Risk Factors for Geriatric Depression: The Importance of Executive Functioning Within the Vascular Depression Hypothesis

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Background. Results from recent studies addressing the vascular depression hypothesis have been mixed, with cerebrovascular risk factors (CVRFs) predicting depression in some geriatric patients but not in others. The current study seeks to examine executive dysfunction as a potential moderator of the relationship between CVRFs and depressive symptoms.

Methods. Data concerning CVRFs, executive functioning, and depressive symptoms from 77 geriatric rehabilitation patients were incorporated to test the hypothesis that patients with executive dysfunction and greater CVRFs would demonstrate the highest levels of depression over time. CVRFs (diabetes, hypertension, atrial fibrillation) were measured via diagnosis by treating physician. Depression was assessed using the 15-item Geriatric Depression Scale (GDS) at baseline and at 6-month and 18-month follow-ups. Executive functioning was measured at baseline using the Initiation/Perseveration (IP) Subtest of the Mattis Dementia Rating Scale.

Results. Multivariate analysis of variance demonstrated a significant statistical interaction between the number of CVRFs and scores on the IP Subtest on depressive symptoms. Patients with two or more CVRFs and lower IP scores demonstrated significantly greater depressive symptoms at baseline and at 18-month follow-up than patients with fewer CVRFs and higher IP scores. The univariate effect at 6 months was not significant.

Conclusion. The current data suggest that scores on an index of executive functioning may moderate the relationship between CVRFs and depressive symptoms. Interpretation of these findings is provided in the context of the vascular depression hypothesis and related frontostriatal dysfunction. Patients with greater CVRF burden and poor executive functioning may be at particularly high risk for depression.

The vascular depression hypothesis, as articulated by Alexopoulos and colleagues (1), postulates that vascular diseases can "predispose, precipitate, or perpetuate" depressive symptoms among older adults (p. 915). This hypothesis is an extension of the poststroke depression construct, with greater emphasis placed on stroke risk factors as potential risk factors for geriatric depression. One implication of this hypothesis is the existence of a distinct depressive syndrome that occurs in stroke-free elders and is characterized by depressive symptoms that co-occur with cerebrovascular risk factors (CVRFs) such as hypertension, diabetes, and heart disease (2,3). The hypothesized pathway for this relationship has been articulated in the following manner: the number of CVRFs increases with age and contributes to the development of small-vessel disease in the frontal and subcortical regions of this brain, which increases the propensity for developing depressive symptoms (4).

This hypothesis has relied on neuroimaging and clinical risk factor research for support. Although neuroimaging studies have demonstrated consistent support for the link between depression and microvascular lesions in the prefrontal and subcortical regions of the brain (5–9), complementary results from clinical risk factor studies have been mixed. For example, Lyness and colleagues (4,10) found that, although CVRFs could be linked to major depression, this effect was severely attenuated by controlling for medical disability and general medical burden. In contrast, a recent study by Mast and colleagues (3) demonstrated a significant relationship between CVRFs and depressive symptoms in a frail geriatric sample after controlling for comorbid medical conditions and disability. In a longitudinal follow-up, patients with two or three CVRFs were nearly five times more likely than those with zero or one CVRF to demonstrate significant depressive symptoms 6 and 18 months later even after controlling for baseline levels of depression, disability, and general medical comorbidity (11).

The mixed findings from clinical risk factor studies raise questions as to why CVRFs might be predictive of depression in some patients but not others. In the context of the current conceptualization of vascular depression as a small-vessel process that disrupts frontal–subcortical function, in our study, we seek to investigate neurocognitive features of this model. More specifically, we tried to determine whether executive dysfunction moderates the relationship between CVRFs and depression.

