Microvascular Endothelial Function and Neurocognition among Adults with Major Depressive Disorder

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Abstract

Background: Cardiovascular risk factors (CVRFs) and endothelial dysfunction have been associated independently with poorer neurocognition in middle-age adults, particularly on tests of frontal-lobe function. However, to our knowledge, no studies have examined markers of microvascular dysfunction and neurocognition or the potential interaction between macro and microvascular biomarkers on neurocognition. Therefore in a secondary analysis of a previously reported clinical trial, we examined this association in adults with major depressive disorder (MDD) in middle-aged and older adults.

Methods: Participants included 202 adults with MDD and not receiving mental health treatment. Microvascular endothelial function was assessed using a non-invasive marker of forearm reactive hyperemia velocity while macrovascular endothelial function was assessed using flow mediated dilation (FMD) of the brachial artery. CVRFs were assessed using the Framingham Stroke Risk Profile and fasting lipid levels. A standardized neurocognitive assessment battery was used to assess three cognitive domains (Executive Function, Working Memory, and Verbal Memory).

Results: Greater microvascular dysfunction was associated with poorer neurocognition across all three domains. In multiple regression analyses, microvascular function continued to predict Verbal Memory performance after accounting for background factors and CVRFs. Macro and microvascular function interacted to predict Working Memory performance ($F = 4.51_{1, 178}$, $P = .035$), with a similar non-significant association for Executive Function ($F = 2.73_{1, 178}$, $P = .095$), with moderate associations observed between microvascular function and neurocognition in the presence of preserved FMD ($r_{61} = 0.40$, $P = .001$), but not when FMD was impaired ($r_{63} = -0.05$, $P = .675$).

Conclusions: Greater microvascular dysfunction is associated with poorer neurocognition among middle-aged and older adults. This association was strongest in participants with preserved

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macrovascular function, suggesting that it may provide a sensitive correlate of neurocognition that is superseded by systemic vascular dysfunction.

INTRODUCTION

Cardiovascular risk factors (CVRFs) and subclinical vascular disease are increasingly recognized as important contributors to cognitive decline and incident dementia.(1) CVRFs, particularly hypertension, are among the most modifiable risk factors for Alzheimer's disease and vascular dementia.(2) In addition, CVRFs have been associated with subclinical cognitive decrements far preceding the development of clinically significant cognitive impairment. (3-7) Although the precise mechanisms underlying the association of CVRF and cognitive impairment have not been fully elucidated, microvascular disease has been suggested to play a central role in the pathogenesis of vascular cognitive impairment,(8) and recent studies have therefore begun to incorporate peripheral microvascular markers as predictors of neurocognitive performance.(9, 10)

Growing evidence suggests that peripheral markers of vascular dysfunction, including endothelial dysfunction, are associated with cognitive performance among middle-aged (11-13) and older adults (9, 14) with CVRFs. These associations may be particularly relevant for depressed adults, who exhibit a higher incidence of microvascular dysfunction (15, 16) and cognitive impairment (17). Peripheral markers of vascular dysfunction have been shown to be most closely associated with performance on cognitive tests of frontal-lobe functioning, including executive function and working memory.(11, 18, 19) Moreover, available evidence suggests that subtle impairments in endothelial dysfunction mediate the observed associations between CVRF and cognitive impairment among middle-aged adults. (11) In addition, preliminary evidence suggests that the influence of microvascular function on neurocognition may be moderated by systemic, macrovascular function, which may supersede the impact of microvascular dysfunction in some domains of cognitive function. (20) To our knowledge, no studies have examined the association between peripheral markers of microvascular dysfunction and cognitive performance. We previously reported that CVRFs and biomarkers of atherosclerosis were associated with impaired executive function and working memory (11, 12), as well as MRI markers of microvascular dysfunction (21), and that FMD mediated these associations. In the present study, we examined the association between microvascular dysfunction and neurocognition, as well as the potential influence of macrovascular function in a convenience sample of middle-aged and older adults with major depressive disorder and comorbid CVRFs. Specifically, we utilized data from the SMILE-II randomized trial: a 4-month randomized, parallel group, placebo-controlled trial of exercise and sertraline treatment for MDD.(22) Results revealed that aerobic exercise treatment was associated with comparable improvements in depression outcomes compared with Sertraline.(22) In addition to examining treatment changes in depression, measures of neurocognition were also obtained, although neurocognition did not improve with treatment.(23)

