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What is This?
The Synergistic Effects of Anxiety and Cerebral Hypoperfusion on Cognitive Dysfunction in Older Adults With Cardiovascular Disease

Michael L. Alosco, MA1, John Gunstad, PhD1, Courtney Beard, PhD2, Xiaomeng Xu, PhD3, Uraina S. Clark, PhD4, Donald R. Labbe, PhD5, Beth A. Jerskey, PhD5, Maura Ladino, BA6, Denise M. Cote, MS7, Edward G. Walsh, PhD8, Athena Poppas, MD9, Ronald A. Cohen, PhD10, and Lawrence H. Sweet, PhD5,11

Abstract

Objectives: Anxiety is a risk factor for cardiovascular disease (CVD) and is associated with neurocognitive outcomes. The effect of anxiety on brain perfusion in a CVD population has yet to be examined, and no study has investigated the interactive effects of anxiety and cerebral perfusion on cognition. Methods: A total of 55 older adults with CVD completed the Beck Anxiety Inventory (BAI) and underwent arterial spin labeling to quantify cortical perfusion and thickness. Participants were administered the Mini-Mental State Examination (MMSE) and the Repeatable Battery for the Assessment of Neuropsychological Status. Results: Reduced perfusion predicted poorer cognition and decreased cortical thickness. Higher anxiety score predicted worse memory performance and decreased frontal perfusion. Frontal lobe hypoperfusion combined with increased BAI scores exacerbated poorer MMSE performance. Conclusions: Higher anxiety may exacerbate the effects of cerebral hypoperfusion on cognitive impairment. Longitudinal studies are needed to confirm our findings and determine whether anxiety treatment improves neurocognitive outcomes in CVD.

Keywords
arterial spin labeling, anxiety, cerebral blood flow, cognitive function, cardiovascular disease, neuroimaging, cerebrovascular disease, magnetic resonance imaging

Introduction

More than half of older adults in the United States exhibit at least 1 risk factor for cardiovascular disease (CVD).1 This is unfortunate, as adverse brain pathology stemming from CVD underlies 25% to 30% of dementia diagnoses.2 Before the onset of dementia-related processes, CVD and its risk factors also play a key role in the development of cognitive impairment and morphological changes (eg, brain atrophy) in older adult populations.3-5 The etiology of such poor cognitive outcomes is believed to partially involve altered cerebral hemodynamics. For example, reduced cerebral perfusion is a contributor to the pathogenesis of Alzheimer disease and vascular dementia,6-8 as well as milder forms of cognitive impairment, and is also linked to abnormalities on neuroimaging (eg, white matter hyperintensities) among older adults with CVD.9,10

The pathological processes associated with aging and accompanying CVD is largely attributable to disrupted cerebral hemodynamics.11,12 However, factors such as psychological
comorbidities are also likely contributors to these adverse neurocognitive outcomes. For example, a growing body of literature links depressive symptoms with cerebral hypoperfusion in medical (eg, CVD) and neurological populations (eg, Alzheimer disease) and also shows that depression interacts with brain hypoperfusion to exacerbate cognitive impairment.13–15

There is also reason to believe that anxiety is another likely correlate of poor neurological outcomes, including brain hypoperfusion and neurocognitive impairment.16–18 Greater anxiety has been linked with cognitive impairment in patients with severe CVD (eg, heart failure)19 as well as in community-dwelling older adults.20 Although not yet examined, a possible explanation for these findings may involve the synergistic effects of anxiety and cerebral hypoperfusion. Past work demonstrates an association between higher anxiety and adverse ischemic brain changes in patients with heart failure,21 suggesting a possible association between anxiety and cerebral blood flow (CBF) in patients with CVD. Moreover, healthy young and older adult individuals also exhibit altered brain perfusion in response to clinically elevated levels of pathological worry, anxiety, or both.22,23

The effect of anxiety on CBF in CVD populations has yet to be examined, and no study has simultaneously examined the impact of anxiety on cerebral perfusion and cognitive function. We investigated the associations among anxiety, CBF (as measured by arterial spin labeling [ASL], a perfusion magnetic resonance imaging [MRI] technique), and cognitive function in older adults with varying degrees of CVD. The interactive effects of anxiety and cerebral perfusion on cognitive function were also examined. We also examined the effects of anxiety and brain perfusion on the cerebral structure (ie, cortical thickness). We hypothesized that increased anxiety would be associated with worse cognitive function and lower brain indices of structural and vascular health.

Methods

Participants

A total of 55 participants were recruited from a larger National Institutes of Health-funded study examining the effects of CVD on neurocognitive outcomes. All participants in this study underwent neuroimaging, had complete neuropsychological, medical, and demographic data (see Table 1), and were recruited from either outpatient cardiology offices or from advertisements in local papers. Participants were recruited and screened for study eligibility according to strict inclusion/exclusion criteria. Specifically, the inclusion criteria were English-speaking men and women older than the age of 50 and normal or corrected vision at the time of testing. Exclusion criteria included significant neurological disease (eg, history of stroke and multiple sclerosis), including a diagnostic history of dementia. Additional exclusion criteria included traumatic brain injury accompanied by a loss of consciousness, history of substance abuse with subsequent hospitalization, or any contraindications for MRI (eg, some metal implants). Participants with a current diagnosis of a severe psychiatric illness (eg, bipolar disorder and schizophrenia) were also excluded. As part of the larger study’s procedures, self-report measures were administered to assess depressive and anxiety symptomatology that is known to affect cognitive performance. Participants were assessed for possible sensory impairments that may impact cognitive test performance, including vision. Although 40.0% of the sample wore glasses during the cognitive assessments, all participants exhibited visual acuity within normal limits. Participants of the current study average 65.6 ± 9.09 years of age and were 60.0% female.

