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

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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

McLennan, S. N., Lam, A. K., Mathias, J. L., Koblar, S. A., Hamilton-Bruce, M. A., Jannes, J. Vasodilation response and cognition in a cohort without advanced cardiovascular disease. Manuscript submitted for publication.

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. Manuscript submitted for publication.

Co-Authors: J. L. Mathias, K.A. Eckert, G. S. Schrader, S. Stewart

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.

J. L. Mathias: Date: 21/7/10

S. Stewart : Date: 21·7·10

L. C. Brennan: Date: 18/07/2010

M. E. Russell: Date: 18/7/2010

A. Lam: Date: 18 JUNE 2010

S. Koblar: Date: 21·7·10

J. Jannes: Date: 8/7/10

A. Hamilton Bruce: Date: 8/7/10·

K. Eckert: Date: 15/7/10

G. Schrader: Date: 12/7/10

Permission for the use of published papers and manuscripts submitted for peer review and publication

Paper Presented in Chapter 3

I give permission for the following paper to be included in Skye McLennan's thesis:

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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L. C. Brennan: Date: 18·07·2010

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Paper Presented in Chapter 4

I give permission for the following paper to be included in Skye McLennan's thesis:

Lam, A. K., Mathias, J. L., Koblar, S. A., Hamilton-Bruce, M. A., Jannes, J. Vasodilation response and cognition in a young patient cohort with low level white matter hyperintensities. Manuscript submitted for publication.

A.K. Lam: Date: 18 JUNE 2010

J. L. Mathias: Date: 21/7/10

S. A. Koblar: Date: 21·7·10

M. A. Hamilton-Bruce: Date: 8/7/10

J. Jannes: Date: 8/7/10.

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M. E. Russell: Date: 21/7/2010

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I give permission for the following paper to be included in Skye McLennan's thesis:

McLennan, S. N., Mathias, J. L. (in press) The Depression-Executive Dysfunction (DED) Syndrome and response to antidepressants: A meta-analytic review. International Journal of Geriatric Psychiatry.

J. L. Mathias: Date: 21/7/10

Paper Presented in Chapter 7

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McLennan, S. N., Mathias, J. L., Eckert, K. Schrader, J. Stewart, S. Antidepressant Response in Cardiac Patients with Executive Dysfunction. Manuscript submitted for publication.

J. L. Mathias: Date: 21/7/10

K. Eckert: Date: 15/7/10

G. Schrader: Date: 12/7/10

S. Stewart : Date: 21.7.10

Preface

Structure of the thesis

People who are affected by cardiovascular disease (CVD) and cardiovascular risk factors (CVRFs) are at increased risk of developing cognitive impairments (Barnes, Alexopoulos, Lopez, Williamson, & Yaffe, 2006; Brady, Spiro, McGlinchey-Berroth, Milberg, & Gaziano, 2001; Elias et al., 2004; Kivipelto et al., 2005; Llewellyn et al., 2008; Sanders, Lyness, Eberly, King, & Caine, 2006; van Exel et al., 2002; Verhaegen, Borchelt, & J., 2003; Vinkers et al., 2005) and of developing depression (Elovainio, et al., 2005; Stek, Gussekloo, Beekman, van Tilburg, & Westendorp, 2004; Tiemeier, et al., 2004). Furthermore, cardiovascular pathology appears to play a causal role in the development of these two problems by damaging neural circuits important for cognitive processing (Au, et al., 2006; Dufouil, Alperovitch, & Tzourio, 2003; Kramer, Reed, Mungas, Weiner, & Chui, 2002; Longstreth, et al., 1996; Mosley, et al., 2005; Prins, et al., 2005; Söderlund, et al., 2006; van der Flier, et al., 2005) and emotional regulation (Herrmann, Le Masurier, & Ebmeier, 2008). This thesis examines a series of questions related to the association between CVD and cognition and depression. It focuses specifically on people who are *not* affected by dementia. The first two chapters present a brief overview of the relevant literature in order to provide background information on what is currently known about the association between cardiovascular pathology and cognitive impairment (Chapter 1) and depression (Chapter 2), and to highlight gaps in existing knowledge.

