

**Measurement, Causes, and Impacts of Vascular Cognitive Impairment and
Vascular Depression**

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Abstract

People with cardiovascular disease (CVD) and cardiovascular risk factors have an increased risk of developing cognitive impairment and depression. One manifestation of CVD, cerebral small vessel disease, causes ischaemic damage in subcortical areas of the brain. This may disrupt neural circuits involved in cognition and mood regulation, explaining the link between cardiovascular illness and cognitive impairment and depression. Five studies were conducted to examine key questions relating to the measurement, causes and clinical significance of vascular-related cognitive impairment and vascular depression.

The first study used a cross-sectional design to assess the sensitivity and specificity of a recently developed screening test for the detection of mild cognitive impairment; the Montreal Cognitive Assessment (MoCA). In a sample with mixed cardiovascular pathology, but without dementia ($n = 110$), the MoCA's sensitivity was high but its specificity was poor, suggesting it will only be useful if secondary comprehensive screening is available.

Study 2 focused on the aetiology of vascular-related cognitive impairment. Prior research suggests CVD can reduce the ability of blood vessels to dilate. Diminished vasodilation capacity may therefore mediate the relationship between CVD and cognitive impairment. To test this hypothesis, the relationship between cognition and vasodilation was examined in 51 participants using a cross-sectional design. Cognition was not related to vasodilation in this group. However, the study sample had low levels of cardiovascular pathology, and consequently the results are not conclusive.

The functional impact of vascular-related cognitive impairment in non-demented patients with CVD has received little research attention. Study 3 examined predictors of

functional difficulties in a cross-sectional multivariate analysis of 219 non-demented people who had CVD or cardiovascular risk factors. Poor cognitive function was associated with a significantly greater likelihood of needing help with instrumental activities of daily living, independent of age, gender, and co-morbidity, thus confirming that cognitive impairment is a clinically important complication of CVD.

The co-occurrence of depression and executive dysfunction is referred to as the Depression-Executive-Dysfunction (DED) Syndrome (Alexopoulos, 2001). It has been suggested that this form of depression is caused by vascular pathology, and may therefore not respond well to traditional antidepressant medications. Previous studies that have examined treatment response in DED patients have used small samples, and have produced mixed findings. Study 4 synthesised data from available research using meta-analytic procedures. Pooled results from 23 studies indicated that people who failed to respond to antidepressant medication could not be reliably distinguished from those who responded on the basis of their pre-treatment executive function, thus failing to support the predictions of the DED model.

The studies in the aforementioned meta-analysis were limited by weaknesses in research design. Thus, Study 5 tested the predictions of the DED model using an alternative research design. Depressed patients with CVD ($n = 43$) were recruited. Patients with executive dysfunction were identified at baseline, and treatment response rates in these and the remaining participants were compared. At 3-month follow-up, 100% of participants with executive dysfunction had failed to respond to treatment, versus 60% of the remaining patients ($p = .04$, Fischer's Exact test). The results are consistent with the DED predictions and, if replicated, provide a basis for exploring alternative treatment options for this group.

Abbreviations

CVD: Cardiovascular Disease

CVRFs: Cardiovascular Risk Factors

DED: Depression - Executive Dysfunction

DRS-IP: Dementia Rating Scale, Initiation-Perseveration Index

IADLs: Instrumental Activities of Daily Living

MCI: Mild Cognitive Impairment

MMSE: Mini Mental Status Examination

MoCA: Montreal Cognitive Assessment

NAB-SM: Neuropsychological Assessment Battery, Screening Module

SSRI: Selective Serotonin Reuptake Inhibitor

WMHs: White Matter Hyperintensities

Declaration

This work contains no material that has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

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Published Works

McLennan, S. N., Mathias, J. L., Brennan, L. C., Stewart, S. (in press). Validity of the Montreal Cognitive Assessment (MoCA) as a screening test for Mild Cognitive Impairment (MCI) in a cardiovascular population. *Journal of Geriatric Psychiatry and Neurology*. doi: 10.1177/0891988710390813

McLennan, S. N., Mathias, J. L., Brennan, L. C., Russell, M. E., Stewart, S. (2010). Cognitive impairment predicts functional capacity in dementia-free patients with cardiovascular disease. *Journal of Cardiovascular Nursing*. 25(5), 390-397. doi: 10.1097/JCN.0b013e3181dae445.

