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Neuropsychological deficits among patients with late-onset minor and major depression

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Abstract

Cognitive ability of minor depressed patients ($N = 28$), major depressed patients ($N = 26$) and healthy elderly ($N = 38$) was examined cross-sectionally to determine if cognitive abilities of patients with late-onset depression decrease with increasing severity of disease and if cognitive scores for minor depressed patients fall between those of healthy elderly and major depressed patients. A pooled within-group principal component analysis of cognitive test scores identified five components, three of which showed significant group differences. Verbal Recall and Maintenance of Set separated controls from major depressed patients and minor from major depressed patients. Executive Functioning separated controls from minor depressed patients, and Working Memory was borderline for separating controls from major depressed patients. The component representing Nonverbal Recognition was not statistically significant. Partial correlations controlling for age and education indicate that cognitive performance does decrease as severity of depression increases, and the magnitude of the change varies

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from a trend to a significant deficit depending on the cognitive domain. This decline in cognitive performance parallels a similar trend observed in neuroanatomical studies in which the volume of the frontal and temporal lobes decrease with increasing severity of depression.

Keywords: Cognition; Depression; Late-onset; Elderly; Minor; Executive

1. Introduction

Elderly people are at greater risk than younger adults of suffering depressive symptoms at a level below what is considered sufficient for a diagnosis of major depressive disorder (MDD) but which meets Diagnostic and Statistical Manual, revised edition IV (DSM-1V; American Psychiatric Association Committee on Nomenclature and Statistics, 1994) criteria for minor depression. Point prevalence studies of depressive symptoms that do not meet criteria for MDD report between 15 and 23% of elderly people queried have current depressive symptomatology (Blazer & Williams, 1980; Kivela & Pahkala, 1988), and 10% meet criteria for minor depression (Beekman, Copeland, & Prince, 1999). In an epidemiological survey, about 5% of elderly community residents reported a lifetime diagnosis of major depression, but 32% reported a history of either minor or recurrent brief depression (Heun, Papassotiropoulos, & Ptok, 2000). The lifetime prevalence for depressive symptoms shows a curvilinear relationship to age: the symptoms increase during young adulthood, decrease during middle age, but then increase again after age 60 (Ernst & Angst, 1995; Gatz, Johansson, Pedersen, Berg, & Reynolds, 1993; Newmann, 1989). Gatz et al. also reported that the proportion of patients meeting the Center for Epidemiological Studies-Depression cut-off criterion for major depression did not increase with age as fast as the simple symptom scores, suggesting that the occurrence of minor depression was increasing more rapidly in elderly patients than was the occurrence of major depression.

Similar to patients with major depression, those with minor depression tend to have reduced physical, social and occupational functioning, worse perceived health, and greater bodily pain than patients with no chronic medical conditions (Judd & Akiskal, 2000; Judd et al., 2000; Van Den Berg, Oldehinkel, Brilman, Bouhuys, & Ormel, 2000; Wells et al., 1989). Depressed patients also have worse functioning than medical patients with chronic conditions. Outpatients with either current depressive disorder or depressive symptoms have worse social role functioning than that associated with eight major chronic medical conditions, and they spend more days in bed and experience more bodily pain than patients with five of the eight major chronic medical conditions (Wells et al., 1989). The presence of major depression is a risk factor for the onset of ischemic heart disease among people initially free of the disease (Glassman & Shapiro, 1998). Furthermore, 25% of adults with minor depression develop a subsequent major depressive episode (Horwath, Johnson, Klerman, & Weisman, 1992). On the other hand, minor depression is also a common residual effect of a major depressive episode and indicates a high likelihood of nonresponse to treatment and relapse (Keller et al., 1992). Among elderly patients, nonresponse has cognitive implications because duration of depressive illness is a stronger predictor of cognitive deficit than demographic characteristics,

medical history, psychoactive medications, or clinical features associated with the depressive episode (LaRue, Goodman, & Spar, 1992). According to Katon et al. (1994), two thirds of minor depressed patients who receive antidepressant therapy recover within 6 months, but the prognosis for those who do not receive treatment may be less optimistic. Both longitudinal and cross-sectional studies report that patients with minor depression are less likely to receive treatment than those with major depression or dysthymia (Angst & Merikangas, 1997; Van Den Berg et al., 2000).

Among patients with major depression, a number of neuropsychological abilities can be compromised. Deficits among older patients with major depression have been reported for psychomotor processing (Boone et al., 1995; Hart & Kwentus, 1987; LaRue, Swan, & Carmelli, 1995), nonverbal memory (Abas, Sahakian, & Levy, 1990; Boone et al., 1994, 1995; LaRue et al., 1995), nonverbal fluency (Crowe, 1996), verbal memory (Channon, Baker, & Robertson, 1993; Hart, Kwentus, Taylor, & Harkins, 1987; Hill, Stoudemire, Morris, Martino-Saltzman, & Markwalter, 1993; King, Caine, Conwell, & Cox, 1991; LaRue, D'Ilia, Clark, Spar, & Jarvik, 1989), learning ability (Abas et al., 1990; Emery & Breslau, 1989; King et al., 1991), reading comprehension (Emery & Breslau, 1989), verbal fluency (Boone et al., 1994; Franke et al., 1993; King et al., 1991), and executive functioning (Abrams & Taylor, 1987; Boone et al., 1994, 1995; Franke et al., 1993; Hart, Kwentus, Hamer, et al., 1987; Lichtenberg et al., 1995). Depressed individuals appear to have the most difficulty with complex tasks that require effortful processing by the prefrontal cortex, that is, greater concentrations of energy, attention, and intentionality, while relatively automatic processing (such as articulatory loop) is preserved (Rogers, Bradshaw, Pantelis, & Phillips, 1998). If minor depression represents an interim point on a continuum of depressive symptomatology, as has been suggested (Angst & Merikangas, 1997; Geiselmann & Bauer, 2000), the cognitive deficits associated with MDD might manifest in milder yet clinically significant form among patients with minor depression.