The subsequent five chapters present five individual studies in manuscript format. The first three studies focus on the measurement, causes, and the immediate consequences of vascular-related mild cognitive impairment. Each study employs a cross sectional design.

- Study 1 assessed the sensitivity and specificity of a recently developed cognitive screening tool, the Montreal Cognitive Assessment (MoCA), to detect vascular-related cognitive impairment.
- Study 2 examined whether pathological changes in blood vessel dilation capacity are associated with ischaemic brain damage and/or cognitive impairment.
- Study 3 investigated whether cognitive impairment is independently associated with disability in day-to-day activities in patients with cardiovascular disease.

The final two studies focus on vascular-related depression, and more specifically, the Depression-Executive-Dysfunction (DED) syndrome, a clinical syndrome purported to indicate the presence of vascular pathology (Alexopoulos, 2001). It has been proposed that people with depression who display the DED syndrome are less responsive to anti-depressant treatment (Alexopoulos, 2001). The fourth study employed meta-analytic techniques to synthesise data from existing studies that have examined this hypothesis, and the fifth study used a case-control design with a three and six month follow-up to retest the hypothesis in a new study. More specifically:

- Study 4 was designed to determine whether existing research supports the hypothesis that people who fail to respond to medication have significantly lower levels of executive function.
- Study 5 examined whether cardiac patients who exhibited executive dysfunction are less likely to respond to antidepressant treatment.

The final chapter discusses the methodological strengths and limitations of the five studies, the implications of the study findings, and recommendations for future research.

Context and focus of the research

The direction and focus of this PhD changed substantially during the course of candidature. The resulting thesis is broader in focus and utilises a more varied set of participants and methodologies than was originally envisaged. The following information provides a brief context for the final focus of the research and an explanation for the choice of research methodology.

This PhD project was originally designed to test a number of hypotheses related to the vascular depression model, which proposes that a proportion of depression cases in older people arise as a result of vascular-related damage to the neural circuits that are involved in mood regulation (Alexopoulos, Meyers et al. 1997). More specifically, the thesis was designed to examine risk factors for depression, the clinical presentation and pattern of depression symptoms, the disease course, and the treatment outcomes in people diagnosed with heart disease in comparison with matched controls. In the original plan, the research was designed as a series of studies that were nested within a large-scale clinical trial funded by the National Health and Medical Research Council (NHMRC) titled the *Take Heart study* (Eckert, et al., 2009).

Unfortunately, the commencement of the Take Heart study was delayed due to a series of administrative problems and problems with participant recruitment and data collection. Ultimately, data collection was delayed by 18 months, and only a third of the anticipated number of subjects was recruited. While it was still possible to complete one of the originally planned studies (Study 5, presented in Chapter 7), it was not possible to continue with the other studies.

It was necessary, therefore, to develop a revised research plan for this PhD. The primary considerations in formulating the new research plan were to:

a) maintain a focus on the broad topic of the psychological consequences of cardiovascular diseases in order to stay within the original area of interest and to fulfil funding obligations to the scholarship provider, the National Heart Foundation;

b) ensure that the proposed research would fulfil the University's requirements to "make a significant and original contribution to knowledge by the discovery of new facts, the formulation of theories, or the innovative reinterpretation of known data and established ideas";

c) ensure that the research could be completed within the time-frame of a PhD; and

d) ensure that funding was available to cover the expenses involved with specialised clinical and cognitive assessments.

It was decided that the best way to accommodate these considerations was to develop a series of new research questions that could be built into other existing projects that were in early planning stages and could, therefore, be modified to include the necessary additional data collection.

Discussions were held with a number of research teams in the cardiovascular field and ultimately three new studies were developed (see Figure 1). Two studies (Study 1 and Study 3) were nested within a large hospital-based observational study that was primarily designed to screen patients with cardiovascular risk factors to determine the prevalence of undiagnosed Peripheral Vascular Disease. One further study (Study 2) was nested within a multi-centre study primarily designed to examine genetic determinants of impaired vessel dilation capacity and cerebral small vessel disease (Lam, et al., 2008). As discussed above, Study 5 drew participants from the treatment arm of the Take Heart Study, which was designed to examine

the effects of a GP-based intervention that aimed to improve depression treatment outcomes in cardiac patients (Eckert, et al., 2009). The remaining study (Study 4) was a meta-analysis that drew data from existing published research.