McLennan, S. N., Mathias, J. L. (2010). The Depression-Executive Dysfunction (DED) Syndrome and response to antidepressants: A meta-analytic review. *International Journal of Geriatric Psychiatry*. 25(10), 933-944. doi:10.1002/gps.2431

Unpublished Works

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McLennan, S. N., Mathias, J. L., Eckert, K., Schrader, G., Stewart, S. Antidepressant response in cardiac patients with executive dysfunction. Manuscript submitted for publication.

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Statements of the contributions on jointly authored papers

Chapter 3

Title: Validity of the Montreal Cognitive Assessment (MoCA) as a screening test for Mild Cognitive Impairment (MCI) in a cardiovascular population.

Co-Authors: J. L. Mathias, L. C. Brennan, S. Stewart

Contributions: L. C. Brennan oversaw the process of participant recruitment, carried out the clinical assessments of cardiovascular diseases and risk factors, and administered the MoCA test. She was also responsible for part of the data entry. J. L. Mathias and S. Stewart acted in a supervisory capacity during all stages of this research and manuscript preparation. I was solely responsible for the study's inception and design. I conducted the cognitive testing used to establish the presence of Mild Cognitive Impairment. I completed the scoring and data entry relating to the cognitive tests. I completed the statistical analyses, data interpretation, and manuscript preparation.

Chapter 4

Title: Vasodilation response and cognition in a cohort without advanced cardiovascular disease.

Co-Authors: A. K. Lam, J. L. Mathias, S. A. Koblar, M. A. Hamilton-Bruce, J. Jannes

Contributions: A. Lam oversaw the process of participant recruitment, and completed the clinical assessment and data entry for all variables other than cognitive function. She was also responsible for the algorithms used to calculate vasodilation response. S. A. Koblar, M. A. Hamilton-Bruce and J. Jannes acted in an advisory role during the planning phase of the study and provided feedback on the final manuscript. J. L. Mathias acted in a supervisory capacity during all stages of this research and manuscript preparation. I was responsible for the study's

inception and design. I conducted the cognitive testing, and associated scoring and data entry and management. I completed the statistical analyses, data interpretation, and manuscript preparation.

Chapter 5

Title: Cognitive impairment predicts functional capacity in dementia-free patients with cardiovascular disease.

Co-Authors: J. L. Mathias, L. C. Brennan, M. Russell, S. Stewart

Contributions: L. C. Brennan oversaw the process of participant recruitment, carried out the clinical assessment of cardiovascular diseases and risk factors, and administered the MoCA test. She was also responsible for part of the data entry. J. L. Mathias and S Stewart acted in a supervisory capacity during all stages of this research and manuscript preparation. M Russell provided feedback on the approach to analysis and on the final manuscript. I was solely responsible for the study's inception and design. I completed the scoring and data entry relating to the cognitive and functional capacity tests. I was solely responsible for the statistical analyses, and manuscript preparation.

Chapter 6

Title: Cognitive impairment predicts functional capacity in dementia-free patients with cardiovascular disease. Manuscript submitted for publication.

Co-Authors: J. L. Mathias

Contributions: J. L. Mathias acted in a supervisory capacity during all stages of this research and manuscript preparation. I was solely responsible for the study's inception and design, systematic literature searches, data extraction, statistical analyses, data interpretation, and manuscript preparation.

Chapter 7

Title: Depression treatment response in cardiac patients with executive dysfunction.

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Contributions: K. Eckert oversaw the process of participant recruitment. J. L. Mathias acted in a supervisory capacity during all stages of this research and manuscript preparation. Myself and paid research assistants conducted the clinical and cognitive assessments. I was solely responsible for the study's inception and design, statistical analyses, data interpretation, and manuscript preparation. All co-authors provided feedback on the final manuscript.

The undersigned agree that the statements made regarding author contributions are accurate and true.

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Paper Presented in Chapter 3

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McLennan, S. N., Mathias, J. L., Brennan, L. C., Stewart, S. Validity of the Montreal Cognitive Assessment (MoCA) as a screening test for Mild Cognitive Impairment (MCI) in a cardiovascular population.

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