The purpose of our study was to examine cognitive deficits in patients' with clinically significant depression (both major and minor) and to determine the domains that appear to become compromised with increasing severity of depression. We hypothesized that cognitive performance of depressed participants would decrease across multiple functional areas and that the scores of minor depressed patients would fall intermediate to performances of healthy elderly and major depressed patients. If the three groups do show significant differences in functioning within cognitive domains, an additional objective of this study would be to identify tests that appear sensitive to discriminating the diagnostic groups.

2. Methods

2.1. Participants

Patients and controls were part of a sample recruited for neuroanatomical and neuropsychological studies of late-onset depression. Many participants in the neuroanatomical study agreed to participate in the neuropsychological study on the cognitive changes associated with depression. Late-onset was operationally defined as onset of the first episode occurring after age 60. Minor depressed patients met DSM-IV research criteria for minor depression, that

is, the presence of depressed mood or loss of interest in activities with at least one but less than four additional symptoms. The duration criterion was increased from 2 weeks to 1 month to facilitate our focus on patients in whom minor depression was sustained for a period of time and was not merely a transient dysphoria. Six patients who concurrently met DSM-IV criteria for dysthymic disorder (minor depression for at least 2 years duration) were included. Minor depressed patients scored between 8 and 16 on the 17-item Hamilton Rating Scale for Depression (HAM-D). A minor depressed patient could score 15 or 16 on the HAM-D yet be classified as minor depressed based on the clinical evaluation by a board-certified geriatric psychiatrist (AK) per DSM-IV research criteria. All patients included in this minor depressed group reported the index episode as their first episode of an affective disturbance. Most patients with minor depression were drug naïve, and all were free of psychotropic medications for at least 2 weeks prior to the time of the study, which is usually considered sufficient for a low-dose antidepressant wash-out period. The minor depressed patients ($N = 28$) and healthy controls ($N = 38$) were volunteers who responded to community advertisements.

Patients with major depressive disorder (MDD; $N = 26$) were recruited from ambulatory and inpatient geropsychiatry programs at a major university medical center. MDD patients met current DSM-IV criteria for the disorder, scored 15 or higher on the HAM-D, and reported the index episode as occurring after age 60. Information on prior episodes and the age of onset for the current episode were obtained from patients and caregivers. About one third of the major depressed patients were on a combination of low dose anxiolytics and/or antidepressants in therapeutic dosages at the time of the study. Although these medications might have contributed to poorer cognitive functioning in major depressed patients, most studies in the literature have found such cognitive effects to be small (Berg & Dellasega, 1996). Additionally, it appears less likely that there was a substantive medication effect given the pattern of cognitive findings fit the proposed hypotheses.

Exclusionary criteria for all participants included any new prescription or significant change in the regimen of an existing prescription in the 3 months prior to the study; use of any medication that may potentially cause psychotropic action (e.g., thyroxine, propranolol); history of dependence or abuse of alcohol or other substances; a current or past history of schizophrenia or other psychotic illness; a current or past history of neurological disease (e.g., tumor, stroke, Parkinson's disease) or dementia of the Alzheimer's type or other cortical or subcortical dementia; a change in a medical condition that required an urgent reevaluation and/or hospitalization within the last 3 month; or presence of a life-threatening condition (e.g., renal or hepatic failure). If the patient met all study criteria, he or she completed a neuropsychological battery administered by trained and blinded research assistants under the supervision of neuropsychological faculty. The cognitive study was approved by the Committee on Studies Involving Human Beings at the University of Pennsylvania.

2.2. Procedure

Participants were initially screened with the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) to evaluate additional past or present Axis I disorders. Participants then received a comprehensive medical and neurological examination by a geriatric psychiatrist (AK) with a standard battery of laboratory tests. None of the subjects had clinical evidence

of another CNS disorder based on history and medical examination. Mental status was examined with the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975) using an exclusionary cut-point of <24. None of the patients had a history or mental status examination consistent with dementia. The Cumulative Illness Rating Scale (CIRS; Linn, Linn, & Gurel, 1968) is a validated instrument that rates dysfunction of six primary organ systems (cardiorespiratory, gastrointestinal, genitourinary, musculoskeletal, neurologic, and general systems) on a 0–4 severity scale and is commonly used in studies involving elderly subjects. The minor depressed and control groups had a few stable comorbid medical disorders of comparable severity such as hypertension, diabetes, and arthritis; MDD patients showed no difference in medical comorbidity, although their average was slightly higher as would be expected in a clinical sample. Controls and patients were comparable in age of onset, duration of episode, sex, MMSE, and handedness.

