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Vascular Burden and Cognitive Functioning in Depressed Older Adults

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Abstract

Background—Vascular burden is known to contribute to geriatric depression and cognitive impairment. The objective of our study was to evaluate the relationship between vascular burden and pattern of cognitive impairment in older adults with depression.

Methods—Ninety-four community-dwelling older adults (mean age = 70.8 years; SD = 7.63) diagnosed with major depression were recruited to participate in the tai chi complementary use study aimed to improve antidepressant response to an antidepressant medication. All participants received comprehensive evaluations of depression, apathy, and vascular risk factors, and completed a battery of cognitive measures of memory, cognitive control, verbal fluency, and attention.

Results—The severity of vascular burden was significantly correlated with depression severity and impaired performance on measures of cognitive control (i.e., inhibition/mental flexibility), and attention, but not memory or verbal fluency. Neither the severity of comorbid apathy nor medical illness burden was related to cognitive impairment.

Conclusions—Vascular burden in older depressed adults contributes to cognitive impairment, particularly in domains of attention and cognitive control. Our findings suggest that aggressive treatment of vascular risk factors may reduce risk for further cognitive decline in depressed older adults.

Keywords

Cerebrovascular risk factors; cognitive impairment; geriatric depression; vascular disease

Depression among older adults is a major public health concern. Approximately, 11% of community-dwelling older adults¹⁻³ and 30% of older adults with dementia^{4,5} report clinically significant symptoms of depression. A large proportion of older adult patients treated for depression have multiple medical comorbidities and cognitive impairment. Among health conditions, cardiovascular risk factors, such as hypertension, hyperlipidemia, or obesity, have been associated with poorer neuropsychological performance, cognitive impairment, and vascular depression.⁶⁻⁸ Comorbid depression and cognitive impairment lead to a host of negative outcomes including higher rates of disability and mortality.^{9,10} Because cognitive impairment remains even after depression remits,⁸ elucidation of factors

that may place older adults with depression at risk for cognitive impairment is needed to improve understanding of the pathogenesis of depression and inform treatment.

The co-occurrence of depression with executive dysfunction, termed the “depression-executive dysfunction” syndrome,¹¹ occurs in a subset of older adults with depression and is characterized by psychomotor retardation, lack of interest, depression, and disability.¹² Depression and executive dysfunction may be linked through disruption to the frontostriatal pathway as the result of small-vessel cerebrovascular disease in both subcortical structures involved in mood regulation and the white matter pathways that connect these structures to the frontal lobes. Vascular risk factors can lead to cerebrovascular disease through several mechanisms including atherosclerosis, endothelial dysfunction, oxidative stress, cerebral hemorrhages, and infarcts.¹³ The relationship between depression, cognition, and brain pathology has been demonstrated repeatedly in the vascular depression model and in post-stroke depression and dementia.¹⁴⁻¹⁶ Neuroimaging studies also report neuroanatomical differences in older adults with vascular depression compared with older adults who are nondepressed particularly in frontal regions, and the amount of neurologic compromise is associated with cognitive impairment.¹⁷⁻²⁰

Patients with depression-executive dysfunction syndrome demonstrate deficits on tests of executive function that assess inhibition, mental flexibility, verbal fluency, planning, and initiation and perseveration.^{6,11,21,22,23} However, degree of executive impairment may depend on several factors including one’s age, depression severity, number of cerebrovascular risk factors (CVRFs), and age of depression onset.^{14,24} Older adults with executive functioning deficits have higher rates of disability and poorer response to antidepressant treatment,^{15,23,25} and are in need of early detection, prevention, and treatment of contributing risk factors.²⁶ The domain of executive functions encompasses diverse components (e.g., generation, cognitive control, planning, and reasoning) that involve distinctly different cognitive skills.²⁷ Because it remains unclear which executive function component may be most affected by vascular burden in depressed older adults, we address this question in our report.