Table 1. Demographic and Medical Characteristics.a

<table>
<thead>
<tr>
<th>Demographic Characteristics</th>
<th></th>
<th>Medical Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>65.64 (9.09)</td>
<td>Cardiac index, mean (SD)</td>
</tr>
<tr>
<td>Sex (% women)</td>
<td>60.0</td>
<td>2.78 (0.58)</td>
</tr>
<tr>
<td>Race (% caucasian)</td>
<td>94.5</td>
<td>BDI-II, mean (SD)</td>
</tr>
<tr>
<td>Education (N = 54), mean (SD)</td>
<td>16.11 (2.60)</td>
<td>4.25 (5.18)</td>
</tr>
<tr>
<td>Medical Characteristics</td>
<td></td>
<td>Angina, %</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>38.2</td>
<td>12.7</td>
</tr>
<tr>
<td>Coronary artery disease, %</td>
<td>18.2</td>
<td>Atrial fibrillation, %</td>
</tr>
<tr>
<td>Heart failure, %</td>
<td>9.1</td>
<td>9.1</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>9.1</td>
<td>Elevated total cholesterol, %</td>
</tr>
<tr>
<td>ACE inhibitor, %</td>
<td>27.3</td>
<td>50.9</td>
</tr>
<tr>
<td>Antidysrhythmics, %</td>
<td>7.3</td>
<td>ACE inhibitor, %</td>
</tr>
<tr>
<td>Antihyperlipidemics, %</td>
<td>52.7</td>
<td>BDI-II, Beck Depression</td>
</tr>
<tr>
<td>Atrial fibrillation, %</td>
<td></td>
<td>Armstrong Inventory II; SD,</td>
</tr>
<tr>
<td>Depression, %</td>
<td></td>
<td>standard deviation.</td>
</tr>
<tr>
<td>Angina, %</td>
<td></td>
<td>*N = 55.</td>
</tr>
<tr>
<td>ACE inhibitor, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antidysrhythmics, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antihyperlipidemics, %</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ACE, angiotensin-converting enzyme; BDI-II, Beck Depression Inventory II; SD, standard deviation.

*N = 55.

Measures

Anxiety. The Beck Anxiety Inventory (BAI) assessed anxiety symptomatology.24 The BAI is a 21-item checklist of common anxiety symptoms that asks participants to indicate the presence and severity of each symptom in the past month. Scores range from 0 to 63 with higher scores reflective of greater anxiety. The BAI demonstrates excellent psychometric properties, including internal consistency, test–retest reliability, and concurrent and discriminant validity.24

Arterial spin labeling. All scans were performed using a 3-T Siemens Tim Trio scanner located on the Brown University campus. A 32-channel head receiver array was used with body resonator transmit coil, and participants were placed head first in the supine position. Foam pads were placed in the space around the head to limit motion.

Following acquisition of a 3-axis localizer scan, a 3-dimensional (3D) T1 magnetization-prepared rapid acquisition with gradient echo (T1-3MPRAGE) scan was acquired with 1 mm isotropic resolution. This scan was acquired using parameters...
repetition time (TR) = 1900 ms, echo time (TE) = 2.98 ms, inversion time (TI) = 900 ms, and readout flip angle = 9° to provide a 3D T1 image data set for gray–white matter segmentation for the analysis of functional MRI and ASL images. Arterial spin labeling scans were acquired using a QUIPSS II (quantitative imaging of perfusion using a single subtraction, version 2), thin slice T1, and periodic saturation (Q2TIPS) using a proximal inversion with a control for off-resonance effects (PICO- CORE-Q2TIPS) technique.25 For ASL scans, 71 pairs (control, perfusion weighted) of motion-corrected images were averaged to provide the ΔM image for perfusion map computation. The first image acquired in the series served as the M0 image. An inversion slab 110 mm in thickness was placed with its proximal edge 12 mm from the inferior boundary of the imaged region. Eighteen slices of 6 mm thickness were acquired over 2 scans (9 slices in the first scan and 9 slices in the second). In-plane voxel size was 3 mm with slice thickness of 6 mm. Timing parameters were TR = 2500 ms, TI1 = 700 ms, and TI2 = 1800 ms (inversion to start of the 642 echo planar image readout sequence with TE = 16 ms). Scan time for each ASL run was 4.5 minutes.