2.3. Measures

The neuropsychological tests were administered to all study participants after the psychiatric and medical examinations. The battery included the following: Modified Card Sort Test (Nelson, 1976); Trailmaking A and B (Lezak, 1995); Block Designs (Wechsler, 1981); California Verbal Learning Test (CVLT; Delis, Kramer, Kaplan, & Ober, 1987); Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983); Continuous Visual Memory Test (Trahan & Larrabee, 1988); semantic fluency using categories of fruits, clothes, and animals (Laine, 1988); and Digit Span forward and backward (Wechsler, 1987).

Scores used for analysis included categories achieved, errors and perseverations on the Modified Card Score Test (MCST); errors and scaled scores on parts A and B of the Trailmaking test; total items recalled and semantic cues received and answered correctly on the Boston Naming Test; hits, false alarms, d prime score (a calculated score from hits and false alarms) and 30-min delayed recognition score for the Continuous Visual Memory Test (CVMT); total words recalled in the fluency categories of fruits, animals, and clothes; scaled score for Block Designs completed; scaled score plus forward and backward scores on the Digit Span; total score, first and fifth trials, short- and long-delayed free recall, short- and long-delayed cued recall, recognition trial, semantic clustering, intrusions and perseverations during the CVLT. Scores standardized for age and sex were available for the Trailmaking tests, CVMT, Block Designs, Digit Span, and CVLT.

2.4. Statistical plan

To reduce the data to component variables representing cognitive domains, the original data were submitted to a principal components analysis to identify test scores that had similar response patterns. These scores could then be combined to make the composite scores for the different domains of interest in this study. Because the sample was drawn from different diagnostic groups, responses were standardized before analyzing based on the mean and standard deviation of each participant's diagnostic group membership. By using individual group membership rather than total sample mean and standard deviation, only within-group variation in response patterns contributed to the derivation of principal components, and the principal

components could be assumed to represent response patterns that occurred across the three groups. This precaution omitted the probability of circular reasoning, that is, creating principal components based on intergroup variability and then testing to determine if the variability was present. A value of .50 was set as the minimum acceptable loading, and Varimax, an orthogonal method, was selected for the rotation of vectors. After factoring, test scores that met our loading criteria were re-standardized based on the mean and standard deviation of the control group, summed, and averaged to make the component scores. The re-standardization made the mean score of the control group zero and allowed the means of the other groups to vary within the principal components to be tested. Component scores then were submitted to a MANCOVA with age and education as covariates and group membership as the between-subjects factor. Follow-up ANCOVAs determined the principal components (or domains) that had significant between-group differences. Pairwise *t* tests then evaluated the group differences. This first phase of the analysis defined the cognitive domains that could become vulnerable during minor depression and the statistical significance of any deficits in performance.

The second phase of the analysis was intended to serve a practical, clinical purpose, and answered the question of what was the smallest set of scores from the current neuropsychological battery that could efficiently separate the groups. Tests from each component were entered into stepwise logistic regressions looking for group differences: controls versus minor depressed patients, controls versus major depressed patients, and major depressed versus minor depressed patients. Tests that entered a regression equation at $\leq$.05 significance level were retained as candidates for the final discriminant analysis to create a parsimonious set of measures that could be evaluated for effectiveness using a kappa statistic. Probability of a Type I error (alpha) was set at .05 for all tests.

3. Results

Demographic variables were examined with chi-square analyses for categorical data and *t* tests for independent samples for interval data (Table 1). Age and education varied between controls and major depressed patients, $t(62) = 3.18$, $P = .002$, and $t(62) = -3.62$, $P = .001$, respectively. On the average, controls were 70 (S.D. 6.4) years old compared to 75 (S.D. 5.6) years for major depressed patients and had 14.6 years (S.D. 2.4) of education compared to 12.2 years (S.D. 3.0) for major depressed patients. Major depressed patients differed from minor depressed patients on education, $t(52) = -2.40$, $P = .02$, but all subgroups did not differ on ethnicity, sex, or right-handedness. Age and education were used as covariates in subsequent analyses.

3.1. Component analysis

Twenty test responses of the original 29 were submitted to the final component analysis with Varimax rotation. Each variable loaded $\geq$.50 on one and only one of five principal components with eigen values >1. The variables also satisfied a criterion of low partial correlations in the anti-image matrix. Cumulatively, the principal components explained 76.7% of the variance in scores (Table 2). As was expected, multiple scores from individual tests tended to load together

Table 1
Principal demographic and clinical characteristics of study groups

	Controls ($N = 38$)	Minor ($N = 28$)	Major ($N = 26$)
Males	11	10	9
Females	27	18	17
Average age	69.6 (6.6)	71.4 (7.7)	74.7 (5.6)*
Years of education	14.6 (2.4)	13.9 (2.3)	12.2 (3.0)**
Hamilton-Depression	N/A	11.9 (2.4)	19.9 (3.7)
Right-handedness	37	27	25
CIRS	2.29 (1.4)	2.75 (2.1)	4.42 (3.7)
Age of onset	N/A	69.5 (1.5)	71.4 (1.1)
MMSE	29.3	28.9	28
Ethnicity			
African American	3	2	4
Latino		1	
Non-Latino white	35	25	22

Standard deviations are in parentheses. CIRS, Cumulative Illness Rating Scale; MMSE, Mini-Mental State Examination.

* $P \leq .05$, difference between controls and major depressed patients only.

** $P \leq .05$, difference between major depressives and both minor depressives and healthy controls.

indicating a specific domain that the test was intended to measure. The components were interpreted and labeled. The Kaiser–Meyer–Olkin Measure of Sampling Adequacy (KMO) assesses the stability of the final solution by the correlation matrix. At .85, the KMO score for this analysis was well above the recommended score of .6.

