

Executive dysfunction and memory in older patients with major and minor depression

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Abstract

Executive function, known to be impaired during late-life depression, is dependent on frontostriatal pathways. Memory is also frequently observed to be impaired among late-life depressed patients, so we assessed the possibility that executive function mediates the learning and recall deficit as a “downstream” effect of the frontostriatal compromise in executive function. A cross-sectional sample of minor and major depressed patients ($N=95$) and nondepressed volunteers ($N=71$), screened for other Axis I disorders, dementia, medical comorbidity, and severity of depression, completed a neuropsychological battery that included the California Verbal Learning Test and other tests selected for convergent and divergent validity testing. Depressed patients differed from controls on learning the word list and on verbal and nonverbal executive tasks. Executive function was a mediator for depressed patients verbal learning scores ($z=-2.67, p=.01$). A nonverbal executive score also mediated verbal learning ($z=-2.18, p=.03$) indicating convergent validity of executive dysfunction during verbal learning exercises. In conclusion, the verbal memory deficits typically attributed to late-life depression may result from impaired executive functioning during the learning phase of the recall task.

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Late-life depression is associated with cognitive deficits, but there is some debate over the profile and significance of the deficits. Performance in episodic memory, verbal fluency, information processing, executive function, and visuospatial ability has been reported as lower among depressed patients compared to healthy volunteers. After treatment, some of the deficits are resolved, but the level of performance on executive and memory tasks often does not reach the premorbid level suggesting that the depression and the residual cognitive deficits are both expressions of an underlying, and related, brain dysfunction. A current model of depression posits that the frontostriatal neural pathways are compromised during depressive episodes. Executive functions are heavily dependent on the frontostriatal circuitry and may serve as an indicator of the degree of frontostriatal compromise. The level of executive dysfunction at baseline has been shown to predict outcomes in terms of increased vulnerability to relapse and resistance to treatment.

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Patients with minor depression show functional and cognitive deficits similar to those demonstrated by patients with major depression. Minor and major depressed patients differ from controls on an executive composite score that includes visuospatial construction, complex attention, and visual naming, but they are not as impaired as major depressed patients on a verbal learning and recall composite score. In turn, the verbal recall scores across both major and minor patients correlated negatively with depression severity as measured by the Hamilton Depression Scale but positively with a composite scale of executive function using scores from the Wisconsin Card Sorting Test. If executive function is conceived as the primary deficit, it may modulate the decreased performance in verbal recall across both minor and major depressed patients. This hypothesis is based on the assumption that executive functions are “domain general” functions that operate on inputs from all other cognitive realms, including memory, language and perception, or heteromodally processed material.

Some studies have suggested a link between the cognitive changes during late-life depression and continuing cognitive decline, but the risk of irreversible decline is higher for patients with late-onset or with cognitive impairment at baseline. A recent study of six patients with late-life depression who came to autopsy showed that 70% of the patients had a clinical diagnosis of dementia ante mortem and that their brains had neuropathology consistent with dementia, primarily of the Alzheimer’s type. This study is still in its preliminary stages, but it does suggest that the rates of pathology may be high among depressed patients with severe memory loss. However, the possibility that the depressed patients with life-threatening neuropathology were the first to come to autopsy must be kept in mind until a larger sample of patients with and without ante mortem dementia can be examined. Furthermore, among depressed patients, continued memory decline is associated with baseline hippocampal volume but not with depression status or hypercortisolemia levels, a physiological marker of depression severity. Those with smaller hippocampal volume were also less likely to achieve remission. Even among healthy elderly, those with smaller hippocampal volume are more likely to progress to dementia. A report from our laboratory that screened elderly depressed patients for evidence of global cognitive loss at baseline showed expected temporal lobe volume but decreased volume in anterior cingulate, gyrus rectus, and orbitofrontal gray matter among depressed patients, suggesting that depression has disease-specific changes that differ from other late-life degenerative processes. Consequently, the memory impairment of some depressed patients includes the loss associated with the neurodegenerative pathology in the medial temporal lobes, but for others the recall deficit may be associated only with an underlying frontostriatal dysfunction that manifests via the mechanism of executive dysfunction. This latter possibility represents a mediated model in which the level of executive dysfunction would explain the variation in learning among depressed patients.