The M0 map for each slice was the first image acquired in the data set. This image was not acquired with any inversion or saturation preparation and was taken with the longitudinal magnetization at full equilibrium. ΔM maps were formed by averaging the 71 pairs of motion-corrected images. The M0 and ΔM maps were used to produce perfusion maps for each slice using a Matlab script (Math Works, Natick, MA). For a full description of methodology used to calculate the perfusion maps refer to Alosco et al.26

The tissue parameters27-29 used were T1a = 1664 ms, T1T = 1300 ms (gray matter) or 1000 ms (white matter), T2 = 1000 ms, and λ = 0.9 mL/g. Inversion efficiency (α) was set to .95 based on scanner manufacturer recommendation (α = 1 corresponds to perfect inversion). Using a formula described in Alosco et al.26 a factor q is calculated that takes into account water exchange between the vascular and the interstitial compartments. Using the above-mentioned tissue parameter values results in values of q = 0.93 for gray matter and 0.85 for white matter. These values of q were applied to the perfusion calculation on a pixel basis based on gray–white matter tissue segmentation.

### Cortical Segmentation

Statistical parametric mapping 5 tissue segmentation30,31 was applied to the T1-MPRAGE data acquired during the same scanning session as the perfusion acquisitions, generating gray matter and white matter posterior probability maps for each participant in native space. The posterior probability maps were then thresholded using a minimum probability of 0.70, minimizing partial volume effects for each tissue type, yielding a binary gray matter mask, and a binary white matter mask. The T1-weighted anatomical acquisition was processed using FreeSurfer reconstruction,32,33 which generated separate left and right cerebral hemisphere cortical ribbon masks and cortical parcellation using the Desikan-Killiany atlas for each participant. Left and right masks were combined to form the cortical ribbon mask.

The whole-brain geometry for each participant’s mean perfusion data was established by concatenating the inferior 9 axial slice and superior 9 axial slice relative CBF maps generated by the scanner, along the slice (z) direction using Analysis of Functional Neuroimages (AFNI).34 The AFNI MATLAB library (http://afni.nimh.nih.gov/afni/matlab) was used to convert each whole-brain perfusion array into an AFNI-compatible 3D format, having the same geometry as the whole-brain reICBF data set. The FreeSurfer cortical ribbon, anatomically based cortical parcellation (Desikan-Killiany atlas) and binary masks, were then aligned with and resampled to the same geometry as the perfusion data using AFNI/Surface Mapping with AFNI (SUMA). A whole-brain perfusion map was then created using the following formula: whole-brain perfusion = (binary gray matter mask + binary white matter mask) × (perfusion data).

Alignment verification of the cortical ribbon mask, cortical parcellation, whole-brain mask, and whole-brain perfusion map in $3 \times 3 \times 6 \mm^3$ space was done for each participant using the AFNI viewer. Following alignment and resampling, the mean and SD of all perfusion values between 1 and 100 were calculated for each region of interest (as outlined in the Desikan-Killiany atlas), the cortical ribbon, and the whole brain.

### Morphometric Analyses

Morphometric data were also acquired on the Siemens 3-T Tim Trio scanner using a sagittally oriented whole-brain Magnetization Prepared Rapid Gradient Echo acquisition with a slice thickness of 1 mm, field of view (FOV) of 256 mm, imaging matrix of 256 × 256, TE/TR/TI/α = 4 ms/9.7 ms/300 ms/12°, and bandwidth = 130 Hz/Px. For morphometric analyses, T1 volumes were normalized to the Montreal Neurological Institute geometry and segmented using standard T1 gray, white, cerebrospinal fluid, and nonbrain templates. These procedures are based on established techniques and procedures for surface and subcortical reconstruction using the FreeSurfer software package and have been described previously.32,33,35,37 The fully automated FreeSurfer v5.0 recon-all processing stream was completed for all participants. After preprocessing, results underwent quality control to confirm absence of any errors or defects in the segmentation. Mean cortical thickness of each brain region including frontal, temporal, parietal, and occipital were calculated using the organization schema as described in Desikan et al.38

### Neurocognitive assessment

The primary cognitive measures of the current study included the Mini-Mental State Examination (MMSE)39 and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS).40 Each of these instruments offers distinct clinical advantages in the assessment of cognitive function. The MMSE is a brief (ie, 5-10 minute) screening measure that taps into several aspects of cognitive function, including attention, orientation, memory, language, and calculation.39 As such, the MMSE can be administered...
in fast-paced clinical settings to help to detect the presence of severe cognitive impairment and/or dementia.

In contrast, the RBANS provides a more comprehensive assessment (ie, 25 minutes) of specific cognitive domains that is often used to help with differential diagnosis of dementia.\(^{40}\) Specifically, the RBANS consists of 10 subtests that assess the following cognitive domains: (1) Immediate Memory—leaning verbal information presented in list and story formats; (2) Language—confrontation naming and semantic fluency; (3) Visuospatial/Construction—production of a complex figure and a modified judgment of line orientation; (4) Attention—digit span and coding; and (5) Delayed Memory—recall of verbal learning tasks and complex figure after a brief delay. From these indexes, an RBANS Total Scale Score is also derived. All RBANS Index scores were converted to standard scores (ie, a distribution with a mean of 100 and a SD of 15) adjusted for age using normative values. The MMSE and the RBANS Total Scale Score were used to operationalize global cognitive function.