The stability of the analysis was investigated further with a bootstrap procedure. The computer randomly selected 10 samples of 92 subjects "with replacement," meaning that one case might be selected more than once and another case not selected at all. Ten principal component analyses were run, one on each sample, and matrices of loadings were intercorrelated for a final component analysis to determine which components "matched" across replications. As expected, the second-order factors were each defined by salient loadings on one factor from each replication. The mean loading for each variable across the ten replications was computed as was the standard error (the average deviation across replications). From these values, the mean and standard errors for each component can then be estimated. The desired outcome is to obtain a high average loading per component, which indicates consistency, and a low standard error, which indicates low variability. The mean and standard errors per component are in Table 2, as are explained variances, eigen values, loadings and interpretive labels.

3.1.1. Component 1: Verbal Recall

The verbal learning and recall indices from the CVLT loaded with the verbal fluency measure. Both the CVLT and the verbal fluency, which in this case was based on categorical rather than phonetic fluency, require semantic processes of retrieval and organization. The CVLT word list is amenable to semantic organization and encoding that, when used, increases performance during the initial presentation, the four additional trials, the short-delayed retrieval, and the final 20-min delayed retrieval. Verbal fluency measures the final phase, that is,

Table 2
Principal component analysis with Varimax rotation produced five components with eigen values greater than 1

Components (KMO = .84)	Test	Loadings					Explained variance	Eigen values
		Verbal	Set Maintenance	Executive	Nonverbal	Working Memory		
Component 1 (0.796 ± 0.041)*	CVLT *T* score	**.845**	.125	.165	.022	.108		
	CVLT Trial 1	**.701**	.061	.108	.060	.250		
	CVLT Trial 5	**.877**	.141	.122	.046	.103		
	CVLT short delay	**.909**	.150	.099	.141	.011		
	CVLT Short delay cued	**.878**	.101	.112	.196	.140		
	CVLT long delay	**.889**	.100	.097	.153	.055		
	CVLT Semantic	**.791**	.080	.166	.174	.020		
	Verbal fluency	**.575**	.170	.390	.139	.221	28.782	5.756
Component 2 (0.865 ± .042)*	Modified WCST	.133	**.929**	.060	.022	.080		
	Modified WCST perseverations	−.162	**−.820**	−.256	−.180	.031		
	Modified WCST errors	.090	**−.909**	−.143	−.043	−.024	14.898	2.980
Component 3 (0.671 ± 0.049)*	Block Design	.175	.444	**.535**	.178	.149		
	Trailmaking B	−.265	−.296	**−.703**	−.061	−.214		
	Trailmaking B errors	−.122	−.015	**−.840**	.010	.064		
	Boston Naming	.289	.353	**.531**	.194	.269	11.368	2.274
Component 4 (0.804 ± .049)*	CVMT total	.230	.162	.149	**.916**	.087		
	CVMT d prime	.218	.250	.311	**.635**	.181		
	CVMT false alarms	−.108	.031	.093	**−.877**	.005	11.356	2.271
Component 5 (0.904 ± .030)*	Digit Span	.235	.065	.132	.102	**.914**		
	Digit Span forward	.136	.026	.076	.056	**.935**	10.291	2.058

Total explained variance = 76.695. Bold numbers indicate the maximum loading for each test. Twenty test scores entered the final solution; nine were eliminated for low loadings and/or high partial correlations in the anti-image matrix. KMO, Kaiser–Meyer–Olkin Measure of Sampling Adequacy with a recommended value ≥.60 to ensure factor stability. Reliability estimates of means and standard errors for each component were derived from bootstrapping procedure.

* The means and standard deviations for each component are estimated with a bootstrapping procedure using 10 replications.

the free retrieval from long-term semantic stores. Success on both measures indicates an ability to utilize semantic strategies spontaneously as a mnemonic device (for the CVLT) and as a retrieval device (CVLT and verbal fluency). The use of semantic organization as a strategy has been shown to be reduced among patients with major depression (Channon & Green, 1999). (Component 1 explains 28.7% of score variance.)

3.1.2. Component 2: Maintenance of Set

The Wisconsin Card Sort (WCST) is well-established as a test of mental flexibility, problem-solving, and accommodation to changing environmental feedback. The MCST version of the WCST taps into some of the same abilities, albeit to a less demanding level, because ambiguous cards are omitted and participants are warned when the sorting criterion changes. Therefore, the focus of the modified version is stronger on the intradimensional or maintenance aspects of the task than the extradimensional or problem-solving and flexibility aspects (Roberts, Robbins, & Everitt, 1988). This conclusion was corroborated by evidence of a ceiling effect that limited the variability of the responses, particularly between patients with minor depression and healthy elderly. Forty-four percent of the 92 subjects achieved a perfect score of 6, and 60% achieved a score of either 5 or 6 categories completed. The mean and standard deviation for major depressed patients were 3.3 (1.9), minor depressed patients 5.0 (1.4), and controls 5.0 (1.4). (14.9% variance explained.)

