Brain Function Is Linked to LDL Cholesterol in Older Adults with Cardiovascular Risk

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OBJECTIVES: To determine how cardiovascular risk is associated with working memory task performance and task-related suppression of default-mode network (DMN) activity in cognitively intact older adults.

DESIGN: A cross-sectional functional magnetic resonance imaging study of older adults with cardiovascular risk factors.

SETTING: Rotman Research Institute, Baycrest Health Sciences.

PARTICIPANTS: Thirty older adults with cardiovascular risk factors.

MEASUREMENTS: Participants provided health information and a blood sample, and underwent functional magnetic resonance imaging during a working memory task and during a breath-hold task to assess cerebrovascular reactivity.

RESULTS: Higher plasma low-density lipoprotein cholesterol (LDL-C) was associated with poorer working memory task performance ($P = 0.008$) and reduced task-related DMN suppression ($P = 0.005$). A composite index of cardiovascular risk, the Framingham General Cardiovascular Risk Profile, showed no associations with task performance or task-related DMN suppression. These findings were independent of white matter burden and cerebrovascular reactivity and thus cannot be accounted for by individual differences in neurovascular health.

CONCLUSION: These findings suggest a deleterious effect of elevated LDL-C on working memory task performance and task-related DMN suppression in older adults with cardiovascular risk. The relations between the Framingham General Cardiovascular Risk Profile, cognitive task performance, and DMN function require further study. J Am Geriatr Soc 65:e51–e55, 2017.

Key words: cognition; aging; imaging; default-mode network; Framingham General Cardiovascular Risk Profile

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Cardiovascular disease risk factors (CVRFs) like hypertension, type 2 diabetes (T2DM), and hypercholesterolemia are highly prevalent and comorbid in older adults, and increase risk of cognitive decline and dementia.[1] While the links between cardiovascular risk and dementia are complex and multifaceted, long-standing metabolic dysfunction in particular (e.g., insulin resistance, elevated cholesterol) contributes to Alzheimer disease (AD) pathology.[2,3] More generally, CVRFs increase oxidative stress and inflammation and tend to "accelerate" brain pathology associated with normal aging.[4,5] A number of studies[1,5,6] suggest that these risk factors in midlife are particularly detrimental to later-life cognitive decline, due to the accumulation of damage related to long-standing metabolic and vascular dysfunction.

The default-mode network (DMN) is of particular interest toward understanding the links between cardiovascular risk and dementia, since DMN integrity is linked closely with cognition, and DMN dysfunction is strongly implicated in the cognitive changes associated with normal aging and AD.[7] Notably, failure to suppress the DMN during cognitive tasks (reflecting inefficient allocation of attentional resources away from the DMN and toward task-related brain regions) has been linked to poorer task performance and is progressively affected on the spectrum of normal aging to AD.[8,9] A number of recent studies have shown that resting-state DMN function is disrupted in individuals with CVRFs, in a similar way to the pattern of

dysfunction seen in normal aging and AD;[10–12] however, only one study has shown reduced task-related DMN suppression in T2DM.[13]

One of the challenges inherent in studying CVRFs is their high comorbidity. Moreover, there is some evidence to suggest that the combined effect of multiple CVRFs may be "more than the sum of the parts."[14] This makes composite risk indices like the Framingham General Cardiovascular Risk Profile[15] (FramRisk) appealing; beyond eliminating the need to disentangle the individual effects of each CVRF, they can account for a number of CVRFs in one metric and as such may provide a more accurate estimate of overall cardiovascular burden. Studies that have examined cognition or brain function in relation to composite indices of cardiovascular risk have found elevated Framingham scores to be associated with reduced resting cerebral blood flow and glucose metabolism in a number of DMN and prefrontal regions,[16,17] as well as poorer performance on tests of attention and executive function.[6,18] We found that the presence of multiple CVRFs over just one affected cerebrovascular reactivity across DMN regions.[19]

The present study examined task-induced DMN suppression in cognitively intact older adults with CVRFs. We collected blood oxygenation level dependent (BOLD) functional magnetic resonance imaging (fMRI) data during a working memory task, and used independent component analysis to identify the DMN. The 2-back working memory task was selected for study because executive/attentional processes are often affected in those with CVRFs.[6,18] We examined associations between task performance, task-related DMN suppression, and two indices of cardiovascular risk: (1) FramRisk, a composite risk score reflecting the probability that an individual will develop cardiovascular disease over a 10-year period; and (2) plasma low-density lipoprotein cholesterol (LDL-C). LDL-C was considered separately as an indicator of cardiovascular risk in accordance with its exclusion in current (but not previous) versions of the Framingham algorithm,[20] and based on guidelines[21,22] that call for close monitoring of LDL-C in primary care settings, particularly for individuals at higher cardiovascular risk (i.e., individuals with hypertension and/ or T2DM). We hypothesized that higher cardiovascular risk would be associated with poorer task performance and reduced suppression of the DMN during task.