Given the etiologic heterogeneity of late-life depression, many factors contribute to cognitive impairment in depressed older adults, and findings are mixed as to whether general medical burden may predict cognitive impairment equally well as examination of vascular burden.^{8,23} Age is a widely accepted risk factor for vascular disease¹³ especially in the context of late onset depression.²⁴ However, clarification of the impact of CVRFs versus general medical burden on cognitive impairment in depressed older adults is needed to target specific risk factors for treatment.

The relationship between CVRFs and other neuropsychiatric symptoms, specifically apathy, is less well-studied. Like depression, apathy is associated with mortality, functional disability, and dementia onset.²⁸⁻³⁰ *Apathy syndrome* is defined as a loss of motivation not due to depression, impaired consciousness, or declines in cognition.³¹ Apathy is frequently attributed to atrophy and neuropathologic lesions of the medial portions of the frontal cortex, and is associated with different brain correlates than depression.³² However, the relationship between apathy and cognitive functioning remains unclear in nondemented, depressed older adults.

The main aim of this article was to examine the relationship between vascular burden and cognitive domains in depressed older adults. We hypothesized that CVRFs would contribute to executive dysfunction in depressed older adults. We also assessed the relationship between CVRFs and specific executive subfunctions, as the relationship between these finer distinctions of executive ability and depression have not been well studied. A secondary

goal of this study was to examine whether medical illness burden or apathy may be associated with cognitive impairment in depressed older adults. We chose to examine these two additional risk factors due to their frequent co-occurrence with depression and vascular burden among older adults. We hypothesized that greater severity of medical burden and apathy would contribute to cognitive impairment.

METHODS

Design Overview

Participants were recruited as part of a randomized, controlled clinical trial for older adults to receive a depression intervention. As this study includes only baseline data, only recruitment methodology will be provided. Participants were recruited through newspaper advertisements that stated the aim of the study as comparing the effects of *tai chi* versus health education on “depression in older adults.” Participants were blinded to the study objectives and outcomes of depression.

Setting and Participants

All subjects met the following inclusion criteria: 1) current episode of major depressive disorder; 2) a 24-item Hamilton Depression Rating Scale (HDRS) score of 15 or higher at baseline; and 3) Mini-Mental State Examination score of 26 or higher. The subjects were excluded if they had the following: 1) a history of any other psychiatric illness or alcohol or substance abuse/dependence; 2) severe or acute medical illness; 3) acute suicidal or violent behavior; or 4) any other CNS diseases or dementia. Patients were free of psychotropic medications for at least 2 weeks before starting the trial.

Procedures

Participants who responded to the advertisement underwent two assessment phases before they were included. A 15-minute telephone interview by a trained project coordinator ensured that participants fulfilled the screening eligibility criteria. The second eligibility-assessment phase included an interview to obtain a medical history and current medication use, followed by administration of the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* diagnoses to diagnose a current episode of major depression. After describing the details of the study to interested subjects, written informed consent was obtained in accordance with the procedures set by the University of California, Los Angeles institutional review board.

Over a period of 30 months, we screened a total of 332 older depressed individuals, and recruited 112 participants aged 60 years or older who met criteria for unipolar major depressive disorder and the study admission criteria. Data were available for 94 of these participants. The HDRS was administered at baseline and in all follow-up visits to determine the rate of remission and change in the severity of depressive symptoms after the initial major depressive disorder diagnosis. All subjects received an initial assessment including complete physical and neuropsychiatric examinations, electrocardiogram, and laboratory testing at baseline, to rule out new-onset medical illnesses that could account for behavioral symptoms.