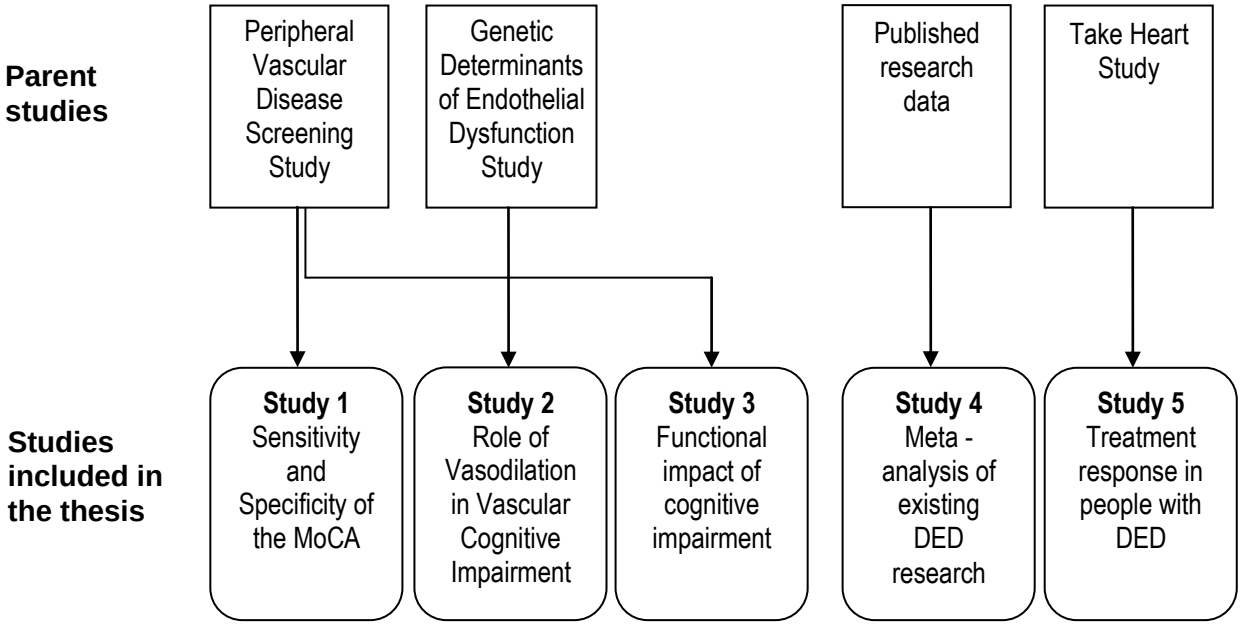

Figure 1. Sources of data used in this thesis.

In all cases, it was possible to add measures of cognition and functional status to the existing study protocols. These variables could then be examined in relation to detailed clinical data already being collected as part of the parent studies, such as information about cardiovascular diagnoses and risk factors derived from clinical assessments; information about brain pathology derived from Magnetic Resonance Imaging (MRI) scans; and information on vessel dilation response measured using applanation tonometry. These detailed clinical data, which would not have been available outside of this multi-disciplinary context, were a strength of the resulting studies.

The trade-off inherent in this approach was that the current studies had to be designed within the constraints of the existing methodology of the parent studies. Thus, it was not possible to dictate methodological factors such as sample size, some aspects of sample selection, and some aspects of the assessment techniques, which had to meet the needs of the parent studies. The methodological limitations specific to each study are discussed in more detail in the final chapter. Another outcome of this approach was that, although the resulting five studies all focus on psychological concomitants of cardiovascular disease, the thesis is relatively broad in its focus.