The current study examined the verbal performance of elderly minor and major depressed patients on a verbal recall task that included quantifiable tasks of learning, executive function, and short- and long-delayed recall. We hypothesized that the cognitive deficit would occur in the initial or learning stages of a task when executive support would be critical for the successful organization of the material for encoding. This model posits a mediated pathway to recall performance via executive function. The deficit would not occur in long-term recall if initial learning was accounted for, and there would be no significant degeneration between immediate recall and long-delayed recall indicative of an underlying neuropathology.

1. Method

1.1. Subjects

Volunteers (major depressed ($N=63$), minor depressed ($N=32$), and healthy comparison subjects ($N=71$)) were living independently and responded to local advertisements in print or radio media in southern California. Minor depression was defined operationally as the presence of low mood and/or loss of interest in activities and at least one additional depressive symptom from the DSM-IV checklist. Duration of illness of 1 month or more was also required to focus on patients in whom the minor depression was sustained for a period of time and did not merely represent transient dysphoria. A Hamilton Rating Scale for Depression score (HDRS) in the 8–16 range on the 17-item HDRS was required. Patients with major depression had to meet DSM-IV criteria for the disorder and have a 17-item HDRS score of 15 or greater. Diagnosis of patients who scored 15 or 16 on the HDRS was decided clinically by a geriatric psychiatrist. Some patients reported previous depressive episodes (major depression $N=30$, minor depressed $N=18$) but for others, the index episode was their first episode (major depressed $N=22$, minor depressed $N=11$). Some patients were not sure whether previous episodes of sadness represented clinical depression. After

complete description of the study, which was in compliance with the Helsinki Declaration, written informed consent was obtained.

Inclusion criteria for all volunteers included age ≥ 60 years and English proficiency. Exclusion criteria included: (1) history of substance abuse or other Axis I disorder per the Structured Clinical Interview for Diagnosis of Axis I Disorders (SCID); (2) clinical evidence of dementia or Mini Mental State Examination ≤ 24 ; (3) neurological disease such as Parkinson's disease; (4) high cardiovascular risk or history of transient ischemic attack; (5) history of head trauma or loss of consciousness; (6) a current or unstable medical illness; (7) chronic disease such as syphilis that could affect cognitive function; or (8) history or evidence of psychotic symptoms or concurrent psychiatric disorder. Stable chronic conditions such as diabetes mellitus, hypertension or past history of cancer were not exclusionary. Depressed volunteers were drug-free for antipsychotics, anxiolytics, and antidepressant medications for at least 2 weeks prior to inclusion in the study, but many were drug naïve. Two volunteers were dropped from the analyses due to poor English skill or severe hearing impairment. Four additional volunteers deemed likely to have mild cognitive impairment (MCI) were dropped from analysis. Currently, there are no standards for identifying MCI among depressed patients, so criteria were set at 2 standard deviations (S.D.) below the CVLT norm for their age and sex and 1.5 S.D. below the mean of their diagnostic group. Consequently, potentially impaired scores were not included in the analysis.

1.2. Measures and procedures

Participants were screened with the SCID to eliminate volunteers with other Axis I disorders. During the course of a neurological and psychiatric examination, a board certified geriatric psychiatrist administered the MMSE, HDRS, Stroke Risk Factor Assessment (CVRF), and the Cumulative Illness Rating Scale (CIRS). The CVRF quantifies the vascular risk for future stroke according to the American Heart Association guidelines. The CIRS, a commonly used measure of medical comorbidity, quantifies the medical burden of geriatric patients on the six primary organ systems (gastrointestinal, musculoskeletal, genitourinary, neurologic, cerebrorespiratory, and general). Following the neurological evaluation, patients completed an EKG, a standard battery of laboratory tests and neuropsychological assessment.