METHODS

The present study represents a secondary, post hoc analysis of novel microvascular endothelial markers and neurocognition from participants in the previously published SMILE-II randomized trial.(11, 21-24) We have previously examined markers of subclinical vascular disease and neurocognition (11, 21) in this cohort and the present study extends these findings by examining a novel, recently validated marker of microvascular functioning (25) that was unavailable at the time of our original analyses.(11) As described previously, (11, 22) participants were recruited between October 2000 and November 2005. In addition to the presence of MDD, eligibility criteria included age 40 years, not currently exercising, and no current psychiatric treatment. Exclusion criteria included the presence of another primary psychiatric diagnosis, such as a history of bipolar disorder or psychosis; and medical comorbidities that would preclude participation in the trial. All participants provided written informed consent and the protocol was approved by the Institutional Review Board at Duke University Medical Center. All data in the present analyses were taken from baseline assessments, collected 1-2 weeks prior to randomization.

Neurocognitive Performance

Details of our neurocognitive test battery have been reported in our prior publications utilizing neurocognitive outcomes from SMILE-II. (11, 23) Briefly, participants completed a neuropsychological test battery in order to assess performance in the domains of Executive Function and Psychomotor Speed. Neurocognitive tests were selected for the availability of multiple test versions, well-established psychometric properties, and accepted clinical utility.

Executive Function subtests included the Trail Making Test (B-A),(26) the Stroop Test (Word, Color, and Color-Word sections),(27) the Verbal Paired Associates test,(28) the Controlled Oral Word Association Test (COWAT),(29) the Digit Span test,(28) and the Verbal Fluency Test (Animal Naming).(29, 30) Psychomotor Speed subtests included the Ruff 2 & 7 Test,(31) and the Digit Symbol Substitution Test.(32) In addition, both the Stroop Test and the COWAT also loaded on our Psychomotor Speed variable. Details regarding the administration and scoring of these tests are provided elsewhere.(11, 23)

Cardiovascular Risk Factors

Details regarding the assessment of CVRFs have been previously reported.(11, 33) Briefly, our primary measure of CVD risk factors used the Framingham Stroke Risk Profile (FSRP), a risk assessment tool used to assess the 10-year incidence of stroke using systolic blood pressure, use of antihypertensive therapy, diabetes mellitus, cigarette smoking, cardiovascular disease, and atrial fibrillation.(34) (35) Because age served as a covariate in our final analyses, it was not included in calculating FSRP scores. We also included the more contemporary Atherosclerotic Disease Risk Score (ASCVD) in our cross-sectional analyses. (36).

Cardiovascular and Microvascular Biomarker Assessments

As previously reported, multiple measures of subclinical vascular disease were collected.(11, 33)

Flow mediated dilation (FMD) of the brachial artery was used to quantify both systemic, macrovascular dysfunction (FMD) and microvascular dysfunction (hyperemic velocity). FMD was assessed in the morning, after overnight fasting. Longitudinal B-mode ultrasound images of the brachial artery, 4 to 6 cm proximal to the antecubital crease, were obtained using an ultrasound platform (Aspen, Mountain View, CA) with a 10-MHz linear array transducer. Images were obtained after 10 minutes of supine relaxation and during reactive hyperemia, induced by 5 minutes of inflation of a pneumatic occlusion cuff placed around the forearm to a supra-systolic pressure (200 mm Hg). End-diastolic images were stored to a magnetic-optical disk and arterial diameters were measured as the distance between the proximal and distal arterial wall intima-media interfaces, using PC-based software (Brachial Analyzer Version 4.0, Medical Imaging Applications LLC, Iowa City, IA). Peak FMD response was assessed from 10 to 120 seconds post deflation of the cuff, with peak arterial diameter quantified using polynomial curve fitting. FMD, used as our measure of macrovascular function, was defined as the maximum percent change in arterial diameter relative to resting baseline.