Assessment Instruments

Participants received a comprehensive assessment of depression, physical and neuropsychiatric examination that included electrocardiogram, assessment of vascular and medical burden, and completed a brief battery of neuropsychological tests. The HDRS³³ 24-item was used to quantify mood symptoms. Medical comorbidity was measured by the

CVRF Prediction Chart³⁴ of the American Heart Association for rating CVRFs. CVRF takes into account age, systolic blood pressure, antihypertensive medication use, history of diabetes, smoking, previous strokes, atrial fibrillation, and left ventricular hypertrophy. The Cumulative Illness Rating Scale-Geriatric³⁵ was used for rating global chronic medical illness burden. The Cumulative Illness Rating Scale-Geriatric measures impairment in specific organs or systems and the evaluator assigns each a score of 0–4 (the higher the grading, the more severe the illness). The Apathy Evaluation Scale³⁶ assessed the severity of apathy. Cognitive performance was initially screened using the Mini-Mental State Examination and then all participants were administered a brief cognitive battery as described later.

Neuropsychological Test Performance

We administered a brief neuropsychological assessment battery that assessed the domains likely to show impairment in geriatric depression. The battery was composed of the following instruments: California Verbal Learning Test II (CVLT II³⁷), Trail Making Test (TMT),³⁸ Stroop Color and Word Test,³⁹ semantic and phonemic fluency,⁴⁰ and Symbol Digit Modalities Test.⁴¹ For data reduction purposes, the cognitive measures were grouped into four composite domains on the basis of prior literature⁴² and clinical knowledge of test characteristics. To form the composite domains, we transformed raw scores to *z* scores for each test score of interest for each participant, and then summed the *z* scores. For variables in which good performance was represented by lower values (i.e., TMT; Stroop), *z* scores were reversed so that a high *z*-value represented a good performance for all measures.

Verbal Memory—This domain assessed the ability to encode and recall verbal information. This domain included CVLT—second edition trial 1 recall (CVLT-II T1) and CVLT-II long-delay free recall. The CVLT-II requires participants to recall and recognize items from a list of orally presented words both immediately (trial 1) and following a 20-minute delay (long-delay free recall).

Cognitive Control—This domain represented abilities related to the allocation of attention, monitoring, and making behavioral adjustments (inhibiting responding/switching attention) depending on the context. This domain included TMT Part B (TMT-B) (time to completion), a paper and pencil test of attentional set switching; and the Stroop Color/Word trial (timed to completion), a measure of the ability to inhibit over learned responses, in which participants are asked to report the color of ink, the name of a color-word is printed in (e.g., if the word “green” is printed in blue ink; subjects must name the color of the ink “blue” and ignore the printed word).

Verbal Fluency—This domain assesses word generation and included both semantic (animal naming) and phonemic (FAS) fluency. These measures require rapid generation of either animal names or words beginning with the letters F, A, and S, respectively, within a 60-second time period. Total score was number of words generated for semantic and phonemic fluency. Although other studies have included verbal fluency under a broader executive functioning domain,^{42,43} we include fluency tests in a separate executive category as they measure different aspects of executive functioning than the TMT-B and Stroop Color/Word trial.²⁷ Specifically, verbal fluency is thought to require strategic searching/organization of verbal knowledge while Stroop Interference and TMT-B probe mental flexibility and inhibition. Functional magnetic resonance imaging findings provide some support for differential activation of frontal lobe regions. Performances on verbal fluency tasks are associated with activation of the left-inferior frontal gyrus,⁴⁴ specifically, activation of the posterior and dorsal region of the left-inferior frontal gyrus is associated with phonologic fluency, while the anterior and ventral area is more highly activated in

semantic fluency. Although Stroop Interference may also be associated with inferior frontal gyrus activation in older adults,⁴⁵ performance on Stroop Interference is most frequently reported to be associated with activation of the anterior cingulate and dorsolateral prefrontal cortex.⁴⁶ TMT-B performance is also correlated with activation of the dorsolateral prefrontal cortex and anterior cingulate, as well as the medial frontal gyrus and supplementary motor area.⁴⁷

Attention—This domain assessed visual attention and sequencing and included Symbol Digit Modalities Test (total correct in 90 seconds), a test requiring rapid copying of symbols paired with numbers; and TMT, Part A (time to completion), a timed test in which participants draw lines connecting the numbers 1 through 25 as quickly as possible; and the average of Stroop Color and Stroop Word (time to completion), a measure of sustained attention in which participants read colors or words aloud.