3.1.3. Component 3: Executive

The Boston Naming Test (BNT), a visual confrontational naming task that uses nonverbal stimuli, requires efficient and flexible searches of semantic stores. Functional magnetic resonance imaging has shown strong correlations between performance on the BNT and frontal as well as temporal metabolism (San Pedro, Deutsch, Liu, & Mountz, 2000). This finding suggests that the BNT precipitates an executive search function that utilizes frontal abilities. The Block Design Test uses nonverbal stimuli, but it requires the patient to conceptualize the model as a grid, which can accommodate the designs on the blocks, and then rotate the blocks manually to construct a facsimile of the model. Trailmaking B is a standard executive test that requires patients to keep numbers and letters in mind concurrently while switching between the two. Consequently, this component demonstrates three slightly different abilities, but all have the underlying requirement of using visual stimuli and monitoring one's responses in working memory while planning the next according to some self-selected strategy. The separation of tests between Maintenance of Set (Component 2) and this component was unexpected initially because it appears that the MCST also requires the development of strategy and monitoring of responses. However, during the administration of the MCST the patient is warned when the strategy needs to be changed. Because all ambiguous cards have been removed from the sort, the patient can depend on the aid of the administrator as to the timing and appropriateness of the matching strategy. The tests in the Executive factor rely on internal feedback for assessing the correctness of each move. Consequently, the Executive factor requires a high level of integration of verbal and nonverbal skills with spontaneous adjustment of strategies. Factor #2 appears to be related to intradimensional set, or the ability to exclude inappropriate stimuli, whereas Factor #3 appears dependent on the ability to continually search and make adjustments as each response is made, a more abstract form of executive function. (11.4% variance explained.)

3.1.4. Component 4: Nonverbal Recognition memory

During the CVMT, participants recognize seven complex abstract target designs from seven foils over seven different trials. During delayed recognition, participants identify each target design, which was seen seven times, from the collection of foils. All drawings used in the CVMT are new to participants, so good performance requires the encoding of subtle differences in shapes, "binding" each shape together in memory (Mitchell et al., 2000), and then recognizing each shape after a delay. This ability differs from the use of nonverbal strategy evaluated by the scores in Component 3 because information is encoded and later recognized for the task but is not manipulated or freely recalled. (11.4% variance explained.)

3.1.5. Component 5: Working Memory

Digit Span assesses the quantity of information that can be rehearsed in working memory. The low loadings on other principal components indicate that among depressed patients Digit Span captures the maintenance, or rehearsal, aspect of working memory but not the manipulation aspect. This characterization appears corroborated by the anti-image matrix, which showed relatively high ($\geq$.25) partial correlations between Digit Span forward and CVLT Trial 1 and short-delayed recall but not other CVLT scores. (10.3% variance explained.)

3.2. MANCOVA and follow-up ANCOVAs

Test scores that loaded at or above the loading criterion established for the principal component analysis were reformulated into *z* scores based on the mean and standard deviation of the control group (Cannon et al., 1994), and averaged into five composite variables representing the principal component analysis. Thus, the mean of each of the new component variables equaled zero in the control group, but the means of the depressed groups could vary. The reformulated five component scores were examined in a MANCOVA using group membership as the between-group factor while controlling for age and education. The principal components demonstrated a significant effect for group membership, $F(10, 166) = 3.00$, $P < .002$, indicating a systematic change in test scores with a change in group membership (see Table 3). Adding comorbidity scores from the CIRS as a control variable did not change the results. Additionally, the means of depressed patients fell between those of healthy elderly and MDD patients on four principal components and fell slightly below those of major depressed patients on the fifth component (Executive). Individual ANCOVAs for each component showed that scores varied in their ability to separate diagnostic groups. Verbal Memory performance and Maintenance of Set were highly significant in separating groups ($P = .001$ and $P = .003$, respectively). Executive Functioning was borderline ($P = .06$). Working Memory and Nonverbal Recognition did not significantly separate groups even though men showed a strong relationship between severity of depression and Nonverbal Recognition ability in the correlational analysis. The smaller percentage of men than women in the study may have contributed to the lack of significance in these ANCOVAs on domains that may be salient among male depressed patients.

Pairwise *t* tests with means adjusted for age and education evaluated the differences between the component means of the three groups. Verbal Recall and Maintenance of Set separated

Table 3
MANCOVA and follow-up univariate values

		Pairwise adjusted *t* contrasts*			Univariate tests of factors for group differences		
	Means (S.D.)	Controls versus minors	Controls versus majors	Minors versus majors	*F* value	d.f.	*P* value
Verbal		$t = -1.63$	$t = -3.91$	$t = -2.44$	7.63	4, 87	.001
Controls	.0001 (.85)	$P = .11$	$P = .0002$	$P = .02$			
Minors	−.41 (.75)						
Majors	−1.16 (.95)						
Maintenance of Set		$t = .50$	$t = 3.37$	$t = 2.90$	6.26	4, 87	.003
Controls	−.006 (.37)	$P = .62$	$P = .001$	$P = .005$			
Minors	.10 (.63)						
Majors	.63 (.67)						
Executive		$t = -2.37$	$t = -1.45$	$t = .64$	2.91	4, 87	.06
Controls	−.0001(.41)	$P = .02$	$P = .15$	$P = .52$			
Minors	−.34 (.46)						
Majors	−.31 (.73)						
Nonverbal Recognition		$t = -1.30$	$t = -1.41$	$t = -.25$	1.28	4, 87	.283
Controls	.0001 (.41)	$P = .196$	$P = .16$	$P = .81$			
Minors	−.23 (.46)						
Majors	−.34 (.73)						
Working Memory		$t = -.23$	$t = -1.78$	$t = -1.56$	1.78	4, 87	.175
Controls	.0001 (.95)	$P = .82$	$P = .08$	$P = .12$			
Minors	−.12 (1.02)						
Majors	−.72 (1.08)						
Overall MANCOVA (Wilks' Lambda)*					3.00	10, 166	.002

Pairwise *t* tests with adjusted covariates for controls and each depressed group.

both the healthy elderly and minor depressed patients from major depressed patients (Table 3). Executive skills separated minor depressed patients from controls. Working Memory trended toward separating the healthy elderly from the major depressed ($P = .08$). Nonverbal Recognition did not reach statistical significance on any comparison.