Microvascular function was determined using hyperemic velocity change during FMD, which has recently been validated as a peripheral marker of systemic microvascular functioning.(25, 37) Pulsed Doppler flow signals in the brachial artery were recorded at baseline and for up to 15 seconds after cuff release. The velocity-time integral for baseline and reactive hyperemia was based upon the mean of triplicate pulsed-Doppler flow tracings recorded at each of these phases. Hyperemic velocity was derived by dividing the velocity-time integral by the inter-beat interval, and hyperemic flow was calculated from hyperemic velocity and brachial artery cross-sectional area.

Statistical Analyses

All analyses were performed in SAS 9.4 (Cary, NC). In order to minimize the number of statistical tests, we first combined subtests into domains to create a unit-weighted composite score, the details of which we have previously published.(11) In order to examine the independent association between CVRFs, microvascular function, and neurocognition, we first examined the unadjusted correlations between neurocognition and markers of microvascular function. We then conducted hierarchical regression analyses, in which 1) markers of microvascular function, 2) demographic characteristics, and 3) CVRFs (including HDL, LDL, BMI, and FSRP) were entered sequentially. We also examined the potential interaction between microvascular function (hyperemic velocity % change) and FMD on neurocognition in a secondary, exploratory step. Assumptions regarding linearity, additivity, and distribution of residuals were assessed and found to be adequate. All statistical tests were based on two-tailed probability values.

RESULTS

Participants

Four hundred fifty-seven participants were screened, of whom 202 met MDD inclusion criteria and were randomized. As shown in Table 1, participants were generally middle-aged

and Caucasian, with relatively few CHD risk factors. Approximately one-third of participants were taking either antihypertensive or lipid lowering medications.

Correlates of Microvascular Function

As shown in Table 2, impaired microvascular function was associated with multiple demographic and CVD risk factors, including greater age, male gender, ASCVD and Framingham stroke risk scores, SBP, DBP, and lower HDL.

Microvascular Function and Neurocognitive Performance

Examination of microvascular assessments and neurocognition demonstrated that poorer microvascular function was associated with poorer neurocognition across all domains in unadjusted analyses. Specifically, greater hyperemic velocity change was associated with better Verbal Memory ($r_{199} = 0.18$, P = .011), Executive Function ($r_{199} = 0.17$, P = .017), and Working Memory ($r_{199} = 0.15$, P = .031).

In order to examine the independent association between microvascular function after accounting for demographic and clinical characteristics, we conducted hierarchical regression models within each cognitive domain. As shown, hyperemic velocity was associated with better neurocognition across domains after controlling for baseline velocity. Accounting for demographic and CVD risk factors impacted the pattern of results differently depending on the domain. For Working Memory and Executive Function, the observed associations between hyperemic velocity and neurocognition were largely attenuated after accounting for demographic characteristics and completely attenuated after further controlling for CVD risk factors. In contrast, examination of Verbal Memory performance revealed that the association with hyperemic velocity was not only robust but tended to strengthen after controlling for demographic characteristics and CVD risk factors. Indeed, in contrast to Executive Function and Working Memory, Verbal Memory performance was more strongly associated with hyperemic velocity response than either age or CVD risk, both of which were strongly associated with performance in other cognitive domains (Table 3).

Interaction of Macro and Microvascular Function on Neurocognition

In exploratory analyses of potential interactions between hyperemic velocity change and FMD, we found that the association between microvascular function and Working Memory was moderated by FMD ($F = 4.51_{1, 178}$, P = .035), with a similar non-significant association for Executive Function ($F = 2.73_{1, 178}$, P = .095). Examination of this interaction revealed microvascular function was moderately associated with Working Memory ($r_{61} = 0.40$, P = .001 in highest FMD tertile) only among individuals with preserved FMD, whereas impaired FMD superseded any association between microvascular function and neurocognition ($r_{63} = -0.05$, P = .675 in lowest FMD tertile) (Figure 2). A similar association was observed for Executive Function, for which microvascular function was moderately associated ($r_{61} = 0.34$, P = .006) with neurocognition, but impaired FMD superseded this association ($r_{63} = -0.04$, P = .737 in lowest FMD tertile). In contrast, we found no evidence that the association between microvascular function and Verbal Memory was moderated by FMD (($F = 0.09_{1, 178}$, P = .759)