Chapter 1: Review of Literature Examining Associations between Cardiovascular Pathology Cognitive Function

1.1 Scope and focus of the review presented in Chapters 1 and 2

People affected by cardiovascular disease (CVD), have a higher risk of developing both cognitive impairment (Barnes, Alexopoulos, Lopez, Williamson, & Yaffe, 2006; Brady, Spiro, McGlinchey-Berroth, Milberg, & Gaziano, 2001; Elias, et al., 2004; Kivipelto, et al., 2005; Llewellyn, et al., 2008; Sanders, Lyness, Eberly, King, & Caine, 2006; van Exel, et al., 2002; Verhaegen, Borchelt, & J., 2003; Vinkers, et al., 2005) and depression (Elovainio, et al., 2005; Stek, et al., 2004; Tiemeier, et al., 2004). It has been argued that cardiovascular pathology may cause or exacerbate both of these problems via small vessel brain pathology (Fish & Bayer, 2004; Pugh & Lipsitz, 2002) (Figure 2). The following two chapters provide an overview of existing research relating to these fields. The first focuses on vascular-related cognitive impairment, particularly mild forms of cognitive impairment, and the second focuses on vascular depression.

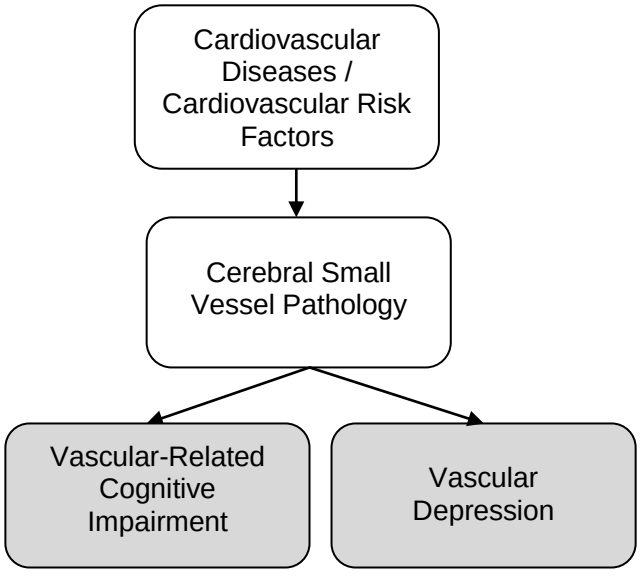

Figure 2. Proposed mechanisms involved in the development of vascular-related cognitive impairment and vascular depression.

In Chapter 1, some key terms and concepts are first defined. Following this, epidemiological research examining the association between CVD and cognitive impairment is reviewed. The types of cognitive deficits typically seen in populations with CVD are described and some of the issues relevant to the measurement and classification of these cognitive impairments are examined. The pathological mechanisms that are believed to cause vascular-related cognitive impairment are then discussed, with a focus on cerebral small vessel disease, which appears to play a central causal role. One particular mechanism that may be involved in the development of cognitive impairment, namely diminished vasodilation capacity, is then considered in detail. Finally, the functional impact of vascular-related cognitive impairment is discussed.

In the second chapter, the association between CVD and depression is examined. The chapter begins with a discussion of dominant models explaining the aetiology of depression, before focusing in more detail on the vascular depression model, which attributes the development of depression directly to vascular-related structural brain pathology. Evidence for the validity of the vascular depression model is reviewed, with a particular focus on research that has examined whether depressed patients with CVD differ in their response to antidepressant treatment.

The literature review presented in the first two chapters endeavours to highlight the fact that, although research into vascular-related cognitive impairment and vascular depression has developed in parallel, and although the two clinical problems can be explained by overlapping aetiological models, research into vascular-related cognitive impairment is relatively more advanced than research into vascular depression. More specifically, there is a much stronger evidence-base supporting the proposition that vascular factors contribute to

cognitive impairment than for the analogous hypothesis that vascular factors directly contribute to depression. As such, the most pertinent gaps in knowledge in the two fields, and therefore, the areas in need of further research, are quite different. In the case of vascular-related cognitive impairment, some of the issues of immediate concern relate to establishing the validity of specialised cognitive screening tools, examining some of the specific biological mechanisms that may contribute to the development of cognitive problems, and quantifying the impact of these cognitive problems in the people affected. In the case of vascular depression, an examination of the validity of the causal model is a more pressing concern. The studies presented in Chapters 3 to 7 of this thesis were designed to address these gaps in the literature. Throughout the two literature review chapters, each of the major gaps in the literature is highlighted and the corresponding study aim presented. The five study aims are then re-presented at the end of Chapter 2.