METHODS

Participants

Thirty right-handed adults between 65 and 85 years of age with hypertension or T2DM were recruited using an internal participant database and advertisements. Demographic, medical, and cognitive questionnaires (Telephone Interview for Cognitive Status[23]) were completed over the telephone. Hypertension criteria were: >2-year self-reported history of hypertension and >2-year history of treatment with long-acting antihypertensive medications. T2DM criteria were >2-year self-reported history of non-insulin-dependent diabetes, treated with diet alone or with hypoglycemic medication. Exclusion criteria included the presence of any other significant medical, neurological, or psychiatric disorder, or any major diabetic complications (e.g.,

retinopathy, nephropathy, and neuropathy). In addition, based on neuropsychological assessment, we excluded those who scored more than 1.5 standard deviations below their estimated IQ on two or more tests within the same domain, as our interest was whether cardiovascular risk affects task performance or DMN function before individuals experience cognitive deficits. Further details regarding exclusion criteria can be found in the Appendix S1. The study was approved by the Research Ethics Board at Baycrest and all participants provided written informed consent.

Cognitive and Health Assessment

In session 1, participants completed a comprehensive neuropsychological assessment, and provided a fasting blood sample to measure glucose, total cholesterol, plasma high-density lipoprotein cholesterol (HDL-C), and LDL-C. All blood analyses were carried out at Mt. Sinai Hospital, Toronto, ON. We also measured blood pressure (BpTRU Medical Devices) as the average of four readings taken after participants had been sitting quietly for 5–10 minutes.

Functional Imaging Tasks and Imaging Parameters

In session 2, BOLD fMRI was acquired during a 2-back working memory task and a breath-hold task. Because the BOLD signal is sensitive to changes in cerebrovascular function associated with normal aging as well as metabolic and vascular dysfunction,[24] the breath-hold task was used to provide an index of cerebrovascular reactivity. Both tasks were administered using E-Prime 2.0 (Psychology Software Tools, Pittsburgh, PA). We also collected high-resolution structural images, and fluid attenuation inversion recovery (FLAIR) images to assess white matter hyperintensity (WMH) burden. Further details regarding the task parameters and the imaging parameters can be found in the Appendix S1.

Image Preprocessing

Preprocessing and analysis of the working memory BOLD data was carried out using probabilistic Independent Component Analysis (ICA) in FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). See Appendix S1 for further details. The spatial map representing the DMN (i.e., the spatial map which included medial and lateral parietal regions and a midline frontal region, most prominently) was identified by group ICA. Then, the group DMN was used as a spatial mask input into a "spatial-temporal" dual regression procedure to produce subject-specific DMN maps. Preprocessing of the breath-hold task to generate participant-specific cerebrovascular reactivity maps and preprocessing of the FLAIR images to determine white matter hyperintensity volumes for each participant are described elsewhere.[25,26]

Statistical Analysis

Statistical analyses were performed using R (ver. 3.1.1; R Core Team, 2014). FramRisk was calculated directly from the Cox model formula,[15] which considers age, total

cholesterol and HDL-C, systolic blood pressure, hypertension treatment status, smoking status, and T2DM status. Task performance on the working memory task was defined as discrimination (hits minus false alarms). To index task-related DMN suppression, activity across the entire DMN was extracted using each subject's normalized spatial map output from the dual regression procedure. To index cerebrovascular reactivity across the DMN, the group DMN map was applied to each participant's cerebrovascular reactivity map. Prior to analysis, task-related DMN suppression was regressed onto white matter hyperintensity burden and cerebrovascular reactivity, to account for variance in BOLD activity associated with neurovascular health. The residuals from this model were entered as the dependent variables in the regression models described below.

To examine associations between working memory task performance, task-related DMN suppression, and cardiovascular risk, we constructed two regression models. In the first model, task performance was regressed onto FramRisk and LDL-C. In the second model, task-related DMN suppression was regressed onto FramRisk and LDL-C. In both models, age was included as a covariate. Education was not significantly associated with any of the variables in the models and was therefore removed. We used robust regression implemented through the robust-base package in R to weight each observation based on the extent to which it was an influential case. We also ran a partial correlational analysis, accounting for the effects of age to verify the expected association between task-related DMN suppression and task performance. Correction for multiple comparisons across all three models was carried out using the Holm-Šídák procedure.

