IM, Boone KB, Mehringer CM, Wohl MA, Miller BL, Berman NG. Cognition and white matter hyperintensities in older depressed patients. *Am J Psychiatry*. 1996;153:1280-1287.
10. Lockwood KA, Alexopoulos GS, Kakuma T, Van Gorp WG. Subtypes of cognitive impairment in depressed older adults. *Am J Geriatr Psychiatry*. 2000;8:201-208.
11. Lichtenberg PA, Ross T, Millis SR, Manning CA. The relationship between depression and cognition in older adults: a cross-validation study. *J Gerontol B Psych Sci Soc Sci*. 1995;1995:1-P2 5.
12. Raskin A. Partialing out the effects of depression and age on cognitive functions: experimental data and methodological issues. In: Poon LW, ed. *Handbook for Clinical Memory Assessment of Older Adults*. Washington, DC: American Psychological Association; 1986:244-256.
13. La Rue A, Spar J, Hill CD. Cognitive impairment in late-life depression: clinical correlates and treatment implications. *J Affect Disord*. 1986;11:179-184.
14. Palmer BW, Boone KB, Lesser IM, Wohl MA, Berman N, Miller BL. Neuropsychological deficits among older depressed patients with predominantly psychological or vegetative symptoms. *J Affect Disord*. 1996;41:17-24.
15. Hickie I, Scott E, Mitchell P, Wilhelm K, Austin MP, Bennett B. Subcortical hyperintensities on magnetic resonance imaging: clinical correlates and prognostic significance in patients with severe depression. *Biol Psychiatry*. 1995;37:151-160.
16. Salloway S, Malloy P, Kohn R, Gillard E, Duffy J, Rogg J, Tung G, Richardson E, Thomas C, Westlake R. MRI and neuropsychological differences in early- and late-life-onset geriatric depression. *Neurology*. 1996;46:1567-1574.
17. Alexopoulos GS, Meyers BS, Young RC, Kakuma T, Silbersweig D, Charlson M. Clinically defined vascular depression. *Am J Psychiatry*. 1997;154:562-565.
18. Alexopoulos GS. Frontostriatal and limbic dysfunction in late-life depression. *Am J Geriatr Psychiatry*. 2002;10:687-695.
19. Massman PJ, Delis DC, Butters N, DuPont RM, Gillin JC. The subcortical dysfunction hypothesis of memory deficits in depression: neuropsychological validation in a subgroup of patients. *J Clin Exp Neuropsychol*. 1992;14:687-706.
20. King DA, Caine ED, Conwell Y, Cox C. The neuropsychology of depression in the elderly: a comparative study of normal aging and Alzheimer's disease. *J Neuropsychiatry Clin Neurosci*. 1991;3:163-168.
21. King DA, Caine ED, Cox C. Influence of depression and age on selected cognitive functions. *Clin Neuropsychol*. 1993;7:443-453.
22. King DA, Cox C, Lyness JM, Caine ED. Neuropsychological effects of depression and age in an elderly sample: a confirmatory study. *Neuropsychology*. 1995; 9:399-408.
23. Boone KB, Lesser I, Miller B, Wohl M, Berman N, Lee A, Palmer B. Cognitive functioning in a mildly to moderately depressed geriatric sample: relationship to chronological age. *J Neuropsychiatry Clin Neurosci*. 1994;6:267-272.
24. Lyness SA, Eaton EM, Schneider LS. Cognitive performance in older and middle-aged depressed outpatients and controls. *J Gerontol B Psychol Sci Soc Sci*. 1994; 49:P129-P136.
25. Baldwin RC, Tomenson B. Depression in later life: a comparison of symptoms and risk factors in early and late onset cases. *Br J Psychiatry*. 1995;167:649-652.
26. Brodaty H, Luscombe G, Parker G, Wilhelm K, Hickie I, Austin MP, Mitchell P. Early and late onset depression in old age: different aetiologies, same phenomenology. *J Affect Disord*. 2001;66:225-236.
27. Greenwald BS, Kramer-Ginsberg E. Age at onset in geriatric depression: relationship to clinical variables. *J Affect Disord*. 1988;15:61-68.
28. Holroyd D, Duryee JJ. Differences in geriatric psychiatry outpatients with early- vs late-onset depression. *Int J Geriatr Psychiatry*. 1997;12:1100-1106.