Statistical Analyses

To identify potential confounders, we first examined relationships between age, depression, and the risk factors of interest (CVRFs, medical illness burden, and apathy) using Pearson product moment correlation coefficients. *Because CVRF scores distribution was skewed, a logarithmic transformation was performed; the log-transformed variable was used for all analyses.* To study the relationship between CVRFs, medical illness burden and apathy with the four neuropsychological domains, *we estimated Pearson correlation coefficients with and without controlling for education*, level of depression, number of medications, antidepressant use, and number of trials of antidepressants in which the subjects had participated. Because age is used to calculate the CVRF variable, it was not included as a separate covariate. Fisher's *z*-test was employed to determine whether significant differences existed in the strength of significant correlations for neuropsychological domains with risk factors of interest. The level of significance was set at the alpha level of $p = 0.05$, two-tailed.

RESULTS

Table 1 presents the baseline demographic and clinical characteristics of the sample and Table 2 presents mean performances on neuropsychological measures.

Preliminary analyses revealed that depression severity was significantly associated with CVRFs (*Pearson's* $r = -0.22$, $df = 92$, $p = 0.03$); the correlations with age (*Pearson's* $r = -0.18$, $df = 92$, $p = 0.09$), medical illness burden (*Pearson's* $r = -0.19$, $df = 92$, $p = 0.07$), and apathy (*Pearson's* $r = -0.16$, $df = 92$, $p = 0.12$) failed to reach significance. CVRFs were also significantly associated with medical illness burden (*Pearson's* $r = 0.54$, $df = 92$, $p < 0.0001$). Apathy was not related to any of the other variables.

Controlling for depression severity, CVRFs were significantly associated with cognitive control (*Pearson's* $r = -0.25$, $df = 86$, $p = 0.02$; Figure 1) and attention (*Pearson's* $r = -0.21$, $df = 86$, $p = 0.05$; Figure 2). CVRFs were not significantly correlated with memory (*Pearson's* $r = -0.10$, $df = 86$, $p = 0.36$) or verbal fluency (*Pearson's* $r = -0.13$, $df = 86$, $p = 0.24$). Using non-parametric (Spearman's) correlations did not change the significance of the associations. The strength of associations between CVRFs with cognitive control or attention did not differ (Fisher's $z = 0.05$; $p = 0.96$). The correlations between CVRFs and the cognitive domains did not change after controlling for educational attainment, antidepressant drug use, the number of current medications or the number of antidepressant trials. Contrary to our expectations, apathy and medical illness burden were not associated with cognitive functioning. *Specifically, correlations with apathy did not achieve statistical significance for verbal fluency (Pearson's* $r = 0.07$, $df = 86$, $p = 0.50$), *cognitive control*

(Pearson's $r = 0.07$, $df = 86$, $p = 0.55$), memory (Pearson's $r = 0.06$, $df = 86$, $p = 0.59$), or attention (Pearson's $r = 0.13$, $df = 86$, $p = 0.23$).

DISCUSSION

This study sought to identify relationships between cognitive performance and CVRFs in a sample of depressed older adults. We found that greater vascular burden is associated with poorer cognitive control and attention, but not verbal memory or verbal fluency. Contrary to our expectation, neither medical burden nor apathy was significantly related to any of the domains of cognitive functioning.