Table 4 provides the means, standard deviations and ranges of scores for men and women in each diagnostic group. Scores were evaluated with *t* tests that controlled for age and education. Most scores did not show a difference between sexes, but control women had higher means on verbal, set maintenance, and working memory components. On the other hand, depressed men had higher working memory scores on average.

3.3. Correlations with severity of depression

Table 5 shows the pattern of correlations between severity of depression and individual principal components, again controlling for age and education. The major depressed women in

Table 4
Means, standard deviations and ranges of scores for components by sex and diagnosis

	Major depressed		Minor depressed		Controls	
	Women	Men	Women	Men	Women	Men
Verbal	−1.17 ± 1.09 −2.66/1.20	−1.13 ± .68 −2.04/.28	−.47 ± .82 −1.97/.92	−.32 ± .64 −1.86/.43	.27 ± .82* −1.95/2.02	−.67 ± .50 −1.39/.18
Set Maintenance	.80 ± .69 −.58/1.87	.33 ± .52 −.58/.90	.28 ± .67* −.68/1.89	−.23 ± .38 −.58/.53	03 ± .37* −.53/.75	−.10 ± .36 −.58/.53
Executive Ability	−.47 ± .74 −1.87/.91	.005 ± .65 −.55/1.56	−.41 ± .42 −1.21/.27	−.23 ± .54 −1.36/.40	−.06 ± .41 −.68/1.31	.15 ± .39 −.42/.85
Nonverbal Recognition	−.37 ± .85 −2.58/.77	−.28 ± .49 −1.10/.40	−.37 ± .65 −1.90/.80	.04 ± .43 −.74/.64	−.03 ± .48 −1.33/.72	.08 ± .43 −.65/.69
Working Memory	−1.09 ± 1.0* −3.01/.54	−.02 ± .88 −.89/1.51	−.15 ± .94 −1.85/1.01	−.08 ± 1.20 −1.60/1.72	.17 ± 1.03* −1.60/2.23	−.41 ± .58 −1.35/.54

* $P \leq .05$, difference between men and women in that diagnostic group. The *t* tests statistically controlled for age and education.

this sample showed a significant relationship between HAM-D and Working Memory and Verbal functioning; depressed men showed a significant association between HAM-D scores and Nonverbal Recognition and Verbal functioning. When men and women were combined, they showed an association between severity of depression and Verbal function and Maintenance of Set, and they trended toward significance in Nonverbal Recognition ($P = .06$). Among only major depressed patients, Nonverbal Recognition was associated with depression severity, an association that appears driven primarily by men. Nonmajor depressed patients—particularly women—showed a strong relationship between performance of the Executive tasks and increasing depressive symptomatology. Examination of the correlations by sex for the individual tests in the Executive component showed that women trended toward an inverse correlation for the Block Design and Trailmaking Parts A and B, but not for the Boston Naming Test ($r = -.301, -.239, -.325$, and $-.138$ respectively). Men's performance, on the other hand, appeared relatively unaffected on the executive tasks by their increasing symptomatology (.302, −.093, .022, and −.071 respectively).

3.4. Identification of specific tests that differentiate diagnostic groups

When it was clear that the groups varied systematically, we used logistic regression to determine which tests were sufficiently sensitive to separate each diagnostic group from *both* the other two groups. For clinical purposes, a test or set of tests sensitive to a specific depression differential diagnosis would be useful, particularly for minor depression. The original standardized test scores, grouped by component, were entered into forward stepwise logistic regressions predicting one of three bivariate outcomes, again controlling for age and education: control versus minor and major depressed, minor depressed versus major depressed and controls, and major depressed versus controls and minor depressed. Major depressed patients

Table 5
Correlations of Hamilton Depression Ratings and cognitive factors

	Hamilton Depression Rating								
	Depressed patients			Major depressed patients			Minor depressed patients		
	All ($N = 54$)	Men ($N = 19$)	Women ($N = 35$)	All ($N = 26$)	Men ($N = 9$)	Women ($N = 17$)	All patients ($N = 28$)	Men ($N = 10$)	Women ($N = 18$)
Verbal	−.338 ($P = .01$)	−.456 ($P = .03$)	−.286 ($P = .05$)	−.215	−.550 ($P = .10$)	−.224	−.149	.195	.155
Maintenance of Set	.259 ($P = .03$)	.386 ($P = .06$)	.239 ($P = .09$)	.010	.032	.060	−.094	−.171	−.040
Executive	.040	.018	.078	.059	−.051	.250	−.334 ($P = .05$)	−.125	−.622 ($P = .005$)
Working Memory	−.156	.179	−.312 ($P = .04$)	−.197	.075	−.179	.195	.351	.246
Nonverbal Recognition	−.218 ($P = .06$)	−.440* ($P = .04$)	−.174	−.380 ($P = .04$)	−.614 ($P = .07$)	−.338	−.109	−.207	−.134