29. Steingart A, Hermann N. Major depressive disorder in the elderly: the relationship between age of onset and cognitive impairment. *Int J Geriatr Psychiatry*. 1991;6:593-598.
30. van Ojen R, Hooijer C, Bezemer D, Jonker C, Lindelboom J, van Tilburg W. 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*. 1995;166:311-315.
31. van Reekum R, Simard M, Clarke D, Binns MA, Conn D. Late-life depression as a possible predictor of dementia: cross-sectional and short-term follow-up results. *Am J Geriatr Psychiatry*. 1999;7:151-159.

©2004 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 08/30/2016

32. Jorm AF, van Duijn CM, Chandra V, Fratiglioni L, Graves AB, Heyman A, Kokmen E, Kondo K, Mortimer JA, Rocca WA, EURODEM Risk Factors Research Group. Psychiatric history and related exposures as risk factors for Alzheimer's disease: a collaborative re-analysis of case-control studies. *Int J Epidemiol*. 1991; 20:S43-S47.
33. Kokmen E, Beard CM, Chandra V, Offord KP, Schoenberg BS, Ballard DJ. Clinical risk factors for Alzheimer's disease: a population-based case-control study. *Neurology*. 1991;41:1393-1397.
34. Speck CE, Kukull WA, Brenner DE, Bowen JD, McCormick WC, Teri L, Pfanschmidt ML, Thompson JD, Larson EB. History of depression as a risk factor for Alzheimer's disease. *Epidemiology*. 1995;6:366-369.
35. van Duijn CM, Clayton DG, Chandra V, Fratiglioni L, Graves AB, Heyman A, Jorm AF, Kokmen E, Kondo K, Mortimer JA, EURODEM Risk Factors Research Group. Interaction between genetic and environmental risk factors for Alzheimer's disease: a reanalysis of case-control studies. *Genet Epidemiol*. 1994;11:539-551.
36. Caine ED, Lyness JM, King DA. Reconsidering depression in the elderly. *Am J Geriatr Psychiatry*. 1993;1:4-20.
37. Lesser IM, Miller BL, Boone KB, Hill-Gutierrez E, Mehringer CM, Wong K, Mena I. Brain injury and cognitive function in late-onset psychotic depression. *J Neuropsychiatry Clin Neurosci*. 1991;3:33-40.
38. La Rue A. Patterns of performance on the Fuld Object Memory Evaluation in elderly inpatients with depression or dementia. *J Clin Exp Neuropsychol*. 1989; 11:409-422.
39. La Rue A, Goodman S, Spar JE. Risk factors for memory impairment in geriatric depression. *Neuropsychiatry Neuropsychol Behav Neurol*. 1992;5:178-184.
40. Krishnan KR, Tupler LA, Ritchie JC, McDonald WM, Knight DL, Nemeroff CB, Carroll BJ. Apolipoprotein E-epsilon 4 frequency in geriatric depression. *Biol Psychiatry*. 1996;40:69-71.
41. Butters MA, Sweet RA, Mulsant BH, Kamboh MI, Pollock BG, Begley AE, Reynolds CF, DeKosky ST. APOE is associated with ago-of-onset, but not cognitive functioning, in late-life depression. *Int J Geriatr Psychiatry*. 2003;18:1075-1081.
42. Kessing LV, Jorgensen OS. Apolipoprotein E-epsilon 4 frequency in affective disorder. *Biol Psychiatry*. 1999;45:430-434.
43. Zubenko GS, Henderson R, Stiffler JS, Stabler S, Rosen J, Kaplan BB. Association of the APOE epsilon 4 allele with clinical subtypes of late life depression. *Biol Psychiatry*. 1996;40:1008-1016.
44. Mulsant BH, Pollock BG, Kirshner M, Shen C, Dodge H, Ganguli M. Serum anticholinergic activity in a community-based sample of older adults: relationship with cognitive performance. *Arch Gen Psychiatry*. 2003;60:198-203.
45. Nebes RD, Pollock BG, Mulsant BH, Kirshner M, Halligan EM, Zmuda M, Reynolds CF. Low-level serum anticholinergicity as a source of baseline cognitive heterogeneity in geriatric depressed patients. *Psychopharmacol Bull*. 1997;33:715-720.