Our study supports prior findings of executive dysfunction associated with vascular burden in patients with geriatric depression characterized by the notions of “depression-executive dysfunction syndrome” and vascular depression.^{11,14,16,43,48,49} Similar to our findings, both Smith et al.⁴³ and Sheline et al.⁴⁹ obtained significant correlations between Framingham vascular risk factor scores and a composite measure of executive functioning in samples of depressed older adults. Cui et al.⁶ also found that CVRFs predicted time on Trails B. However, our work expands upon these studies because we separated executive functioning measures into two domains (verbal fluency versus cognitive control). Our finding that only cognitive control was related to vascular burden while verbal fluency was not suggests that different components of executive functioning (i.e., inhibition and mental flexibility) may be uniquely related to vascular burden. This is also supported by neuroimaging studies demonstrating different neuroanatomical correlates of measures of verbal fluency versus inhibition/flexibility.⁵⁰ Although both memory and verbal fluency have been shown to be poorer in depressed versus nondepressed older adults,^{8,42,51} neither domain was associated with degree of vascular burden in the depressed older adults in our study. This finding is consistent with previous work.^{43,52,53}

Our findings are supported by extensive neuroimaging literature demonstrating that cerebrovascular disease can interfere with the integrity of frontostriatal pathways.²⁷ Subcortical ischemic lesions are more common in older adults who are depressed and are associated with deficits in attention and executive functioning.⁵⁴⁻⁵⁷ Murphy et al.²⁰ found that among a sample of depressed older adults, performance on the Stroop interference task was associated with microstructural abnormalities in the prefrontal cortex as well as the white matter lateral to the anterior cingulate. Supporting the link between vascular health and neuroanatomical changes, Raz et al.⁵⁸ demonstrated that progression of both white matter hyperintensities (WMH) and cognitive declines over a 5-year period were significantly greater in older adults with higher vascular risk as compared with healthy controls and that vascular health versus age was the best predictor of the rate of white matter hyperintensities progression. Furthermore, they reported longitudinal declines in a working memory measure for participants with high vascular risk but did not find similar declines in controls. We found that medical illness burden was not associated with depression severity or cognition. Previous studies have reported mixed findings regarding the contribution of medical illness burden to cognitive status in individuals with late-life depression.^{6,23,49,56} The discrepancy may be explained by the relatively lower CIRS scores in comparison to studies that did report a relationship between medical illness burden and cognition.

Although we report a nonsignificant relationship between level of apathy and cognition, previous studies have found significant associations in depressed older adults with and without cognitive impairment.^{10,56,59} It is possible that the relatively small size and preserved cognitive status of our sample limited our ability to detect a relationship between apathy and executive dysfunction. Although it has been proposed that executive dysfunction can occur secondarily because of lack of motivation observed in depressed older adults,⁶⁰

our findings suggest that apathy can co-occur with depression and not account for executive dysfunction in late-life depression in cognitively intact older adults. Imaging research has demonstrated a connection between apathy, cerebrovascular disease, and disruption of frontosubcortical pathways, but regions associated with higher levels of apathy differ from those observed in depression suggesting that different patterns of cognitive impairment may be associated with apathy and depression.^{10,61}

Executive dysfunction continues to be an important marker of functioning in late life and differentiates depressed individuals in remission from healthy controls.⁶² Depressed adults with executive dysfunction have a greater risk for relapse, are less responsive to pharmacologic interventions, and have poorer functional status.⁶³⁻⁶⁵ Because late-life depression is associated with persisting cognitive impairment⁸ and may be a sign of prodromal dementia,⁶⁶ prevention and early treatment of both vascular conditions and depression are important. Treating modifiable risk factors, such as hypertension, hyperlipidemia, obesity, and diabetes, and implementing health behaviors, such as increasing exercise, are key primary prevention strategies.²⁷ Such treatment may reduce risk of declines in cognitive functioning, preserve functional abilities, and extend quality of life for these patients.

In addition, as argued by Sneed et al.,⁶⁷ it might be useful to establish the internal validity of vascular depression as a distinct clinical entity separate from major depressive disorder. Future prospective studies should address the “divergent diagnostic criteria”⁶⁷ investigating relationships between vascular burden, depression, and cognitive functioning.