The cognitive battery utilized the standardized version of the California Verbal Learning Test (CVLT) for learning and recall, and the Wisconsin Card Sorting Test (WCST), Letter–Number Sequences from the WAIS-III and Stroop, Part 1 for validity analyses. During the CVLT, the participant is asked to remember an auditorily presented list of 16 words from 4 semantic categories that are presented over 5 trials (List A). After an interference test (List B), a short-delayed free recall of List A is administered followed by a cued recall of List A in which volunteers are asked for words that belong to the four semantic categories represented by the list words. After 20 min of diversionary tasks, a long-delayed free recall of List A is administered, followed by a long-delayed cued recall and recognition test of List A words. According to the CVLT manual, the strategies of organization used for learning and recalling the words are serial clustering (maintenance of words in working memory in the order presented) and semantic clustering (organizing the words according to semantic categories), both of which can be quantified. Spontaneous semantic organization of the words is considered an executive strategy because it requires reorganizing the words by abstract categories for efficient recall, but serial clustering suggests a deficit in executive processing and a subsequent reliance on working memory (Delis et al., 2000). The administration of List A and List B were considered the learning variables with spontaneous learning represented by trial 1 and cumulative learning represented by trial 5 and trials 1–5. List B is also spontaneous learning, but it has the additional burden of suppressing prospective interference from List A. The short- and long-delayed recall scores and the recognition score represented memory functioning. Convergent and divergent validity of the mediation effect was assessed with the WCST (a widely-used test of executive function), Letter–Number Sequences (working memory-manipulation), Stroop, Part 1 (information processing speed), and serial clustering (working memory-maintenance).

1.3. Data analysis

Sample demographic descriptive characteristics were examined with one-way three-group ANOVAs for continuous variables and χ^2 for nominal variables. Age and education have well-established effects on different types of cognitive function, so a priori they were to be included in all tests as covariates. To determine if diagnostic groups differed on the CVLT scores, three-group MANCOVAs were computed across the three types of scores: learning, recall, and

Table 1
Demographic and clinical characteristics of healthy comparison subjects and depressed patients

	Controls (<i>N</i> = 71)	Elderly depressed patients		Model		
		Minor depressed (<i>N</i> = 32)	Major depressed (<i>N</i> = 63)	<i>p</i> -Value	d.f.	Statistic
<i>N</i> (%)						
Male/female	29/42 (41/59)	16/16 (50/50)	16/47 (25/75)	.04	2	$\chi^2 = 6.42$
Caucasian	59 (83)	25 (78)	52 (83)	.91	8	$\chi^2 = 3.33$
Handedness—right	61 (86)	28 (88)	59 (94)	.64	4	$\chi^2 = 2.53$
Mean (S.D.)						
Education (years)	14.9 (2.7)	14.3 (2.7)	15.2 (2.7)	.33	2163	<i>F</i> = 1.23
Age (years)	71.5 (7.6)	71.6 (7.9)	69.2 (7.8)	.18	2163	<i>F</i> = 1.73
Mini Mental State Examination	29.4 (1.1)	29.2 (1.2)	28.9 (1.4)*	.04	2163	<i>F</i> = 3.24
Cumulative Illness Rating Scale	2.4 (1.7)	3.0 (1.9)	3.1 (1.8)	>.05	2153	<i>F</i> = 2.99
Hamilton Depression Rating		10.8 (2.0)	17.4 (4.4)	n.a.		
Stroke Risk Assessment	10.7 (5.0)	10.4 (3.7)	10.6 (4.8)	.97	2119	<i>F</i> = .03
Age of onset of mood disorder		44.1 (25.5)	51.7 (22.1)	.08	76	<i>F</i> = 1.39

* *p* ≤ .05 compared to control group.

organizational strategies. Significant overall results were followed by *t*-tests of pairwise contrasts to determine if minor and/or major depressed patients differed from the comparison group. Effects of late- or early-onset of depression on performance among patients with minor and major depression were evaluated with MANCOVAs: depression group × onset × cognitive function for learning, recall, or organizational strategies.

The mediating effect of executive function on the association between depression and the learning variables was then examined, per our hypothesis. Mediation occurs when a relationship between an independent and dependent variable can be explained in terms of an indirect effect of a third intervening variable, so the third variable is considered the direct cause of the change in the DV rather than the IV. In this case, we were hypothesizing that the relationship between depression and verbal learning was mediated by executive ability as quantified by semantic clustering. To determine if semantic clustering represents simply the optimal strategy for learning unstructured word lists or if it represents a critical and more generalized ability of executive functioning, an unrelated executive function score (Wisconsin Card Sort categories) would be tested for mediation. Tests that assess working memory and information processing speed would also be tested as mediators to establish divergent validity. Testing mediation requires that: (1) the independent variable (depression diagnosis) correlates with the dependent variable (e.g., trial 1), (2) the independent variable correlates with the mediating variable (e.g., semantic clustering), and (3) the mediator remains correlated with the dependent variable when the independent variable (depression diagnosis) is included in the regression equation, but the direct path from the independent variable to the dependent variable is meaningfully attenuated or even eliminated. Thus, the test for mediation calculates whether the indirect effect of the IV on the DV via the mediator is significantly different from zero. We report the multiplicative Goodman test because it is an unbiased test of the mediation effect.