Note. Results are for one-tailed correlations. Only probabilities ≤.10 are reported. Age and education are statistically controlled.

are separated from other groups by verbal fluency ($\chi^2 = 18.25$, $P < .0001$), MCST preservations ($\chi^2 = 16.92$, $P < .0001$), Trailmaking B scaled score ($\chi^2 = 21.00$, $P < .0001$) and Digit Span scaled score ($\chi^2 = 8.28$, $P < .004$). Minor depressed patients are best separated from other groups by the MCST number of categories ($\chi^2 = 3.54$, $P < .06$; $\chi^2 = 12.93$, $P < .0003$). On the third contrast of controls versus other groups, verbal fluency ($\chi^2 = 13.59$, $P < .002$), MCST perseverations ($\chi^2 = 8.23$, $P < .004$), BNT total ($\chi^2 = 7.22$, $P < .007$), Trailmaking B time ($\chi^2 = 6.48$, $P < .01$), Trailmaking B errors ($\chi^2 = 7.10$, $P < .008$), and Digit Span ($\chi^2 = .4.61$, $P < .03$) best separated the groups.

By submitting the above battery of seven variables to a discriminant function analysis, the usefulness of the battery for separating the groups could be estimated. The abbreviated battery in general identified 63% of the healthy elderly, 43% of the minor depressed patients, and 82% of the major depressed patients. Using the criteria for kappa values of <.40 as poor, the range of .40–.70 as acceptable to good, and >.70 as excellent (Fleiss, 1981), the ability to classify patients using these tests was mixed: major depressed (=.53, $P = .0001$), minor depressed (=.18, $P = .08$), and controls (=.63, $P = .0001$). The kappa value for the minor depressed was low indicating that the abbreviated battery was useful only for separating major depressed from healthy controls.

4. Discussion

The hypothesis that domains of cognitive functioning would vary inversely with the severity of depressive disorder was supported by our findings. In this sample of minor and major depressed patients and healthy elderly controls, scores from a neuropsychological test battery produced five components or composite scores that represent five different types of cognitive functioning. On four of the five components, means of minor depressed patients fell intermediate to those of healthy controls and major depressed patients. The three diagnostic groups differed across two of the five components (Verbal and Maintenance of Set), and a third component (Executive) was borderline at $P = .06$. Means of the two groups were not different from each other on the last two components (Working Memory and Nonverbal Recognition). However, the last two components showed significant correlations with the severity of depression suggesting that the severity of depression modulated performance in working memory for women and in Nonverbal Recognition for men.

Our results support the conceptualization of minor and major depression as representing a gradual continuum that is associated with increasing cognitive deficits, but with the degree of difference dependent on the specific domain of cognitive ability. The domains that appear to be compromised first with minor levels of depression involve the use of executive functioning and recall abilities, particularly Verbal Recall. Executive abilities are associated with the functioning of the prefrontal cortex, so our neuropsychological findings are in agreement with the neuroanatomical data reported by Kumar, Zhisong, Bilker, Udupa, and Gottlieb (1998). They found that normalized prefrontal lobe volumes in minor and major depressed patients were significantly smaller than those of control subjects. Prefrontal lobar volumes in the minor depression group lay between the means of the healthy elderly and the major depressed groups.

Of relevance here is a second finding from Kumar et al. (1998) that temporal lobe volumes also tended to show a similar linear reduction in size with increases in depression, although the difference was not statistically significant. The underlying commonality of the cognitive tests on which minor depressed patients had significant deficits compared to controls was the utilization of executive strategies in combination with temporal abilities, whether it was for quickly organizing a list of words for learning and recall, accessing semantically-related information, conceptualizing nonverbal stimuli, or integrating nonverbal cues with semantic stores. Major depression has previously been found to be associated with dysfunction in executive processes and poor use of executive strategies (Channon et al., 1993; Channon & Green, 1999), although we are unaware of a similar deficit being reported for minor depressed patients.

The ability to avoid becoming distracted by irrelevant stimuli, as represented by the Maintenance of Set component, produced differences between major depressed patients and other groups. On the other hand, there was no difference between minor depressed patients and controls. The modified administration removes all ambiguous cards and warns participants when the sorting principle has changed. As a result, a ceiling effect developed that could be seen on the stem-and-leaf plots (not reported). The original Wisconsin Card Sorting Test, which uses ambiguous stimuli, is more difficult than the MCST and might provide sufficient variability to separate minor depressed patients from controls. This speculation is supported by the emergence of MSCT categories as one of the best individual scores for separating minor depressed patients from other groups despite its limited variability. Furthermore, scores on MCST perseverations efficiently separated major depressed patients from other participants. Electrophysiological studies and lesion analyses indicate that orbital prefrontal cortex and the anterior cingulate play a role in modifying behavioral responses when environmental contingencies change (Morgan et al., 1993; Rolls, 1995). Depressed patients demonstrate increased orbital frontal and anterior cingulate glucose metabolism (Baxter et al., 1987; Biver et al., 1994; Cohen et al., 1992; Drevets, 1998; Drevets, Spitznagel, & Raichle, 1995), which correlates positively with increased perseverative behavior (George, Ketter, & Post, 1994). Consequently, the abnormal perseverative behavior suggested by our results might become more salient with the original version of card sort and better represent the depression-related pathophysiological changes in the orbital frontal-anterior cingulate pathway for both minor and major depressed patients.