1.2 Cardiovascular Disease (CVD) and Cardiovascular Risk Factors (CVRFs)

Cardiovascular disease (CVD) is caused by pathology affecting the heart and the blood vessels. One of the primary causal mechanisms in the development of CVD is plaque formation, a process marked by the abnormal build-up of fat, cholesterol and other substances in the inner lining of the arteries (Australian Institute of Health and Welfare, 2008). CVD may manifest in a range of clinical presentations, depending on the type of pathology, and on which vessels in the body are affected. The main clinical manifestations are ischaemic heart disease (also referred to as coronary artery disease), which may manifest as chronic angina pectoris (chest pain) and/or an acute cardiac arrest; chronic congestive heart failure, which occurs when the heart's pumping action fails to meet the metabolic needs of the body; disorders involving the heart valves; atrial fibrillation (a form of arrhythmia); cerebrovascular

diseases, including cerebrovascular accidents (strokes); and peripheral vascular disease, which affects the vessels in the legs and, less commonly, arms (World Health Organization, 2004). There are a number of clinical risk factors linked to the development of CVD, including elevated blood pressure (hypertension), elevated serum cholesterol levels, high body mass index, and diabetes (Mackay, Mensah, Mendis, & Greenlund, 2004). Lifestyle factors such as tobacco smoking, physical inactivity, a diet low in fruit and vegetables, as well as advancing age also increase the risk of developing CVD (Mackay, et al., 2004). These clinical and lifestyle factors are collectively referred to as cardiovascular risk factors (CVRFs).

1.2.1 Recent demographic changes in the prevalence of CVD and implications for cognitive and depressive problems

Around 16% of Australians are affected by CVD, and this figure increases to 62% in people aged over 75 years (Australian Bureau of Statistics, 2009). The proportion of the population affected by CVD is projected to rise in western countries due to the aging demographic structure (Truelsen, et al., 2006). Although CVD accounts for around 35% of all deaths in the USA and Australia (Australian Bureau of Statistics, 2006; Lloyd-Jones, et al., 2009), mortality from CVD has actually fallen dramatically over the last few decades (Australian Institute of Health and Welfare, 2008; Lloyd-Jones, et al., 2009; Rothwell, et al., 2004). This fall has, in part, been attributed to a reduction in CVRFs (e.g. smoking and elevated cholesterol levels) (Ford, et al., 2007; Rothwell, et al., 2004). However, the increased use of life-prolonging therapies, such as surgical revascularisation of coronary arteries after cardiac arrest, has also contributed to improved survival rates (Ford, et al., 2007). People who might otherwise have died from a cardiac event or stroke are therefore now more likely to survive into old age (Australian Institute of Health and Welfare, 2008), albeit with underlying vascular pathology.

Although multiple pathological processes are involved in the development of different forms of CVD, they share a common pool of risk factors (D'Agostino, et al., 2008; Mackay, et al., 2004) and tend to co-occur (Barreto, et al., 2001; Genest Jr & Cohn, 1995). Thus, a person presenting with a cluster of symptoms associated with cardiovascular pathology in one region of the body (e.g. exercise-induced leg pain caused by peripheral vascular disease) is likely to have vascular pathology in other regions of the body, such as the heart or the brain (D'Agostino, et al., 2008). People who have been diagnosed with multiple clinical CVD diagnoses, or who have multiple CVRFs, are assumed to be affected by a higher burden of systemic cardiovascular pathology. Therefore research examining the association between CVD/ CVRFs and cognition or depression frequently groups different CVD diagnoses and/or CVRFs together (e.g. Holley, Murrell, & Mast, 2006; Llewellyn, et al., 2008; Lyness, King, Conwell, Cox, & Caine, 2000). In this context, specific CVD diagnoses are less important than the collective 'burden' of cardiovascular illness (i.e. the weighted or unweighted tally of CVD diagnoses and/or CVRFs). When viewed this way, different CVD diagnoses are all considered to be clinical manifestations of an underlying systemic pathology. Although this approach is an imprecise method for quantifying the extent or severity of underlying cardiovascular pathology, in this research context, the total cardiovascular burden is more important than the specific clinical diagnoses.