2. Results

The three groups did not differ on age, education, CIRS categories, CVRF scores, handedness, or ethnicity (Table 1), but age and education were decided a priori to be included as covariates in the ANCOVAs. MMSE scores differed with major depressed differing from controls but not minor depressed patients. The distribution of sex across groups differed with a greater percentage of women in the major depressed group than in the control or minor depressed groups.

As can be seen in Table 2, major and minor patients differed from controls on trial 1 of List A and on List B, and major depressed patients differed from controls on the total of trials 1–5. The recall and recognition MANCOVA was nonsignificant for depression diagnosis. The two tests of organizational strategies varied across groups with both major and minor depressed patients differing from the comparison group on semantic clustering and serial clustering. The means for major and minor depressed patients showed that both strategies were used less effectively among the depressed patients.

Major and minor depressed patients were also compared for differences related to their age of onset of first depressive episode. Early-onset was defined as a minor or major depressive episode prior to age 60. Factorial MANCOVAs

Table 2
Means, standard deviations, and association of diagnostic group with the CVLT after controlling for age, gender, and education

Scale	Unadjusted means (S.D.)			ANCOVA		
	Comparison (N=71)	Depressed		Effect of depression diagnosis		
		Minor (N=32)	Major (N=63)	p	F	d.f.
Learning				<.000	3.71	8,316
Trial 1 immediate recall	5.9 (1.8)	5.1 (2.1)*	5.4 (1.7)*	.02	3.92	2,160
Trial 5 immediate	10.9 (2.6)	10.1 (2.4)	10.6 (2.4)	.26	1.37	2,160
Trials 1–5 cumulative score	44.5 (9.5)	42.3 (10.3)	42.7 (9.2)*	.10	2.37	2,160
List B immediate recall	6.0 (1.9)	4.6 (1.8)***	5.0 (1.8)***	.00	10.85	2,160
Recall and recognition				.61	.75	6,318
Short-delayed free recall	8.6 (3.3)	8.0 (3.4)	8.1 (3.3)			
Short-delayed cued recall	9.7 (2.9)	9.6 (2.7)	9.8 (3.0)			
Long-delayed free recall	8.9 (3.1)	8.3 (3.3)	8.8 (3.1)			
Long-delayed cued recall	9.7 (2.9)	9.5 (3.0)	9.6 (2.9)			
Recognition hits	13.6 (2.2)	13.9 (2.2)	13.6 (2.1)			
Strategies				.000	5.21	4,320
Semantic clustering	1.7 (.9)	1.1 (1.2)**	1.4 (1.1)*	.01	4.79	2,160
Serial cluster	2.2 (1.6)	1.5 (1.6)*	1.4 (1.4)**	.01	4.80	2,160
Validity tests						
Wisconsin Card Sorting Test	4.6 (1.9)	3.6 (2.0)*	4.0 (1.9)	.06	2.81	2,163
Letter–Number Sequences	10.0 (2.8)	9.8 (2.0)	9.0 (2.4)*	.11	2.25	2,163
Stroop, Part 1	68.0 (12.3)	73.1 (13.2)	70.1 (13.3)	.17	1.77	2,163

The learning, recall, and strategy variables were analyzed with multivariate ANCOVAs with post hoc *t*-tests for subgroup differences. The validity measures were analyzed with univariate ANCOVAs because they represent different domains. Significant differences between the comparison group and a depressed subgroup are indicated by * ≤ .05, ** ≤ .01, and *** ≤ .001.

(diagnosis × onset group) were computed for the CVLT learning, recall and organization variables while controlling for age, education, and sex. There were no main effects of onset age and no onset × diagnosis interactions (see Table 3). The minor and major depressed groups were then combined for the test of mediation.