DISCUSSION

Results from the present study suggest that a novel marker of peripheral microvascular function was associated with cognitive function, with the strongest associations observed with verbal memory. The associations between microvascular function and tests of frontal lobe function were largely mediated through greater age and CVRFs, whereas microvascular function was the factor most strongly associated with verbal memory performance. In addition, we found that macrovascular and microvascular function may interact to predict performance on frontal lobe tests, such that the association between microvascular function and neurocognition is eclipsed by systemic macrovascular dysfunction. However, among individuals with preserved macrovascular function, microvascular function was moderately associated with performance, suggesting it may provide important prognostic information in the earliest stages of CVD progression. These findings extend previous work demonstrating an association between peripheral markers of endothelial function and cognitive performance by demonstrating that markers of conduit artery function are more strongly associated with frontal lobe performance, whereas microvascular markers were more strongly associated with memory performance.

The present findings extend our prior work demonstrating that conduit artery assessments of endothelial function are associated with performance on cognitive tests assessing executive function and working memory, which we previously observed in patients with MDD (11) and hypertension.(12) These findings have subsequently been replicated, with systematic literature reviews demonstrating that flow-mediated dilation (FMD), a marker of endothelial function,(13, 38) demonstrates consistent inverse associations with frontal-lobe dependent test performance.(39) Consistent with the present findings, prior studies have reported that flow-mediated dilation is not related to memory performance,(39) despite numerous recent studies demonstrating that endothelial dysfunction is commonly observed among individuals with Alzheimer's disease (8, 9, 40-42) and may play an important role in the pathogenesis of neurodegeneration. (8, 43, 44)

The finding that CVRFs and conduit artery endothelial function are more closely associated with frontal-lobe dependent tests may reflect the differing arterial distribution to neurocircuitry subserving these distinct neurocognitive functions. (45, 46) Executive function and working memory subtests are particularly reliant on subcortical-cortical functional connections, including projections between 'watershed' brain regions including the anterior cingulate,(47, 48) ventral striatum,(49) and dorsolateral prefrontal cortex.(50) Due to the relative lack of arterial redundancy in these regions, it is possible that they are more susceptible to perturbations in cerebral autoregulation or perfusion compared to mesial temporal lobe regions subserving memory functions, such as the hippocampal gyrus. Microvascular endothelial dysfunction has been shown to differentiate from macrovascular function to cause target organ damage in other disease processes.(37, 51) This is consistent with the finding that only memory performance was robustly associated with our most sensitive endothelial marker of microvascular function.

Limitations. The present study must be viewed with several limitations in mind. First, this was a cross-sectional analysis and future longitudinal studies are needed to replicate the

observed pattern of findings. Second, we did not collect additional markers of microvascular disease, such as neuroimaging markers of white matter damage or ankle-brachial pressure indices. It should therefore be noted that, although our marker of microvascular endothelial function has been validated in other samples,{Dubin, 2016 #84114} future studies should attempt to further delineate peripheral markers of microvascular and macrovascular endothelial functioning. Finally, our study used a convenience sample of adults with MDD participating in an exercise and pharmacological intervention, such that individuals with ortopaedic comorbidities, taking psychotropic medications, engaging in exercise were excluded. It is therefore unclear to what extent the observed associations would be observed in a more representative sample of older adults with.

In conclusion, our findings extend prior work demonstrating that subtle perturbations in microvascular function may provide important information on risk of cognitive impairment. Future studies should attempt to replicate the present findings in larger, prospective studies utilizing sensitive neuroimaging markers. If replicated, peripheral markers of microvascular disease could represent a potential treatment target in efforts to reduce risk of vascular cognitive impairment.