There are several limitations to our study. First, because this study design was cross-sectional, that precludes establishing an etiologic relationship between CVRFs, depression, and cognition. Second, our relatively small convenience sample was composed of predominantly white, college-educated, and relatively healthy older adults. These factors limit our study’s generalizability. Our goal was to examine relationships between cognition and depression in depressed older adults with minimal cognitive impairment, as reflected in our mean Mini-Mental State Examination score of 29, and these findings may not generalize to older adults with poorer cognitive functioning. Likewise, we excluded individuals based on comorbid substance use or anxiety disorder. Though these exclusionary criteria help to recruit a relatively homogenous sample of participants limiting potential confounds to our findings, they also exclude some “real world” patients with depression. Finally, although we included four measures of executive functioning, these do not cover all of the multiple components included under the construct of executive functioning. Future studies could extend our work by examining correlations between CVRFs and other measures of executive functioning, such as planning or nonverbal reasoning, that do not involve a processing speed component.

Our study contributes to the growing literature elucidating the relationship of CVRFs to cognitive impairment in depressed older adults confirming that greater vascular burden can contribute to executive dysfunction in geriatric depression, and specifically to cognitive flexibility and cognitive control.

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FIGURE 1. Correlation between Cognitive Control and Cerebrovascular Risk Factors
Note: Pearson's $r = -.21$, $df = 86$, $p < .05$.

FIGURE 2. Correlation between Attention and Cerebrovascular Risk Factors

Note: Pearson's $r = -.21$, $df = 86$, $p < .05$.

TABLE 1**Clinical and Demographic Characteristics of the Participants**

Variable	(N = 94)	
Demographics	Range	
Women, number (%)	56 (59%)	
Age in years, mean (SD)	70.8 (7.6)	59–91
Race, number (%)		
White	73 (77.7%)	
African American	10 (10.6%)	
Asian American	3 (3.2%)	
Hispanic	8 (8.5%)	
Age at depression onset in years, mean (SD)	43.8 (24.0)	5–85
Education in years, mean (SD)	15.4 (2.6)	10–22
Family history of depression, number (%)	64 (68.1%)	
Psychiatric Symptoms		
Hamilton depression rating score, mean (SD)	17.4 (2.0)	15–25
Apathy evaluation scale, mean (SD)	33.4 (9.0)	9–52
Comorbid medical/neurologic symptoms		
CIRS-G, mean (SD)	5.6 (3.1)	0–13
CVRF, mean (SD)	11.1 (5.1)	3–26
Medications		
Currently using antidepressants (%)	37 (41.6%)	
Number of trials of antidepressants (SD)	1.6 (3.3)	0–21
Number of medications (SD)	3.9 (3.1)	0–18

Note: CIRS-G: Cumulative Illness Rating Scale-Geriatric Version; CVRF: cerebrovascular risk factor chart.

TABLE 2**Cognitive Test Performance of the Participants**

Measure	N	Mean (SD)	Range
MMSE		29.1 (1.2)	26–30
Memory			
CVLT Trial 1-5	94	48.1 (13.4)	6–74
CVLT LDRF	94	10.4 (3.8)	0–16
Fluency			
FAS	94	44.0 (13.4)	15–75
Animal naming	94	20.3 (5.4)	10–32
Cognitive control			
Stroop Color/Word	89	138.6 (37.6)	70–245
TMT-B	91	88.6 (31.4)	38–169
Attention			
DSMT	94	60.6 (15.8)	22–94
TMT-A	91	39.4 (11.7)	15–71
Stroop Color	91	65.7 (15.7)	34–154
Stroop Word	91	47.3 (8.2)	31–70

Note: CVLT: California Verbal Learning score for trials 1–5 and delayed verbal recall; DSMT: digit symbol modalities test; LDRF: Long Delay Free Recall; MMSE: Mini-Mental State Examination; Stroop errors: test of executive function; TMT: Trail Making Test, parts A and B.