2.1. Mediating effect of semantic clustering

The four learning variables (trial 1, trial 5, trials 1–5, and List B) were examined using multiple regressions to determine which ones met Baron and Kenney’s (1986) criteria for possible mediation. First, depression diagnosis was examined as a predictor of performance on each of the four learning variables (path c as shown in Fig. 1), and all *p*-values were ≤ .05. Second, semantic and serial clustering and the three validity measures were regressed individually

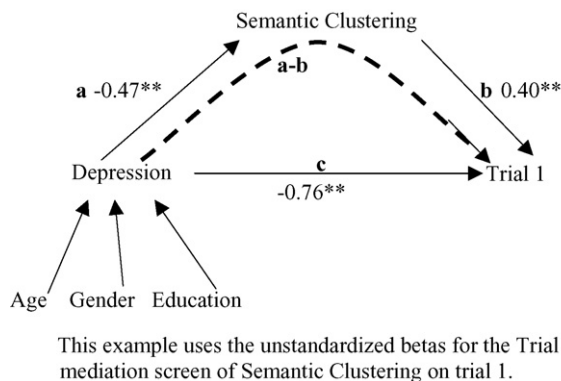


Fig. 1. Paths a, b, and c are initially tested for significance. If all paths are significant, path ab, the mediation path, is tested.

Table 3
Means of minor and major depressed patients with a prior major depressive episode or without a prior major depressive episode

CVLT tasks	Minor depressed (<i>N</i> = 29)		Major depressed (<i>N</i> = 52)		Model					
	No prior episode (<i>N</i> = 11)	Prior episode (<i>N</i> = 18)	No prior episode (<i>N</i> = 22)	Prior episode (<i>N</i> = 30)	Group		Onset		Interaction	
					<i>p</i>	<i>F</i>	<i>p</i>	<i>F</i>	<i>p</i>	<i>F</i>
Trial 1	4.6 (1.9)	5.3 (2.4)	5.0 (1.8)	5.8 (1.6)						
Trial 5	9.8 (2.2)	10.6 (2.7)	10.0 (2.3)	10.9 (2.2)						
Trials 1–5	40.8 (7.3)	44.3 (11.9)	39.4 (8.6)	45.2 (8.1)						
List B	4.3 (1.3)	5.1 (2.0)	4.6 (1.7)	5.6 (1.9)	.39	1.03	.72	.45	.79	.35
Short-delayed free recall	7.5 (3.0)	8.4 (3.8)	7.2 (2.8)	8.8 (3.3)						
Long-delayed free recall	8.0 (3.3)	8.8 (3.5)	7.9 (2.7)	9.1 (3.2)						
Recognition	14.0 (1.9)	13.8 (2.4)	13.2 (2.4)	14.0 (1.7)	.93	.75	.86	.15	.87	.14
Semantic cluster	1.1 (.8)	1.2 (1.4)	1.2 (.8)	1.5 (.8)						
Serial cluster	1.7 (1.8)	1.7 (1.4)	1.8 (1.7)	1.4 (1.3)	.42	.67	.21	1.59	.67	.18
Age	75.0 (8.5)	69.2 (7.4)	72.5 (9.1)	68.0 (6.7)	.32	1.02	.01	7.76	.72	.13
Education	13.3 (2.6)	14.6 (2.5)	15.0 (2.5)	14.9 (2.7)	.10	2.92	.36	.84	.25	1.33
MMSE	28.8 (1.1)	29.4 (1.2)	28.9 (1.3)	28.7 (1.6)	.10	2.84	.90	.02	.22	1.55
Stroop, Part 1	77.2 (13.1)	71.4 (13.6)	70.3 (8.8)	70.7 (15.9)	.03	5.03	.30	1.10	.92	.01
Letter–Number Sequences	9.7 (2.5)	9.9 (2.0)	9.2 (2.7)	9.0 (2.5)	.57	.32	.93	.01	.35	.88
WCST categories	2.6 (1.7)	4.2 (2.0)	3.7 (2.1)	4.0 (1.8)	.60	.29	.26	1.27	.20	1.69

81/95 patients provided whether or not they had a previous depressive episode. There were no differences between the diagnostic groups relative to the age of onset except for age, which was expected, and there were no interactions.

onto depression diagnosis and the covariates to determine if depression diagnosis was significantly correlated with the proposed mediators (path a). Stroop, Part 1, did not correlate with depression diagnosis and was dropped from further analysis. Depression diagnosis correlated with semantic clustering ($B = -.47$, $S.E. = .17$, $p = .004$), serial clustering ($B = -.75$, $S.E. = .24$, $p = .002$), Letter–Number Sequences ($B = -.774$, $S.E. = .39$, $p = .05$), and WCST ($B = -.819$, $S.E. = .27$, $p = .003$). Next, the CVLT variables (i.e., the proposed DVs) were regressed on the individual mediators plus the covariates to examine path b. Semantic clustering was significantly correlated with all learning variables, but serial clustering was related only to List B, so it was dropped from further analysis. The WCST and Letter–Number Sequences were related to all dependent variables except trial 1. Thus, the screens for paths a, b, and c showed that semantic clustering met all screens, and WCST and Letter–Number Sequences met criteria for three of the four learning variables (trial 5, trials 1–5, and List B).