If CVD diagnoses are indicators of underlying pathology, as described above, then it follows that, although life-prolonging surgical procedures, such as implantation of a coronary stent or aortic aneurysm repair, and pharmacological interventions, such as anti-clotting agents following cardiac arrest or stroke, may provide symptom relief and prevent death, they don't actually remedy the underlying systemic pathology. Therefore, the net effect of these treatments is to increase the proportion of the population with significant underlying vascular

pathology. Consequently, there is likely to be an increasing pool of people who are susceptible to the complications of vascular-related cognitive impairment and vascular-related depression. These two psychological problems are therefore a growing area of concern in first-world countries that are characterised by aging population structures and increased access to life-prolonging secondary treatments for CVD.

1.2.2 Association between CVRFs/CVD and cognitive impairment

Epidemiological studies have demonstrated that several individual CVRFs and CVD diagnoses are independently associated with reduced cognitive function, including hypertension (Qiu, Winblad, & Fratiglioni, 2005), diabetes mellitus (Arvanitakis, Wilson, & Bennett, 2006), chronic heart failure (Bennett & Sauve, 2003; Verhaegen, et al., 2003), carotid artery disease (Johnston, et al., 2004; Verhaegen, et al., 2003), and peripheral vascular disease (Breteler, Claus, Grobbee, & Hofman, 1994; Haan, Shemanski, Jagust, Manolio, & Kuller, 1999; Woo, et al., 2006). Moreover, the risk of cognitive impairment increases with the total burden of cardiovascular pathology, as measured indirectly by the number of CVD diagnoses and/or CVRFs a person has (Barnes, et al., 2006; Brady, et al., 2001; Elias, et al., 2004; Kivipelto, et al., 2005; Llewellyn, et al., 2008; Sanders, et al., 2006; van Exel, et al., 2002; Verhaegen, et al., 2003; Vinkers, et al., 2005), or by more direct markers of blood vessel health such as arterial stiffness (Elias, et al., 2009; Hanon, et al., 2005; Waldstein, et al., 2008), or thickening of the artery walls (Haley, et al., 2007; Sander, et al., 2009). Although these associations are strongest in elderly cohorts where cardiovascular pathology is likely to be more advanced, they have also been observed in middle-aged populations (Pavlik, Hyman, & Doody, 2005; Singh-Manoux, Britton, & Marmot, 2003).

1.3 Cognitive Impairment

1.3.1 Cognitive domains affected by cardiovascular pathology

People with CVRFs and CVD may experience declines in a number of high-level cognitive processes including memory, visuospatial processing, language, information processing speed and executive functioning (Nordlund, Rolstad, Klang, & Lind, 2007; Singh-Manoux, et al., 2003). However, research indicates that information processing speed and executive functioning are affected more frequently, or with equal frequency to memory or other cognitive functions (Nordlund, et al., 2007; Saxton, et al., 2000; van Exel, et al., 2002; Wiederkehr, Laurin, Simard, Verreault, & Lindsay, 2009). This distinguishes vascular-related cognitive impairment from Alzheimer's Disease, which is more frequently characterised by memory and language problems (Graham, Emery, & Hodges, 2004; Reed, et al., 2007).