46. Rusinek H, De Santi S, Frid D, Tsui WH, Tarshish CY, Convit A, de Leon MJ. Regional brain atrophy rate predicts future cognitive decline: 6-year longitudinal MR imaging study of normal aging. *Radiology*. 2003;229:691-696.
47. Salthouse TA, Kausler D, Saults JS. Investigation of student status, background variables, and feasibility of standard tasks in cognitive aging research. *Psychol Aging*. 1988;3:29-37.
48. Zelinski EM, Gilewski MJ. Effects of demographic and health variables on Rasch scaled cognitive scores. *J Aging Health*. 2003;15:435-464.
49. Kuller LH, Shemanski L, Manolio T, Haan M, Fried L, Bryan N, Burke GL, Tracy R, Bhadelia R. Relationship between ApoE, MRI findings, and cognitive function in the Cardiovascular Health Study. *Stroke*. 1998;29:388-398.
50. Salthouse TA. The processing-speed theory of adult age differences in cognition. *Psychol Rev*. 1996;103:403-428.
51. Nebes RD, Butters MA, Mulsant BH, Pollock BG, Zmuda M, Houck PR, Reynolds CF. Decreased working memory and processing speed mediate cognitive impairment in geriatric depression. *Psychol Med*. 2000;30:679-691.
52. Mulsant BH, Pollock BG, Nebes R, Miller MD, Sweet RA, Stack J, Houck PR, Bensasi S, Mazumdar S, Reynolds CF. A twelve-week double-blind randomized comparison of nortriptyline and paroxetine in older depressed inpatients and outpatients. *Am J Geriatr Psychiatry*. 2001;9:406-414.
53. First MB, Gibbon M, Spitzer RL, Williams JBW. *Structured Clinical Interview for DSM-IV Axis I Disorders SCID I: Clinician Version, Administration Booklet*. Washington, DC: American Psychiatric Press; 1997.
54. Mattis S. Mental status examination for organic mental syndrome in the elderly patient, In: Bellak L, Karasu TB, eds. *Geriatric Psychiatry: A Handbook for Psychiatrists and Primary Care Physicians*. New York, NY: Grune & Stratton; 1976:77-101.
55. Mattis S. *Dementia Rating Scale (DRS)*. Odessa, Fla: Psychological Assessment Resources; 1988.
56. Mulsant B, Sweet RA, Rifai AH, Pasternak RE, Zubenko GS. The use of the Hamilton Rating Scale for Depression in elderly patients with cognitive impairment and physical illness. *Am J Geriatr Psychiatry*. 1994;2:220-229.
57. Miller MD, Paradis CF, Houck PR, Mazumdar S, Stack JA, Rifai AH, Mulsant B, Reynolds CF. Rating chronic medical illness burden in geropsychiatric practice and research: application of the Cumulative Illness Rating Scale. *Psychiatry Res*. 1992;41:237-248.
58. Pollock BG, Mulsant BH, Nebes R, Kirshner MA, Begley AE, Reynolds CF. Serum anticholinergicity in elderly depressed patients treated with paroxetine or nortriptyline. *Am J Psychiatry*. 1998;155:1110-1112.
59. Bryan RN, Manolio TA, Schertz LD, Jungreis C, Poirier VC, Elster AD, Kronmal RA. A method for using MR to evaluate the effects of cardiovascular disease on the brain: the cardiovascular health study. *Am J Neuroradiol*. 1994;15:1625-1633.
60. Bilder BH, Goldman RS, Robinson D, Reiter G, Bell L, Bates JA, Pappadopulos E, Willson DF, Alvir JMJ, Woerner MG, Geisler S, Kane JM, Lieberman JA. Neuropsychology of first-episode schizophrenia: initial characterization and clinical correlates. *Am J Psychiatry*. 2000;157:549-559.
61. Rosen TJ. Statistical practice in aging and dementia research. In: Boller F, Grafman J, eds. *Handbook of Neuropsychology*. Amsterdam, the Netherlands: Elsevier; 1990.
62. Folstein MF, Folstein SW, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975; 12:189-198.
63. Wechsler D. *Wechsler Adult Intelligence Scale-III*. San Antonio, Tex: The Psychological Corporation; 1996.
64. Matthews CG, Klove H. *Instruction Manual for the Adult Neuropsychology Test Battery*. Madison: University of Wisconsin Medical School, 1964.