**Depressive symptoms.** The Beck Depression Inventory II (BDI-II) assessed depressive symptomatology and served as a covariate in the current study. It is a widely used self-report measure of depressive symptoms that demonstrates good psychometric properties in persons with medical conditions.\(^{41,42}\) Beck Depression Inventory II scores range from 0 to 63 with higher scores indicative of greater symptomatology.

**Physiological examination.** Participants’ height and weight were measured to calculate body mass index (BMI). A transthoracic echocardiogram was conducted with 2-dimensional apical views from each participant according to standards of the American Society of Echocardiography.\(^{43}\) Cardiac index was calculated by dividing cardiac output by BMI, which yielded a measure of cardiac output that controlled for body size.

**Demographic and medical characteristics.** The patient’s medical history and currently prescribed medications were self-reported during 2 interviews and confirmed by medical records when possible. Medications were categorized by class, and those identified as cardiovascular medications were reviewed and confirmed by a clinical cardiologist.

### Procedures

Institutional review board approval was granted, and written informed consent was obtained from all participants prior to study enrollment. All participants completed medical and psychosocial self-report measures (eg, BAI and BDI-II) and were administered a comprehensive neuropsychological battery by trained research assistants under the supervision of a licensed clinical neuropsychologist. During a separate study visit, participants underwent a transthoracic echocardiogram, and their height and weight were measured. Arterial spin labeling was conducted during a third study visit. Participants were compensated US$50 for each study visit for a possible total of US$150.

### Statistical Analyses

For lobar perfusion (eg, frontal, temporal, parietal, and occipital), left and right hemisphere composites were computed that consisted of the mean of brain regions that comprise their respective lobe; the mean of the left and right hemisphere was then calculated and used in analyses. Due to individual differences in neuroanatomy, there were cases in which some neuroanatomical structures were too small to generate a reliable perfusion value. For these instances, the lobar composites were based on complete data of the remaining regions that comprise that lobe. A total brain perfusion composite was also computed which consisted of the mean of the frontal, temporal, parietal, and occipital lobe perfusion.

Partial correlations adjusting for age, sex, BDI-II, cardiac index, and diagnostic status of hypertension and type 2 diabetes mellitus (T2DM) were first conducted to examine the effects of total brain perfusion on the MMSE and RBANS Total Scale Score. Because certain brain regions exhibit greater sensitivity to cognitive function than others, follow-up partial correlations adjusting for the same medical and demographic variables were then performed to investigate the associations among regional perfusion, the MMSE, and each RBANS Index.

To first identify the association between anxiety and cerebral perfusion, a hierarchical regression model was performed to quantify the relationship between anxiety and total brain perfusion. To clarify these findings, regression models then examined the association among the anxiety and frontal, temporal, parietal, and occipital lobe perfusion. To account for the known effects of medical and demographic variables on cerebral perfusion, age, sex (0 = male and 1 = female), BDI-II, cardiac index, and diagnostic status of hypertension and T2DM (1 = yes and 0 = no) were entered in block 1 for all models. Block 2 included total BAI score.

The above-described regression model was again conducted to examine the effects of anxiety on the MMSE, RBANS Total Scale Score, and each RBANS Index. A multivariable hierarchical regression-based moderation model was then performed to examine the interactive effects of anxiety and cerebral perfusion on each of the cognitive measures. These analyses were limited to those lobes that demonstrated a significant association with BAI in the above-mentioned analyses. According to the standard moderation procedures, continuous predictor variables were transformed to z-scores. The above-listed medical and demographic variables were entered in block 1. The BAI total score and brain perfusion were entered in block 2. Finally, an interaction term that consisted of the product of BAI total score and brain perfusion was computed and entered in block 3 to determine the interactive effects of anxiety and CBF on cognitive function. The interactive effects of anxiety and cerebral perfusion from the regression model were then plotted on to the significant criterion using the simple slopes test.\(^{44}\) Lines were computed for individuals 1 SD above the mean BAI score of the sample (ie, individuals with high anxiety), those at the mean (ie, average anxiety of the sample), and 1 SD below the mean BAI score (ie, individuals with low anxiety).
Table 2. Descriptive Statistics of Cognitive Test Performance. *

<table>
<thead>
<tr>
<th>Cognitive Test Variable</th>
<th>Mean (SD)</th>
<th>% 1.5 SD Below Average</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBANS Immediate Memory</td>
<td>105.69 (13.65)</td>
<td>7.3</td>
</tr>
<tr>
<td>RBANS Visuospatial/ Construction</td>
<td>105.02 (15.16)</td>
<td>14.5</td>
</tr>
<tr>
<td>RBANS Language</td>
<td>104.44 (11.57)</td>
<td>1.8</td>
</tr>
<tr>
<td>RBANS Attention</td>
<td>105.31 (13.66)</td>
<td>7.3</td>
</tr>
<tr>
<td>RBANS Delayed Memory</td>
<td>103.51 (12.02)</td>
<td>7.3</td>
</tr>
<tr>
<td>RBANS Total Index</td>
<td>106.71 (12.43)</td>
<td>3.6</td>
</tr>
<tr>
<td>MMSE</td>
<td>28.98 (1.58)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: MMSE, Mini-Mental State Examination; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; SD, standard deviation.
*% 1.5 SD Below Average refers to those participants that scored 1.5 SD below the normative average of the RBANS (ie, 100) and N = 55.