Test scores on the Verbal Recall and Executive components may be associated with another region of the prefrontal cortex. Previous neuroimaging research has identified the dorsolateral regions of the prefrontal cortex as having a significant role in the executive processing of both verbal and nonverbal information (D'Esposito, Postle, & Rypma, 2000; Petrides, 2000a, 2000b). Among depressed patients, these areas have reduced glucose metabolism (Baxter et al., 1989; Bench et al., 1992; Biver et al., 1994; Mayberg et al., 1997) and suffer structural abnormalities, particularly among late-onset depression (Kumar et al., 1997, 1998; Rogers et al., 1998). Among healthy subjects, blood flow normally increases in this region when subjects perform tasks involving visuospatial memory, pictorial memory for visual objects, maze navigation, speech production, or manipulation of memorized verbal information (George et al., 1994; Ranganath et al., 2000). Excluding maze navigation, these functions are utilized in the Block Design, BNT, verbal fluency, or CVLT, respectively. Drevets (1998) concluded that the biochemical and neuroanatomical deficits of the dorsolateral prefrontal cortex appear to

impair executive functioning, and this impairment manifests in depression of varying severity. Our findings corroborate Drevets' conclusions. Also, the correlations between the cognitive components and the HAM-D suggest that abilities associated with the dorsolateral region, here represented by tests in the Executive component, may be more strongly associated with the onset and severity of subsyndromal depression than those of the orbitofrontal region, represented by the perseverations during the MCST.

Among minor depressed female patients, executive functioning was strongly correlated with severity of depression, but the significance did not hold among major depressed patients. The closeness in age and CIRS scores between the two diagnostic groups indicates that the correlation is unlikely to be the result of cormorbid conditions. A possible explanation lies in the white matter hyperintensities that frequently accompany late-onset depression. The minor depressed patients were experiencing their index episode during the study indicating a relatively recent onset. Although both sexes show a relationship between white matter hyperintensities and depression (Campbell & Coffey, 2001; Carmelli et al., 1999; de Leeuw et al., 2001; Krishnan et al., 1993; Schmidt, Fazikas, Kapeller, Schmidt, & Hartung, 1999; Sivan et al., 2000) and patients with late-onset are more likely than early-onset patients to have white matter hyperintensities, (Figiel et al., 1991) women are more likely than men to have periventricular hyperintensities (de Leeuw et al., 2001). Fibers essential for proper movement and balance course through the periventricular region (Baloh, Yue, Socotch, & Jacobson, 1995; Masdeu et al., 1989), suggesting that tests that require psychomotor response may be slowed disproportionately in women. Correlations for women in the individual tests in the Executive component were largest for the Block Design and Trailmaking, Parts A and B, which require a timed psychomotor response. The Boston Naming Test (on the same component but not timed) did not show a correlation between performance and depressive symptomatology. Furthermore, Maintenance of Set, which is not timed, also did not show a correlation by sex. Consequently, women may exhibit a psychomotor deficit after the late-life onset of depression because they are at a higher risk for the development of periventricular lesions.

Although the effect of medication on one third of the major depressed patients is unknown, it is possible that major depressed patients may have demonstrated slightly improved performance on tasks requiring executive skills because about one third of the major depressed patients were on therapeutic dosages of anti-depressants. Improvement in cognitive functioning after pharmacological interventions is well reported (Dunkin et al., 2000; Kindermann, Kalayam, Brown, Burdick, & Alexopoulos, 2000; Kramer-Ginsberg et al., 1999; Van Den Berg et al., 2000). Executive functioning, specifically, is known to improve with medication that normalizes glucose metabolism in the dorsolateral and ventrolateral prefrontal regions (Brody et al., 2001, 1999; Kennedy et al., 2001). A small number of major depressed patients were taking anxiolytics, which are more likely to impair recall and recognition than are antidepressants (Mintzer & Griffiths, 2000; Settle, 1998). The magnitude of medication effects on cognition in the extant literature have tended to be small, however (Berg & Dellasega, 1996), and any such effects in the current study would likely suppress the overall neuropsychological profile only slightly. Further examination of the scatterplots did not indicate the existence of a small subset of patients with poor performance across the component variables, although medication effects can not be entirely ruled out. The minor depressed patients were drug-free, and most were drug naïve.

5. Conclusion

Our findings indicate that in a combined sample of community residents and inpatients, cognitive functioning is related to severity of depressive illness. Deficits among nonmajor depressed patients appear prominently in executive functioning although they also trended toward a significant deficit in verbal learning and recall. Major depressed patients show pronounced deficits in verbal resources and maintenance of a response set. Slightly less salient is deterioration in the patient's ability to mobilize the resources of the working memory to accomplish integrated verbal and nonverbal tasks. Consequently, the presentation of depression by elderly may be heterogeneous in terms of symptoms, course, social context, medical comorbidity and cognition. The degree of cognitive loss for both major and minor depressed patients appears sufficient to contribute to the impaired daily functioning that has been observed among depressed elderly patients by other researchers (Rapaport & Judd, 1998). However, the Epidemiological Catchment Area Study of diagnosis and treatment of depression in late-life reports that the rate of treatment for depression drops sharply among elderly adults (Reynolds, 1993). Given the progression of approximately 25% of minor depressed patients to a major depression episode (Kessler, Zhao, Blazer, & Swartz, 1997; Sherbourne et al., 1994) and the degree of cognitive dysfunction, further studies are warranted among broader samples of patients in other community and institutionalized settings.

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