Executive Dysfunction in Geriatric Depression

Executive dysfunction has been conceptualized as a consequence of lesions within the frontal–subcortical circuitry (12). Late-life depressive symptoms have shown
consistent associations with small lesions within the prefrontal and subcortical regions (5–9) as well as decreased prefrontal cortical volumes on magnetic resonance imaging (13,14). These findings have led to a greater emphasis on disruption of the frontostriatal circuitry and resultant executive dysfunction within late-life depression (15). Recent research has demonstrated that depressed geriatric patients demonstrate poorer executive functioning than control subjects across a variety of tasks (16). Furthermore, depressed geriatric patients with poor executive functioning have demonstrated greater disability (instrumental activities of daily living [ADLs]) and poorer response to antidepressant medications (17,18). In this context, Alexopoulos and colleagues have argued for a potentially distinct geriatric depressive syndrome: depression–executive dysfunction (DED) syndrome of late-life depression (15,17).

Vascular depression and DED syndromes have been conceptually linked to disruption within the frontal–subcortical circuitry. Yet, in spite of the implied connection between CVRFs and executive dysfunction via frontostriatal dysfunction (15), we are aware of no studies to date that have focused explicitly on the interaction between vascular risk and executive functioning on depressive symptoms. If an interaction exists such that patients with vascular risk and executive dysfunction demonstrate the greatest levels of depression, then one factor that identifies patients for whom CVRFs will be most predictive of depression (i.e., which moderates the impact of CVRFs on depression) may be clarified.

In a prior study, we reported a significant link between vascular risk and late-life depressive symptoms (11). The current study sought to extend this finding by examining the moderating role of executive dysfunction within the vascular depression hypothesis. We hypothesized that executive dysfunction moderates the relationship between vascular burden and depression in geriatric patients, such that cumulative CVRF burden will be more predictive of depressive symptoms among patients with executive dysfunction than among those with better executive functioning. Patients with the poorest executive functioning scores and the greatest CVRF burden will demonstrate the greatest number of depressive symptoms.

METhODS

Participants

The current sample has been previously described and reported (11). In brief, participants were consecutive admissions to a free-standing university-based urban medical rehabilitation hospital who were over the age of 60, were living alone prior to hospitalization, and agreed to participate in an interview and testing session within 1 week of admission. Principal diagnoses were stroke (17%), fracture (11%), spinal cord injury (7%), arthritis (32%), and amputation (7%). The remaining patients (26%) were admitted for rehabilitation associated with generalized weakness, gait disturbance, or severe deconditioning.

Patients were assessed during their initial hospital stay and at 6 and 18 months post discharge. One hundred patients remained in the study at the 18-month follow-up. Major reasons for attrition included death (n = 36), inability to contact (n = 13), refusal to participate in follow-up assessment (n = 6), acute hospitalization (n = 3), and incomplete data due to inability or unwillingness to complete a portion of the follow-up assessment (n = 36). As previously reported, patients with complete data did not differ from those with incomplete data in terms of race or gender representation, ADL functioning, general medical burden, and baseline depressive symptoms. Patients with incomplete data were older, had slightly less formal education, and demonstrated poorer cognitive functioning.

The current sample represented a subsample of the 100 patients remaining in the study at the 18-month follow-up. Stroke patients (n = 22) were excluded from the current analyses because the presence of stroke could affect depressive symptoms and executive dysfunction. One patient had missing data on the Mattis Dementia Rating Scale (MDRS) Initiation/Perseveration (IP) Subscale and was excluded from the current analyses, leaving a final sample of 77 patients in the current analyses.

Measures

Depression.—Depression was assessed using the 15-item Geriatric Depression Scale (GDS-15) (19), which has been shown to be significantly correlated with the long form in geriatric psychiatric patients as well as in nonclinical elderly subjects. The GDS short form is equivalent to the original version in terms of sensitivity and specificity (20–22).

Executive functioning.—Executive functioning was measured using the IP Subscale of the MDRS (23) at the baseline assessment. The MDRS was designed as a broad measure of cognitive functioning for use among demented patients. The MDRS has proven useful in the detection of dementia and in discriminating levels of impairment (24,25). Previous research has documented the utility of the MDRS among geriatric patients with cerebrovascular disease (26). The IP Subscale has frequently been used in geriatric research as an index of executive functioning (17,18). The IP score comprises several tasks associated with executive functioning but does not measure all aspects of executive functioning. The IP tasks include complex verbal initiation and perseveration (e.g., rapid oral generation of a list of supermarket items), vowel and consonant perseveration (e.g., repetition of “bee-kee-gee” and “bee-bah-boh”), alternating movements with fingers/hands, and copying alternating shapes and figures (e.g., “XOXO”).