RESULTS

Study Sample Characteristics

Demographic and clinical variables are detailed in Table 1. All participants had medication-controlled hypertension. Thirteen participants also had T2DM and all but two were on hypoglycemic medication. Sixteen participants were on lipid-lowering medications (8 with hypertension and 8 with hypertension and T2DM). All were on a statin (atorvastatin, n = 8; rosuvastatin, n = 6; simvastatin, n = 2), with three participants also on an adjunct medication (fenofibrate, n = 1; ezetimibe, n = 2).

Seventeen participants had FramRisk scores within the high-risk range (>0.20; Mean = 0.32, SD = 0.07), including nine individuals with hypertension (4 of whom were also on cholesterol medication) and eight individuals with hypertension and T2DM (5 of whom were also on cholesterol medication). Mean FramRisk for the remaining participants was 0.14 (SD = 0.05), which is considered to be moderate risk. This group included eight individuals with hypertension (4 of whom were also on cholesterol medication) and five individuals with hypertension and T2DM (3 of whom were also on cholesterol medication).

Two-thirds of participants (n = 20) had LDL-C levels above the recommended target of 2 mmol/L for those at moderate to high risk of cardiovascular disease. In contrast, only nine participants had total cholesterol levels in

the borderline-high or high range, while only another two had low HDL-C levels (>5.2 and <1 mmol/L, based on standard guidelines). Among these individuals, only three had a total cholesterol/HDL-C ratio higher than recommended (>4). Since total cholesterol and HDL-C are the metrics used to calculate Framingham risk, it was our impression that variability in LDL cholesterol in the present sample was not being captured by the Framingham algorithm. This is consistent with the finding of no association between FramRisk and LDL-C ($r = 0.07$, $P = 0.70$), and low multicollinearity within the regression models (variance inflation factors ~1).

DMN Characterization

The DMN included medial and lateral parietal and temporal regions, as well as a small region in the right anterior cingulate and medial frontal gyrus (Figure S1). Importantly, reduced DMN suppression during the 2-back task was associated with poorer task performance ($r = -0.41$, $P = 0.03_{corrected}$).

Cardiovascular Risk, Task Performance, and Task-Induced DMN Suppression

The regression model examining the association between 2-back task performance and cardiovascular risk showed that LDL-C ($P = .008$), but not FramRisk, was predictive of poorer performance (Table 2A). The second regression model examining the association between task-related DMN suppression and cardiovascular risk showed that higher LDL-C was associated with reduced DMN suppression ($P = 0.005$; Table 2B). There were no associations between FramRisk and task-related DMN suppression.

Table 1. Demographic and Clinical Information

	Mean (SD) n = 30	Range
Age	72.2 (5.7)	65–83
Sex (male/female)	14/16	
Education (years)	15.6 (2.9)	11–21
Duration of hypertension (years)	10.2 (6.7)	3–25
Duration of type 2 diabetes (years)	11.2 (6.8)	2–22
Duration of cholesterol treatment (years)	9.0 (5.3)	1–22
Shipley Vocabulary (T score)	58.8 (6.5)	45–76
WASI Matrix Reasoning (T score)	61.2 (8.5)	42–75
BMI (kg/m^2)	26.1 (2.5)	21.0–29.8
Systolic blood pressure (mmHg)	133.1 (17.1)	100–168
Diastolic blood pressure (mmHg)	74.8 (10.3)	61–92
Fasting glucose (mmol/L)	6.1 (1.2)	4.8–8.8
HbA1c (%)	6.2 (.73)	4.8–7.6
Total cholesterol (mmol/L)	4.7 (1.2)	3.1–7.7
HDL-C (mmol/L)	1.6 (0.4)	0.9–2.8
LDL-C (mmol/L)	2.4 (1.0)	0.8–4.7
Volume – WMH (cc)	2.2 (4.1)	0–17.8
2-back discrimination (%)	0.66 (0.14)	0.3–0.9

WASI = Wechsler Adult Scale of Intelligence; BMI = body mass index; HbA1c = hemoglobin A1C; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; WMH = white matter hyperintensities.

Table 2. Regression Analyses

Model	Dependent Variable	Predictors	b	95% CI	P
A	2-back task performance	Age	−0.002	−0.01 to 0.01	0.65
		FramRisk	0.19	−0.29 to 0.67	0.41
		LDL-C	−0.08	−0.14 to −0.02	0.008
B	2-back DMN suppression	Age	−0.02	−0.04 to 0.01	0.16
		FramRisk	0.74	−0.56 to 2.05	0.25
		LDL-C	0.23	0.08 to 0.38	0.005

DMN = default mode network. Full model statistics: (A) R^2adj = 0.22, $F(3, 29)$ = 10.69, P = 0.03; (B) R^2adj = 0.20, $F(3, 29)$ = 10.77, P = 0.03. Note: the P-value for each full regression model reflects correction for multiple comparisons using the Holm-Šídák method.