Finally, regression analyses controlling for age, sex, BDI-II, cardiac index, diagnostic status of hypertension, and T2DM then examined the possible effects of anxiety on total brain and lobar mean cortical thickness. Partial correlations adjusting for the same medical and demographic variables also investigated the associations between perfusion and cortical thickness.

Results

Medical, Clinical, and Cognitive Characteristics

The sample exhibited an average cardiac index of 2.78 (SD = 0.58). Many (45.5%) participants exhibited a cardiac index below 2.6 L/min/m², although no participants fell below 1.8 L/min/m². Cardiovascular disease and its risk factors were prevalent in the current sample. Specifically, conditions like hypertension and elevated cholesterol were common. See Table 1 for medical and demographic characteristics of the current sample.

The sample exhibited an average BAI total score of 3.56 (SD = 3.27), and no participant reported severe levels of anxiety (ie, BAI total score > 26). Indeed, only 7.3% of the sample was prescribed anxiolytic medications. There were no differences between those individuals with or without antianxiety medication treatment on cognitive function or cerebral perfusion (P > .05 for all domains and brain regions). The BAI total score was not associated with any demographic or medical variables (P > .05), although higher scores on the BAI corresponded with greater depressive symptoms on the BDI-II, r(53) = .55, P < .01. The BDI-II did not demonstrate associations with perfusion to any of the lobes or cognitive function in any domains (P > .05).

Refer Table 2 for cognitive test performance in the sample. Cognitive performance was generally intact in study participants, as the average MMSE score in the sample was 28.98 (SD = 1.58) and RBANS Total Scale Score was 106.71 (SD = 12.43). However, many participants exhibited impairments on the RBANS Index scores. Specifically, when using a cutoff of 1.5 SD below the mean of normative standards, 14.5% exhibited impairments on the Visuospatial/Construction Index and 7.3% on the Immediate Memory, Delayed Memory, and Attention Index.

Brain Perfusion and Cognitive Function

Partial correlations controlling for medical and demographic variables showed that lower total brain mean perfusion was associated with worse scores on the RBANS Total Scale Score, r(47) = .32, P = .03. No such pattern emerged for the MMSE (P > .05). Follow-up analyses revealed that reduced frontal lobe perfusion demonstrated a significant association with worse performance in the following RBANS Indices: Immediate Memory, r(47) = .51, P < .001, Language, r(47) = .34, P = .02, Delayed Memory, r(47) = .48, P < .001, and the RBANS Total Scale Score, r(47) = .44, P < .01. This pattern did not emerge for the RBANS Attention or Visuospatial/Construction Index (P > .05 for all). Reduced temporal, r(47) = .39, P = .01, and parietal lobe, r(47) = .37, P = .01, perfusion corresponded to poorer performance on the RBANS Immediate Memory Index and Delayed Memory Index, r(47) = .46, P = .001 and r(47) = .34, P = .02, respectively. Temporal lobe perfusion was also associated with the RBANS Total Scale Score, r(47) = .44, P < .01. Occipital lobe perfusion was only associated with the RBANS Delayed Memory Index, r(47) = .28, P = .048.

Anxiety and Brain Perfusion

Refer Table 3 for a summary of regression analyses examining the independent effects of anxiety on brain perfusion. After accounting for key medical and demographic variables, the BAI did not demonstrate predictive validity for total brain perfusion (P > .05), although regional analyses showed that the BAI total score emerged as a significant correlate of reduced frontal lobe perfusion (β = -.37, P = .03). No such pattern emerged for the temporal, parietal, or occipital lobe (P > .05).

Anxiety and Cognitive Function

Regression analyses with medical and demographic variables in block 1 and only BAI entered in block 2 showed higher scores on the BAI was associated with worse performance on the RBANS Total Scale Score (ΔF1, 47 = 4.67, P = .04; β = -.35), the RBANS Immediate Memory Index (ΔF1, 47 = 10.39, P < .01; β = -.48), and the RBANS Delayed Memory Index (ΔF1, 47 = 5.71, P = .02; β = -.41). This pattern did not emerge for any of the other RBANS Indices (P > .05). The BAI was not associated with the MMSE (P > .05).

Additive Effects of Anxiety on Brain Perfusion and Cognitive Function

Given the association between anxiety and frontal lobe perfusion, CBF to this lobe was used in the moderation model. Table 4 presents a full summary of regression analyses examining the independent and interactive effects of anxiety and
CBF on cognitive function. Regression analyses showed that the interaction between BAI total score and frontal lobe perfusion emerged as a significant predictor of the MMSE ($b = .29, P = .03$), even after adjustment of age, sex, BDI-II, cardiac index, and diagnostic status of hypertension and T2DM. Increased anxiety and worse frontal lobe perfusion interacted to exacerbate cognitive impairment on the MMSE. Figure 1 displays the synergistic effects of anxiety and perfusion on cognitive function. Specifically, the figure shows that for those individuals with higher levels of within-sample anxiety (ie, 1 SD above the mean of the sample on the BAI), lower CBF demonstrated greater detrimental effects on MMSE performance relative to persons with lower levels of within-sample anxiety (ie, 1 SD below the mean of the sample on the BAI). This association was not present for the RBANS Total Scale Score or any of the RBANS Indices ($P > .05$ for all).