Last, path ab was tested for mediation using only mediators that passed all screens for that particular dependent variable. When the a–b pathway between depression and trial 1 that goes through semantic clustering was tested, it was found to be significantly different from zero (Table 4). Semantic clustering also mediated the effect of depression on recall during trials 5 and 1–5 but not during List B recall. WCST mediated the effect of depression during trial 5, but not during trial 1, trials 1–5, or List B. Letter–Number Sequences did not mediate any pathways below $\alpha = .05$.

Table 4
Tests for mediation to determine which CVLT learning variables are mediated by one or more of the proposed mediators representing executive function, working memory, and information processing speed

	Tests for mediation		
	Semantic clustering	WCST	Letter–Number Sequence
Trial 1	$z = -2.03$, $p = .04$		
Trial 5	$z = -2.67$, $p = .01$	$z = -2.18$, $p = .03$	$z = -1.69$, $p = .09$
Trials 1–5	$z = -2.63$, $p = .01$	$z = -1.69$, $p = .09$	$z = -1.71$, $p = .09$
List B	$z = -1.63$, $p = .10$	$z = -1.84$, $p = .07$	$z = -1.68$, $p = .09$

2.2. Early- and late-onset patients

Early- and late-onset patients were separated for a post hoc analysis. Although the reduced power was problematic, the trends would indicate if one or both groups were responsible for the mediation effect. Depression diagnosis was associated with the mediators of semantic clustering and WCST for patients with both early-onset ($B = -.46$, $S.E. = .18$, $p = .01$, and $B = -.79$, $S.E. = .33$, $S.E. = .02$, respectively) and late-onset ($B = -.52$, $S.E. = .18$, $p = .004$, and $B = -1.00$, $S.E. = .38$, $p = .01$, respectively) (i.e., path a). Semantic clustering was associated with trials 1, 5, and 1–5 for both early- and late-onset patients (all p -values $< .05$), and WCST was associated with trial 5 for both early- and late-onset patients ($B = .34$, $S.E. = .26$, $p = .004$, and $B = .42$, $S.E. = .12$, $p = .001$, respectively) (i.e., path b). In the analysis for mediation of path c, semantic clustering trended toward a mediation effect among early-onset patients' scores for trial 1 ($z = -1.69$, $p = .09$). Late-onset patients showed a mediation effect in trial 5 for both semantic clustering ($z = 2.10$, $p = .04$) and WCST ($z = -1.50$, $p = .01$) indicating that the mediation results occurred most strongly among late-onset patients.

3. Discussion

Data from this study indicate that the difference between late-life depressed patients and controls on trial 5 of the CVLT is secondary to executive dysfunction. Semantic clustering, an executive strategy for learning a list of words, was tested as the mediator, but another task that was unrelated to list-learning also mediated performance on trial 5. The convergent validity of the two executive tasks as successful mediators provides evidence that executive resources in general are compromised during depression rather than just poor selection of verbal strategy, and that the compromise then disturbs verbal recall. Semantic clustering also mediated trial 1 and the cumulative score from trials 1–5 while the WCST approached significance for trials 1–5. When the depressed sample was subdivided into early- and late-onset patients for post hoc analyses, both semantic clustering and the WCST significantly mediated trial 5 among late-onset patients despite the lowered power from the small subgroups. It was not surprising that trial 5 was the strongest indicator of the mediated pathway as it represents the fifth attempt by the subject to learn the words. It seems logical that an underlying executive dysfunction would become most salient by the final trial 5 rather than the initial trial 1.

Divergent validity for our hypothesis was provided by the finding that working memory and processing speed tasks did not mediate learning. Two working memory tasks were tested as mediators, one that utilized maintenance and one manipulation, and neither was productive. The manipulation test, particularly, was intended to clarify whether depressed patients are not responding as well as controls due to a motivational or personality factor difference that would show up on an effortful task. Earlier research reported that depressed patients scored lower than controls on a test of sustained effort with information processing, although they scored comparable to controls on a less effortful procedure. Our results suggest that it is not effortful processing per se that compromises the performance of depressed patients. It appears to be a general deficit in their frontal–striatal neural networks. The domain of executive functioning is not clearly defined as it incorporates many diverse functions of strategy selection, organization, sequencing, evaluating, or inhibiting, yet they all are dependent on the rich neural networks that bidirectionally connect the frontal and subcortical nuclei.