CVRFs

As previously reported (3,11), CVRFs (hypertension, atrial fibrillation, diabetes) were diagnosed by the patients’ treating physicians and were entered using International Classification of Disease (9th ed.) codes in the patients’ charts at baseline only. These CVRFs were chosen based on prior associations with depression (diabetes and atrial fibrillation) (4), their frequency within this particular population (hypertension), and their identification as powerful risk factors for stroke (27). These CVRFs were
predictive of depression in our previous work with geriatric rehabilitation patients (3,11). Although other vascular risk factors may have been present, they could not be addressed with the available data.

**Statistical Analysis**

A two-way multivariate analysis of variance (MANOVA) was conducted with the IP score and CVRF burden as factors and depression scores at baseline, 6-month follow-up, and 18-month follow-up as dependent variables. This approach has been recommended as an alternative approach to repeated measures ANOVA because it does not have the assumption of homogeneity of covariance. This approach provides an overall multivariate effect (Wilks $\lambda$) for each independent variable and the interaction among the independent variables on a linear composite of the multiple dependent variables and also provides a corresponding follow-up univariate $F$ test for each of the dependent variables. The IP Scale was dichotomized based on a median split within this sample, such that those with scores of $\leq 32$ were placed into one group reflecting better executive functioning and those with scores of $>32$ were characterized as having poorer executive functioning. The IP score was dichotomized in this fashion because of its nonnormal distribution (negative skew) and to allow for a contrast between patients with higher and lower scores with a similar number of subjects in each group. The CVRF variable ranged from zero to three based on the presence of hypertension, atrial fibrillation, and diabetes. Based on prior analyses concerning depression symptoms, the maximal difference is observed between those patients with two CVRFs versus those with zero to one CVRF (3,11). Consistent with these prior results, we analyzed this variable as dichotomous. The two-way MANOVA thus had two dichotomous predictors; CVRFs and IP score. Effect sizes are reported as partial $\eta^2$.

**RESULTS**

The mean age for the sample was 72.4 ($SD = 8.7$) years, 63 subjects were African American (81.8%), 14 were European American (18.2%), 62 (80.5%) were women, and mean years of formal education was 11.5 ($SD = 3.4$). The mean MDRS score was 126.6 ($SD = 13.3$), and 15 subjects (19.5%) scored above the cut-score for depression on the GDS-15 (i.e., $>5$) at baseline.

The two-way MANOVA revealed an overall multivariate main effect for CVRFs on depressive symptoms ($F[3,74] = 6.405, \ p < .001$, partial $\eta^2 = .206$). This finding is consistent with our previous report on the sample (13). Consistent with the stated hypothesis, there was also a significant multivariate interaction between CVRFs and IP scores ($F[3,74] = 3.840, \ p < .05$, partial $\eta^2 = .135$) on depression scores. There was no multivariate main effect for IP scores ($F[3,74] = 1.651, \ p = .185$, partial $\eta^2 = .063$). Follow-up univariate $F$ tests indicated that the multivariate effect of the CVRF and IP interaction was attributable to an interaction at baseline ($F[1,76] = 7.475, \ p < .01$, partial $\eta^2 = .090$) and at 18-month follow-up ($F[1,76] = 6.218, \ p < .05$, partial $\eta^2 = .076$) but not at the 6-month follow-up ($F[1,76] = .417, \ p = .520$, partial $\eta^2 = .005$).

The means for the follow-up univariate $F$ tests are presented in Figure 1. At baseline, there was an increase in depressive symptoms as the number of CVRFs increased among patients with IP scores below the median (i.e., poorer executive functioning). There was no increase in depressive symptoms in concert with the increase in CVRFs among patients with IP scores above the median (i.e., better executive functioning). At 6 months, there was a main effect for baseline CVRFs on depressive symptoms but no main effect for baseline IP score or an interaction between baseline CVRFs and baseline IP scores. Patients with two CVRFs demonstrated higher levels of depression than did patients with zero to one CVRF. At the 18-month follow-up, the significant increase in depressive symptoms as the number of baseline CVRFs increased from zero to one to two was greater among patients with baseline IP scores below the median than those with baseline IP scores above the median.