DISCUSSION

We examined the associations between cardiovascular risk, cognitive task performance, and task-related DMN suppression in cognitively intact older adults. Higher LDL-C, but not FramRisk, was related to poorer performance on a working memory task, as well as reduced task-induced DMN suppression. Critically, all associations with DMN suppression accounted for white matter hyperintensity burden and cerebrovascular reactivity; thus, these results were not driven by individual differences in neurovascular health.

The observed relations between elevated LDL-C, poorer task performance, and reduced DMN suppression suggest that uncontrolled LDL-C has a deleterious effect on brain health, at least in the presence of other CVRFs in older adults. This likely reflects the contribution of multiple pathological processes. Elevated LDL-C has been implicated in the development Alzheimer disease pathology.[2] Moreover, although the current associations were independent of cerebrovascular health, the relations between elevated LDL-C and vascular dysfunction cannot be discounted. Previous work has shown associations between increased intima-media thickness in the carotid artery (a condition exacerbated by high LDL-C), decreased integrity of frontal subcortical networks, and reduced attention/executive function.[27] It may be that these vascular effects evolve slowly over time in the face of chronically elevated LDL-C.

Previous work has shown associations between elevated Framingham risk and dysfunction in DMN regions, including reduced glucose metabolism, reduced cerebrovascular reactivity, and resting cerebral blood flow declines.[16,17,19] However, the current results suggest that Framingham risk does not contribute to changes in working memory-related DMN suppression or task performance. Future research incorporating older adults with low cardiovascular risk may increase power to detect associations across a broader range of risk scores. Importantly, the differential effect of LDL-C versus Framingham risk on task performance and DMN suppression in the present sample may reflect the fact that a large portion of the sample had elevated levels of LDL-C, while fewer were outside of recommended ranges on HDL-C or total cholesterol, the variables used in the Framingham algorithm. Further research is needed to clarify how composite scores and biological markers of cardiovascular risk relate to behaviour and brain function in middle-age and older adults to elucidate those variables that are most predictive of acute and long-term cognitive change.

In the present sample, participants on lipid-lowering medications had lower LDL-C values (1.96 ± 0.63 vs 3.00 ± 0.98 in untreated participants). We did not have a large enough sample to investigate the mediating effect of treatment; however, the finding of lower LDL-C associated with better task performance and DMN suppression suggests that regardless of mechanism, maintaining low LDL-C has beneficial effects on cognitive and brain processes, at least in cognitively intact individuals with other CVRFs. These findings are in line with the current guidelines for statin therapy,[21,22] which suggest an assertive approach to the management of LDL-C in higher risk individuals. While the cognitive effects of statin therapy have been a topic of interest recently, the results of reviews and meta-analyses suggest little evidence of a negative effect of statin therapy on cognitive function in the short term, and no increased incidence of mild cognitive impairment or dementia associated with statin therapy over the longer term.[28–30] Some meta-analyses even suggest that long-term statin therapy may actually confer a degree of cognitive benefit;[30] however, there is marked heterogeneity across studies and further research is required, in this regard.

The present study showed that elevated LDL-C in cognitively intact older adults with cardiovascular risk had a negative effect on task performance and DMN function. Larger studies powered to examine the individual effects of vascular and metabolic dysfunction are needed to better understand how these different factors independently and collectively contribute to brain dysfunction, and to elucidate how these relations change across middle age and into senescence. Clarifying how CVRFs affect the DMN in the context of task performance is highly relevant toward understanding their contribution to cognitive decline and dementia.

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Author Contributions: Dr. Meusel was involved in data acquisition, analysis and interpretation of the data, and in drafting and finalizing the manuscript. Dr. Anderson was involved in the conception and design of the study, supervision of the analysis and interpretation, and in revisions to the manuscript. Dr. Parrott was involved in aspects of the data analysis and in revisions to the manuscript. Mr. Yuen was involved in aspects of the data analysis and in revisions to the manuscript. Dr. Tchistiakova was involved in aspects of the data analysis and in revisions to the manuscript. Dr. MacIntosh was involved in the conception and design of the study, supervision of the analysis and interpretation, and in revisions to the manuscript. Dr. Feldman was involved in interpretation of the data and revisions to the manuscript. Dr. Greenwood was involved in the conception and design of the study, supervision of the analysis and interpretation, and in revisions to the manuscript.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Supplementary Methods.
Figure S1. Default-Mode Network (DMN) Identification.
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