Acknowledgments

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Highlights:

- The present findings are the first to demonstrate an association between peripheral microvascular endothelial function and neurocognition among adults with major depressive disorder

- These findings extend previous findings by demonstrating an interaction between systemic vascular dysfunction and microvascular disease on neurocognition

- Findings suggest that microvascular dysfunction is more closely associated with some aspects of neurocognition, including memory performance, than chronological age
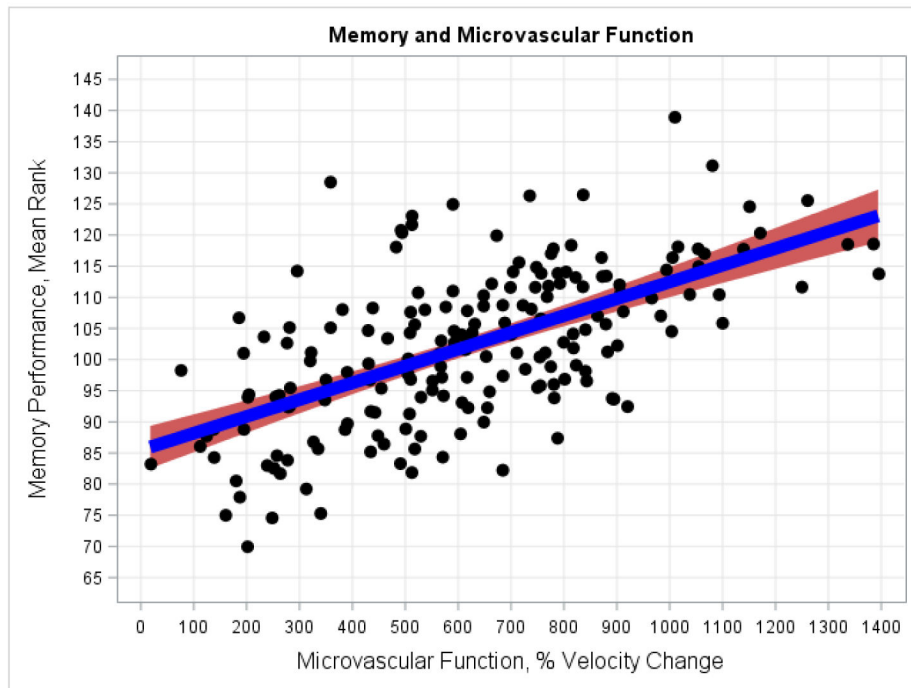
Figure 1.

Microvascular function and Verbal Memory performance. As shown, greater microvascular function was associated with better Verbal Memory performance after accounting for background characteristics and CVRFs.
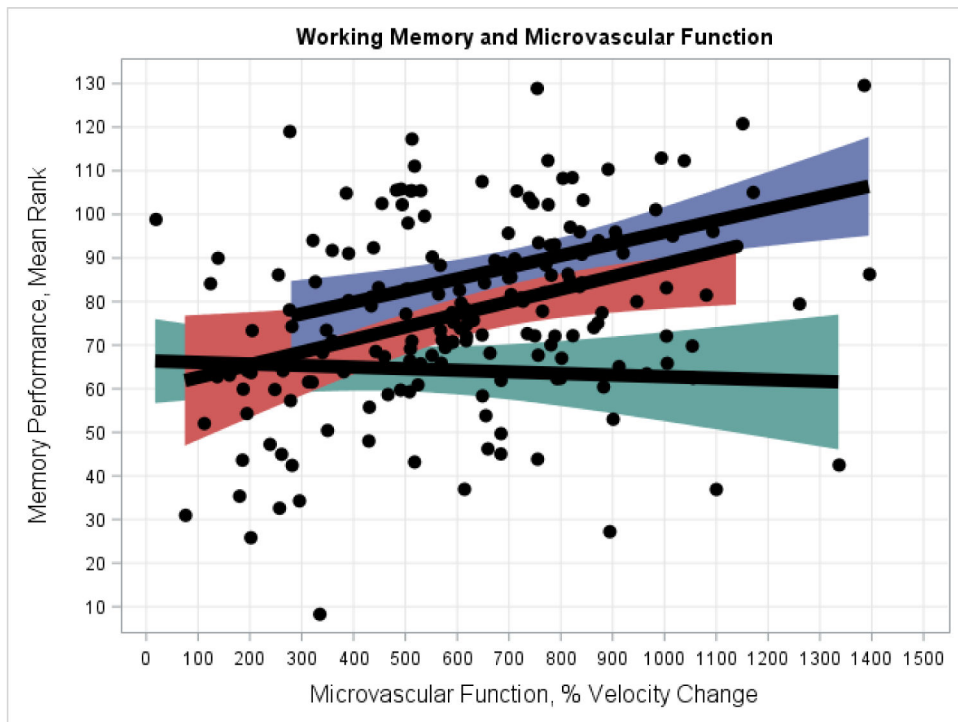
Figure 2.
Interaction between FMD and microvascular function predicting Working Memory performance. As shown, the association between microvascular function and Working Memory varied by FMD level, with the strongest associations observed among individuals with preserved FMD. In contrast, individuals with impaired FMD showed no association with microvascular function: highest FMD tertile (blue: r = 0.40, P = .001), middle FMD tertile (red: r = 0.31, P = .022), and lowest FMD tertile (green: r = −0.05, P = .675).