**DISCUSSION**

The main finding of this study was that there was a significant interaction between CVRFs and executive functioning.
functioning on depressive symptoms. Patients with poorer baseline executive functioning scores and two CVRFs demonstrated significantly greater depression scores than did the other patient groups at baseline (in hospital) and 18 months later. To our knowledge, this is the first study to date to identify a significant interaction between clinically defined CVRFs and poorer executive functioning on depressive symptoms among older adults. This extends our previously reported finding by demonstrating that both the general level of vascular risk and the statistical interaction between vascular risk and executive functioning scores have significant links to depressive symptoms.

These findings are also the first to demonstrate a clinical variable that appears to moderate the influence of vascular risk on depressive symptoms in late life. The search for such interactions was one of the recommendations of a consensus statement by a National Institutes of Health panel on late-life depression (28) and remains a key task within the geriatric depression literature. There is evidence suggesting that CVRFs are related to late-life depression, but the circumstances and the patients in which the presence of significant vascular risk poses a risk for the development of depression have not yet been clarified. The current data suggest that CVRFs show a strong link to depressive symptoms in patients with executive dysfunction. This combination of risk factors may identify those older patients who are at highest risk for developing depressive symptoms.

One interpretation of these results is that executive dysfunction represents a potential marker for frontostriatal dysfunction (15). Prior research has demonstrated that CVRFs are not predictive of depression in all patients (4,10). Furthermore, CVRFs may not be associated with frontostriatal dysfunction in all patients. Therefore, one explanation for the current findings and the mixed findings from previous studies is that CVRFs are predictive of depression only when they cause or are associated with frontostriatal dysfunction. The lack of relationship between IP scores and depression in patients with fewer CVRFs could be interpreted as indicating that lower IP scores in patients with low vascular risk are due to causes other than frontostriatal dysfunction (e.g., low education, nonfrontal brain damage). Each of these findings could be consistent with the neuropsychological literature that indicates that executive functioning tasks are sensitive, but not necessarily specific, to frontal lobe dysfunction (29).

Limitations in the current study include a limited assessment of CVRFs, the use of only a brief measure of executive functioning, and the absence of clinical data concerning formal depression diagnoses and treatment. Future research should incorporate a broader range of CVRFs such as the Probability of Stroke Risk Profile from the Framingham Study, a broader range of executive functioning tasks, and structured interviews to establish formal depression diagnoses. Extending the measure of these potential risk factors may allow investigators to identify a broader range of patients at risk for depression. A second limitation concerns the absence of systematic neuroimaging data to identify microvascular lesions in the frontal and subcortical regions of the brain, which may be associated with increased vascular risk, depressive symptoms, and executive dysfunction (30).

This is particularly important for the current model, as executive dysfunction can be caused by lesions in regions of the brain other than the prefrontal cortex and frontostriatal circuitry. Although the inclusion of imaging data could strengthen this study, the current study may be particularly useful in identifying clinical markers for depression risk, which may be useful to clinicians seeking to identify those patients most likely to present with depression in medical settings.

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**Editor Nominations**

**Journal of Gerontology: Biological Sciences**

The Gerontological Society of America’s Publications Committee is seeking nominations for the position of Editor of the *Journal of Gerontology: Biological Sciences*.

The position will become effective January 1, 2006. The Editor makes appointments to the journal’s editorial board and develops policies in accordance with the scope statement prepared by the Publications Committee and approved by Council (see the journal’s masthead page). The Editor works with reviewers and has the final responsibility for the acceptance of articles for his/her journal. The editorship is a voluntary position. Candidates must be dedicated to developing a premier scientific journal.

Nominations and applications may be made by self or others, but must be accompanied by the candidate’s curriculum vitae and a statement of willingness to accept the position. **All nominations and applications must be received by April 1, 2005**. Nominations and applications should be sent to the GSA Publications Committee, Attn: Patricia Walker, The Gerontological Society of America, 1030 15th Street, NW, Suite 250, Washington, DC 20005-1503.