The strength of the executive mediating effect on trial 5 may have its basis in the different memory systems that are activated by the CVLT. Episodic memory, such as retaining material after an initial presentation, has been attributed to the medial temporal memory system. A second system, the frontostriatal system, is associated with probability learning, procedural memory, and memories modulated by environmental feedback. This second system is thought to be strongly associated with the frontal executive processes rather than the limbic process of the temporal cingulate region, although there may be some indirect communication between the systems in the frontal cortex. The protocol for the CVLT, i.e., presenting the list five times, is similar to a feedback situation in which learning has been traced to the same subcortical centers that are activated during procedural learning. Categorical learning, which may be represented by semantic organization of the list words, has also been traced to subcortical centers. An unexpected finding was the strong difference between the depressed patients and controls on the recall of List B, yet none of the tests in this analysis successfully mediated those scores. The results suggest that a measure that specifically addresses interference effects rather than executive ability or working memory may be needed to understand the source of the difference.

One additional point on the procedural aspect of the CVLT is that it provides a cued recall trial in which the four semantic categories are provided to the patient. According to research from amnesic and Alzheimer's patients,

cueing helps patients with subcortically mediated amnesia consolidate information but it does not help Alzheimer's patients with extrahippocampal (cortical) or hippocampal damage. Thus, if a recall deficit is subcortically mediated, scores should improve slightly after being given the semantic categories. As was shown by the unadjusted means table, depressed patients had a slight but nonsignificant disadvantage on short-delayed free recall, but they improved their mean scores after receiving the semantic cues so that their long-delayed scores were essentially the same as the nondepressed controls for both recall and recognition.

The findings are consistent with an earlier report from our research team in which we reported that patients' and controls' recall of a complex geometric design, the Rey Osterrieth Complex Figure, was a consequence of mediation by executive organization. Executive function, quantified as the degree of systematic organization used in the initial copy of the design, accounted for patients' scores on the recall of the figure. There were no differences between groups in recognition of the figure, indicating that depressed patients encoded the figure as well as controls. However, patients were unable to reconstruct the figure as well as controls after the 3-min delay and their mean score on organization during the copy phase was below that of controls.

Butters and coworkers reported that among late-life depressed patients, information processing mediated deficits in multiple domains. Information processing was operationalized with timed tests that depended on speed of motor responding. They concluded that widespread neural connectivity between geographically diverse areas might be responsible for the cognitive deficits. Our research supports their conclusion but indicates that it may be executive resources rather than slowed motor responding that are compromised during depression. This sample of subjects was carefully screened to preclude possible confounding effects from incipient neuropathological disorders (MMSE scores average 29 for both groups) as well as serious comorbid conditions. The present study used categorization of words by semantic relatedness, which is known to increase recall. The earlier nonverbal study from our laboratory used the recognition of the *gestalt* of the design and its internal components as the executive measure. Thus, both of these tasks, the verbal and nonverbal, used executive measures that were not dependent on speed of information processing but efficient activation of related stored information and analysis.

A limitation of this study is the use of cross-sectional data. The mediation hypothesis posits a specific causal sequence. Even if the independent variable (i.e., depression) and the mediator (executive function) are measured at the same time, the mediation effects are presumed to be caused by the independent variable and therefore assumed to manifest themselves as a result of changes or differences in the independent variable. Thus, the current findings must be considered theoretical and consistent with current thinking of a frontostriatal etiology of depression, but they are inconclusive in terms of a causal chain that requires longitudinal evaluation. We started this analysis with a conceptual model that resulted from examining the plausibility of various models. We found the biological plausibility of the current model, i.e., depression leading to executive impairment and then indirectly to memory impairment, to be the most plausible and parsimonious based on current biological understanding of depression. Current MRS and DTI reports suggest that subtle biochemical and structural changes may be occurring early in depressed patients, and these changes may lead to minor or subclinical mood changes before cognition is sufficiently impaired that it becomes manifest. However, the possibility of a reverse causal chain, for example, cerebrovascular disease leading to memory impairment, which increases dysphoria remains possible but may be more appropriate for depressed patients with high cerebrovascular risk factors or increased white matter hyperintensity burden.

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