### Anxiety, Brain Perfusion, and Cortical Thickness

To help clarify the neural underpinnings of anxiety and brain perfusion, we examined the effects of these variables on cortical thickness. Anxiety did not demonstrate an association with

### Table 3. Predictive Validity of Anxiety on Brain Perfusion.*

<table>
<thead>
<tr>
<th></th>
<th>Frontal Lobe, $\beta$ (SE $\beta$)</th>
<th>Temporal Lobe, $\beta$ (SE $\beta$)</th>
<th>Parietal Lobe, $\beta$ (SE $\beta$)</th>
<th>Occipital Lobe, $\beta$ (SE $\beta$)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Block 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Age</td>
<td>.19 (0.12)</td>
<td>.01 (0.12)</td>
<td>.07 (0.13)</td>
<td>-.29 (0.17)</td>
</tr>
<tr>
<td>Sex</td>
<td>.19 (2.18)</td>
<td>.08 (2.17)</td>
<td>.28 (2.23)</td>
<td>.27 (2.93)</td>
</tr>
<tr>
<td>BDI-II</td>
<td>-.05 (0.20)</td>
<td>-.22 (0.20)</td>
<td>-.14 (0.21)</td>
<td>-.09 (0.27)</td>
</tr>
<tr>
<td>Cardiac index</td>
<td>.02 (1.84)</td>
<td>.22 (1.83)</td>
<td>.00 (1.88)</td>
<td>.02 (2.48)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>-.16 (2.18)</td>
<td>-.34 (2.17)$b$</td>
<td>-.11 (2.23)</td>
<td>-.20 (2.93)</td>
</tr>
<tr>
<td>T2DM</td>
<td>.02 (3.69)</td>
<td>.08 (3.67)</td>
<td>.01 (3.78)</td>
<td>.15 (4.97)</td>
</tr>
<tr>
<td>$R^2$</td>
<td>.10</td>
<td>.22</td>
<td>.11</td>
<td>.25</td>
</tr>
<tr>
<td>$F$</td>
<td>8.86</td>
<td>2.24 ($P = .056$)</td>
<td>1.03</td>
<td>2.65$^b$</td>
</tr>
<tr>
<td><strong>Block 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BAI</td>
<td>-.37 (.36)$^b$</td>
<td>-.26 (.37)</td>
<td>-.16 (.38)</td>
<td>.14 (.51)</td>
</tr>
<tr>
<td>$R^2$</td>
<td>.18</td>
<td>.26</td>
<td>.13</td>
<td>.26</td>
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<tr>
<td>$F$ for $\Delta R^2$</td>
<td>4.99$^b$</td>
<td>2.68</td>
<td>.87</td>
<td>.79</td>
</tr>
</tbody>
</table>

**Abbreviations:** BAI, Beck Anxiety Inventory; BDI-II, Beck Depression Inventory II; T2DM, type 2 diabetes mellitus; SE, standard error.

$^aN = 55$.

$^bP < .05$.