65. Reitan RM, Wolfson D. *The Halstead-Reitan Neuropsychological Test Battery*. Tucson, Ariz: Neuropsychology Press; 1993.
66. Goodglass H, Kaplan E. *The Assessment of Aphasia and Related Disorders*. Philadelphia, Pa: Lea & Febiger; 1983.
67. Rouleau I, Salmon DP, Butters N, Kennedy C, McGuire K. Quantitative and qualitative analyses of clock drawings in Alzheimer's and Huntington's disease. *Brain Cogn*. 1992;18:70-87.
68. Royall DR, Mahurin RK, Gray KF. Bedside assessment of executive cognitive impairment: the Executive Interview. *J Am Geriatr Soc*. 1992;40:1221-1226.
69. Trenerry MR, Crosson B, DeBoe J, Leber WR. *The Stroop Neuropsychological Test*. Odessa, Fla: Psychological Assessment Resources; 1989.
70. Berg EA. A simple objective technique for measuring flexibility in thinking, using a sorting method. *J Gen Psychol*. 1948;39:15-22.
71. Kaplan EF, Goodglass H, Weintraub S. *The Boston Naming Test*. Philadelphia, Pa: Lea & Febiger; 1983.
72. Borkowski JG, Benton AL, Spreen O. Word fluency and brain damage. *Neuropsychologia*. 1967;5:135-140.
73. Baddeley A, Emslie H, Smith IN. *The Speed and Capacity of Language Processing (SCOLP) Test: A Manual*. Bury St Edmunds, England: Thames Valley Test Co; 1992.
74. Wechsler D. *Wechsler Memory Scale-III*. San Antonio, Tex: The Psychological Corp; 1997.
75. Osterrieth PA. Le test de copie d'une figure complexe. *Arch Psychol*. 1944;30: 206-356.
76. Rey A. Psychological examination of traumatic encephalopathy. *Arch Psychol*. 1941;28:286-340.
77. Delis DC, Kramer JH, Kaplan E, Ober BA. *California Verbal Learning Test Manual*. New York, NY: Psychological Corp; 1987.
78. Abas MA, Sahakian BJ, Levy R. Neuropsychological deficits and CT scan changes in elderly depressives. *Psychol Med*. 1990;20:507-520.
79. Pearlson GD, Rabins PV, Kims WS, Speedie LJ, Moberg PJ, Burns A, Bascom MJ. Structural brain CT changes and cognitive deficits in elderly depressives with and without reversible dementia ("pseudodementia"). *Psychol Med*. 1989;19:573-584.
80. Nebes RD, Reynolds CF, Boada F, Meltzer CC, Fukui MB, Saxton J, Halligan EM, DeKosky ST. Longitudinal increase in the volume of white matter hyperintensities in late-onset depression. *Int J Geriatr Psychiatry*. 2002;17:526-530.
81. O'Brien J, Thomas A, Ballard C, Brown A, Ferier N, Jaros E, Perry R. Cognitive impairment in depression is not associated with neuropathologic evidence of increased vascular or Alzheimer-type pathology. *Biol Psychol*. 2001;49:130-136.
82. Degl'Innocenti A, Agren H, Backman L. Executive deficits in major depression. *Acta Psychiatr Scand*. 1998;97:182-188.
83. Stebbins GT, Gabrieli JD, Shannon KM, Penn RD, Goetz CG. Impaired frontostriatal cognitive functioning following posteroventral pallidotomy in advanced Parkinson's disease. *Brain Cogn*. 2000;42:348-363.
84. Almkvist O, Wahlund LO, Andersson-Lundman G, Basun H, Backman L. White-matter hyperintensity and neuropsychological functions in dementia and healthy aging. *Arch Neurol*. 1992;49:626-632.
85. Coffey CE, Wilkinson WE, Weiner RD, Parashos IA, Djang WT, Webb MC, Figiel GS, Spritzer CE. Quantitative cerebral anatomy in depression: a controlled magnetic resonance imaging study. *Arch Gen Psychiatry*. 1993;50:7-16.
86. Drevets WC. Geriatric depression: brain imaging correlates and pharmacologic considerations. *J Clin Psychiatry*. 1994;55:71-81.
87. Krishnan KRR. Neuroanatomic substrates of depression in the elderly. *J Geriatr Psychiatry Neurol*. 1993;6:39-58.

©2004 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 08/30/2016