Table 1.

Background and demographic characteristics of the sample.

Variable	Cohort (n = 202)
Age, years	51.7 (7.6)
Female Gender, n (%)	153 (76)
Race, n (%) Black Caucasian Other Ethnicity	52 (26) 137 (68) 13 (6)
Hamilton Rating Scale for Depression	16.8 (4.3)
Antihypertensive Medications, n (%)	47 (32)
Diabetes, n (%)	14 (7)
Current Tobacco Use, n (%)	32 (16)
Systolic Blood Pressure, mm Hg	124 (17)
Diastolic Blood Pressure, mm Hg	79 (9)
Lipid-Lowering Medications, n (%)	19 (9)
Total Cholesterol, ng/ml	207 (40)
High Density Lipoprotein, ng/ml	57 (16)
Low Density Lipoprotein, ng/ml	122 (34)
Flow-Mediated Dilation, %	5.9 (4.3)
Intima Medial Thickness, mm	0.63 (0.13)
ASCVD Risk Score, 10-year % Risk	4.7 (6.1)
Framingham Stroke Risk Profile	3.9 (2.4)
Hyperemic Velocity Change, %	728 (339)

Table 2.

Associations between background characteristics microvascular function. Values represent unadjusted correlations between each variable and hyperemic velocity (degrees of freedom = 199).

Variable	Hyperemic Velocity %
Age	−0.29[**]
Male Gender	−0.13[†]
Framingham Stroke Risk Score	−0.41[**]
ASCVD Risk Score	−0.43[**]
Systolic Blood Pressure	−0.40[**]
Diastolic Blood Pressure	−0.21[**]
High-Density Lipoprotein	0.14[*]
Low-Density Lipoprotein	−0.07
Intima Medial Thickness	−0.21[**]
Flow Mediated Dilation	0.33[**]

[†]P<.10

[*]P<.05

[**]P<.01

Table 3.

Hierarchical regression models demonstrating the associations between hyperemic velocity change and neurocognition. Values represent standardized regression coefficients. HRSD = Hamilton Rating Scale for

Predictor	Model 1	Model 2	Model 3
Working Memory			
Age	------	−0.30[**]	−0.28[**]
Education	------	0.41[**]	0.33[**]
Gender	------	−0.01	0.01
HRSD	------	0.11[†]	0.09
HDL	------	------	0.05
LDL	------	------	0.03
Framingham Stroke Risk	------	------	−0.18[*]
Base Velocity	0.19[*]	0.17[*]	0.14[†]
Hyperemic Velocity %	0.25[**]	0.15[†]	0.06
Executive Function			
Age	------	−0.44[**]	−0.43[**]
Education	------	0.30[**]	0.23[**]
Gender	------	−0.09	−0.05
HRSD	------	0.05	0.03
HDL	------	------	0.09
LDL	------	------	0.08
Framingham Stroke Risk	------	------	−0.16[*]
Base Velocity	0.22[**]	0.17[*]	0.14[†]
Hyperemic Velocity %	0.28[**]	0.11	0.03
Verbal Memory			
Age	------	0.00	0.06
Education	------	0.23[**]	0.20[**]
Gender	------	−0.03	−0.04
HRSD	------	−0.01	−0.01
HDL	------	------	−0.08
LDL	------	------	−0.03
Framingham Stroke Risk	------	------	0.08
Base Velocity	−0.05	−0.06	−0.04
Hyperemic Velocity %	0.15[†]	0.15[†]	0.21[*]

Depression; HDL = high density lipoprotein; LDL = low density lipoprotein.

[†]P<.10

[*]P<.05

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