### Table 4. Interactive Effects of Anxiety and Cerebral Perfusion on Cognitive Function.*

<table>
<thead>
<tr>
<th></th>
<th>Immediate Memory, $\beta$ (SE $\beta$)</th>
<th>Visuospatial, $\beta$ (SE $\beta$)</th>
<th>Language, $\beta$ (SE $\beta$)</th>
<th>Attention, $\beta$ (SE $\beta$)</th>
<th>Delayed Memory, $\beta$ (SE $\beta$)</th>
<th>Total Scale, $\beta$ (SE $\beta$)</th>
<th>MMSE, $\beta$ (SE $\beta$)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Block 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>-.01 (1.83)</td>
<td>.06 (2.33)</td>
<td>.00 (1.68)</td>
<td>-.07 (2.11)</td>
<td>.07 (1.63)</td>
<td>.07 (1.75)</td>
<td>-.33 (0.21)$^b$</td>
</tr>
<tr>
<td>Sex</td>
<td>.21 (3.78)</td>
<td>.05 (4.81)</td>
<td>.31 (3.48)$^b$</td>
<td>.29 (4.36)</td>
<td>.16 (3.37)</td>
<td>.29 (3.60)</td>
<td>.26 (0.43)</td>
</tr>
<tr>
<td>BDI-II</td>
<td>.19 (1.72)</td>
<td>.20 (2.20)</td>
<td>.09 (1.59)</td>
<td>.18 (1.99)</td>
<td>.27 (1.54)</td>
<td>.28 (1.64)$^b$</td>
<td>.10 (0.20)</td>
</tr>
<tr>
<td>Cardiac index</td>
<td>.35 (1.82)$^b$</td>
<td>.08 (2.31)</td>
<td>.01 (1.67)</td>
<td>-.11 (2.10)</td>
<td>.04 (1.62)</td>
<td>.01 (1.73)</td>
<td>.20 (0.21)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>-.19 (3.71)</td>
<td>.06 (4.72)</td>
<td>.30 (3.41)</td>
<td>.21 (4.28)</td>
<td>-.05 (3.30)</td>
<td>.07 (3.54)</td>
<td>.10 (0.42)</td>
</tr>
<tr>
<td>T2DM</td>
<td>.09 (6.65)</td>
<td>-.07 (8.47)</td>
<td>.03 (6.12)</td>
<td>.14 (7.68)</td>
<td>.01 (5.93)</td>
<td>.03 (6.35)</td>
<td>.03 (0.75)</td>
</tr>
<tr>
<td>$R^2$</td>
<td>.28</td>
<td>.06</td>
<td>.16</td>
<td>.14</td>
<td>.10</td>
<td>.19</td>
<td>.23</td>
</tr>
<tr>
<td>$F$</td>
<td>2.89$^b$</td>
<td>.51</td>
<td>1.44</td>
<td>1.18</td>
<td>.86</td>
<td>1.79</td>
<td>2.21 (P = .06)</td>
</tr>
<tr>
<td><strong>Block 2</strong></td>
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<td></td>
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<tr>
<td>Frontal lobe perfusion</td>
<td>.33 (1.57)$^c$</td>
<td>.02 (2.44)</td>
<td>.29 (1.63)$^b$</td>
<td>.20 (2.15)</td>
<td>.40 (1.45)$^c$</td>
<td>.33 (1.64)$^b$</td>
<td>.20 (0.21)</td>
</tr>
<tr>
<td>BAI</td>
<td>-.34 (1.71)$^b$</td>
<td>.11 (2.66)</td>
<td>-.18 (1.78)</td>
<td>-.12 (2.34)</td>
<td>-.28 (1.58) ($P = .06$)</td>
<td>-.21 (1.79)</td>
<td>-.09 (0.23)</td>
</tr>
<tr>
<td>$R^2$</td>
<td>.52</td>
<td>.07</td>
<td>.29</td>
<td>.19</td>
<td>.36</td>
<td>.36</td>
<td>.28</td>
</tr>
<tr>
<td>$F$ for $\Delta R^2$</td>
<td>10.89$^c$</td>
<td>.019</td>
<td>3.82$^b$</td>
<td>1.55</td>
<td>8.67$^c$</td>
<td>5.47$^c$</td>
<td>1.58</td>
</tr>
<tr>
<td><strong>Block 3</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interaction term</td>
<td>-.05 (1.58)</td>
<td>.21 (2.41)</td>
<td>.07 (1.64)</td>
<td>.21 (2.11)</td>
<td>.19 (1.43)</td>
<td>.16 (1.62)</td>
<td>.29 (0.20)$^b$</td>
</tr>
<tr>
<td>$R^2$</td>
<td>.52</td>
<td>.11</td>
<td>.29</td>
<td>.23</td>
<td>.39</td>
<td>.38</td>
<td>.36</td>
</tr>
<tr>
<td>$F$ for $\Delta R^2$</td>
<td>.23</td>
<td>1.90</td>
<td>2.27</td>
<td>2.15</td>
<td>2.12</td>
<td>1.56</td>
<td>4.90$^b$</td>
</tr>
</tbody>
</table>

**Abbreviations:** total, total index; BAI, Beck Anxiety Inventory; BDI-II, Beck Depression Inventory II; T2DM, type 2 diabetes mellitus; interaction term, frontal lobe perfusion $\times$ BAI total score; MMSE, Mini-Mental State Examination.

$^aN = 55$.

$^bP < .05$.

$^cP < .01$. 
We found that greater anxiety was independently associated with poorer cognitive function in multiple cognitive domains. Extant evidence demonstrates anxiety as a negative correlate of cognitive function in patients with severe CVD (eg, heart failure). Anxiety is a prevalent psychiatric comorbidity in the elderly patients\textsuperscript{16} and may increase risk of cognitive decline and/or neurodegenerative disorders. For example, there is an independent association between higher anxiety and future risk of dementia.\textsuperscript{47} These findings are noteworthy in light of the elevated risk of Alzheimer disease in patients with CVD.\textsuperscript{48} Unfortunately, both heightened anxiety and cognitive impairment in older adult CVD populations are both associated with poor treatment adherence and increased mortality risk.\textsuperscript{49-52} In turn, it is possible that synergistic effects of these factors may exacerbate poor outcomes in older adults with and without CVD, and future work should explore this possibility.

The current study is the first to show that greater anxiety exacerbates the effects of cerebral hypoperfusion on cognitive dysfunction in older adults with CVD. There are several possible explanations for these findings. It is possible that increased anxiety may further compromise cerebral autoregulatory mechanisms to exacerbate cognitive impairment through its associated risk for CVD-related factors (eg, hypertension and coronary heart disease).\textsuperscript{53-57} Interestingly, past work correlates greater anxiety with increased white matter disease in patients with CVD and such adverse brain changes are believed to underlie cognitive impairment in this population.\textsuperscript{9,21} A similar phenomenon may be occurring in the current sample, although this awaits empirical test. Alternatively, high levels of glucocorticoids associated with increased stress from anxiety may also lead to cerebral hypoperfusion, brain neurotoxicity, and atrophy to result in poor neurocognitive outcomes.\textsuperscript{48,58,59} Regardless of the etiology, anxiolytic medication and mindfulness therapy help normalize cerebral perfusion levels\textsuperscript{60,61} and future studies should examine whether such treatment corresponds to improved cognitive function in older adults with CVD.

Interestingly, the synergistic effects of anxiety and cerebral hypoperfusion emerged for the MMSE but not for the RBANS. The RBANS demonstrated significant independent associations with both anxiety and cerebral perfusion, and this pattern did not emerge for the MMSE. This is not entirely surprising, as the sample exhibited largely intact cognitive function and subclinical levels of anxiety, and the more comprehensive nature of the RBANS battery (ie, cognitive domain assessment) may have been more sensitive to these subtle deficits. In the context of this premise, anxiety likely did not produce deficits on the RBANS that extended beyond those associated with cerebral hypoperfusion and thus precluded a significant interaction. In contrast, the MMSE lacks sensitivity to subtle brain abnormalities among nondemented older adults.\textsuperscript{62} and the combination of anxiety and cerebral hypoperfusion was necessary in order to reach threshold to negatively impact MMSE scores (ie, anxiety and cerebral hypoperfusion alone was not sufficient for reduced MMSE scores). Future work should employ more thorough assessments of cognitive function to elucidate the effects of anxiety and cerebral perfusion on cognitive function.

**Discussion**

Reduced cerebral perfusion was associated with poorer cognitive function and decreased cortical thickness in this sample of older adults with CVD. These findings are consistent with past work demonstrating the negative impact of cerebral hypoperfusion on cognitive function in patients with CVD in addition to the contributory role of altered cerebral hemodynamics in the pathogenesis of Alzheimer disease, possibly via cortical thinning.\textsuperscript{7,10,45,46} Past work identifies many demographic, clinical, and psychological modifiers of cerebral perfusion in older adults that exacerbate cognitive impairment.\textsuperscript{11-15} The current study suggests that anxiety also interacts with CBF to negatively impact global cognitive status in a representative sample of older adults with CVD. These findings warrant further discussion.

![Figure 1. Anxiety exacerbates the adverse effects of frontal lobe hypoperfusion on cognitive dysfunction. This figure shows that for individuals with higher levels of anxiety, the negative effects of cerebral perfusion on Mini-Mental State Examination (MMSE) scores is exacerbated relative to those with lower levels of anxiety. Lines reflect model specifics and not individual data points. Lower scores on the x-axis are also within-sample z-scores.](Image 44x491 to 281x706)
The current study found a specific association between higher anxiety and reduced perfusion to the frontal lobe. The frontal lobe is comprised of structures that mediate emotion regulation, and anxiety has been suggested to impair such processes via frontal lobe hypoperfusion (eg, anterior cingulate cortex). Insult to the frontal lobe is also linked with impulsivity and poor affective regulation, including heightened anxiety. In turn, it is possible that there is a bidirectional relationship between frontal lobe perfusion and anxiety, and prospective studies are much needed to elucidate the temporal relationship of the current findings. Future work should also clarify the specific frontal lobe structures responsible for the manifestation of anxiety subsequent to cerebral hypoperfusion in older adults with CVD.

Anxiety was not associated with cortical thickness in this sample. Cerebral hypoperfusion is believed to be the primary underpinning of adverse brain outcomes in CVD populations. Indeed, we also found a significant association between reduced lobar perfusion and decreased cortical thickness. It is likely that the subclinical levels of anxiety in this sample of participants did not disrupt cerebral hemodynamics beyond a necessary threshold to produce additive insult on the brain. Prospective studies in patients with more severe levels of anxiety and CVD are needed to clarify the effects of anxiety symptomatology on the cerebral structure.

The current findings are limited in several ways. As noted previously, the present study consisted of cross-sectional data, and future studies should employ longitudinal designs to confirm our findings and determine whether anxiety accelerates poor neurocognitive outcomes in older adults with CVD. Indeed, it is possible that anxiety is a neuropsychiatric consequence stemming from cerebral hypoperfusion and subsequent brain injury. However, independent of the etiology of anxiety, the physiological response to anxiety (eg, elevated heart rate and glucocorticoids) may also negatively impact cognitive function over time. Case-controlled longitudinal studies are much needed to help elucidate the exact mechanisms underlying the associations among anxiety, brain perfusion, and cognitive function, as well as examine the role of psychotropic and CVD medication in these relationships.

The current study used the BAI to assess anxiety symptomatology, which is a widely used and psychometrically sound instrument. However, its self-report nature may introduce possible biases, and future studies that employ objective measures of anxiety (eg, semistructured interviews) and measure serum levels of cortisol are needed to clarify our findings. The current sample is relatively homogenous, and future studies with more diverse samples are needed to validate the effects of anxiety on neurocognitive function in patients with CVD. Likewise, the relatively modest sample size of the current study may have precluded necessary power to detect small effects, and future studies with larger samples are much needed to confirm our findings.

Conclusions

In brief summary, the current study shows that higher anxiety exacerbates the adverse effects of cerebral hypoperfusion on cognitive dysfunction in older adults with CVD. Prospective studies are needed to clarify directionality of the current findings and determine whether treatment of anxiety corresponds to improved neurocognitive outcomes in older adults with CVD.

Declaration of Conflicting Interests

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