Definitions of Information Processing Speed and Executive Function

Of these two characteristic cognitive deficits seen in cardiovascular populations, information processing speed refers to the time it takes to carry out mental tasks. A decline in information processing speed typically affects performance across a wide range of mental tasks (Kail, 2000). Executive functions are a set of higher-order cognitive processes that are involved in optimising performance in situations where several cognitive processes need to be coordinated simultaneously (Lezak, Howieson, & Loring, 2004; Ylikoski & Hanninen, 2003). Planning, initiation, and monitoring of behaviours and mental processes are all considered to be executive functions (Royall, et al., 2002). Although classifications vary, working memory and more complex aspects of attention, such as attentional switching and inhibition, are often described as executive functions (Royall, et al., 2002). People with impaired executive functions may experience problems with planning and organising their behaviour, problems with maintaining their motivation to pursue goals, and with shifting mental sets or modifying

behaviour that is well-learned or normally prompted by environmental cues (Ylikoski & Hanninen, 2003). Deficits in executive functioning may not be obvious without specific testing, particularly in circumstances where a person is operating in a highly structured environment or is carrying out tasks that are routine and do not require novel responses (Kahokehr, Siegert, & Weatherall, 2004).

1.3.2 The continuum of Vascular Cognitive Impairment

Cognitive impairments that develop in people who have CVD or CVRFs range in severity from very subtle impairment to diagnosed Vascular Dementia. The term *Vascular Cognitive Impairment* is used to refer to this full spectrum of deficits (O'Brien, et al., 2003) (depicted in Figure 3). At the most severe end of the range, a diagnosis of dementia is assigned when a decline in memory and at least one other aspect of cognitive function occurs, which is severe enough to impact on the capacity to carry out basic activities of daily living such as dressing or feeding (American Psychiatric Association, 2000; Roman, et al., 1993; World Health Organization, 2004). Vascular Dementia (i.e. dementia with suspected vascular aetiology) is the second most common form of dementia in western countries, following Alzheimer's Disease (Canadian Study of Health and Aging Working Group, 1994; Fitzpatrick, et al., 2004; Lobo, et al., 2000).

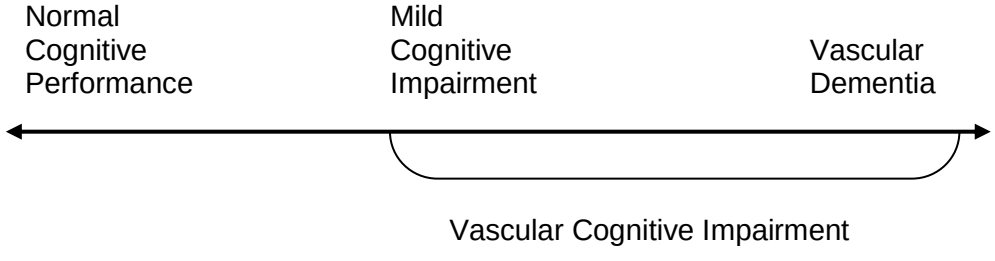

Figure 3. Continuum of cognitive problems in people with CVD and CVRFs.

Longitudinal population-based studies have demonstrated that, in most cases, the onset of Vascular Dementia is slow and gradual, with most people progressing through a period of milder cognitive impairment in the 3 to 5 years preceding the dementia diagnosis (Hayden, et al., 2005; Ingles, Wentzel, Fisk, & Rockwood, 2002; Waite, et al., 2005). Over the past decade, the distinction between mild cognitive impairment and Vascular Dementia has been down-played in the context of a greater recognition that the difference between the two clinical states is relatively arbitrary (O'Brien, Reisberg, & Erkinjuntti, 2003). That is, the same cognitive domains that are affected in MCI and dementia, and the pathological processes are also identical. The distinction between mild cognitive impairment and Vascular Dementia primarily relates to the *severity* of the impairment.

1.3.3 Mild Cognitive Impairment (MCI)

Heightened awareness of the period of early and subtle cognitive decline that often precedes Vascular Dementia has highlighted the opportunity for prevention of more serious cognitive deterioration (Bowler, 2003; O'Brien, et al., 2003), and has facilitated new lines of intervention-based research aimed at halting or reducing this decline. In order to achieve consistency across research and clinical settings, a variety of operational definitions have been developed to describe this mild form of cognitive deterioration, which is distinguishable from normal cognition but less severe than Vascular Dementia (Mariani, Monastero, & Mecocci, 2007). The most pervasive and enduring of these definitions is the diagnostic system proposed by Peterson et al (1999), who coined the term Mild Cognitive Impairment (MCI). The criteria for MCI are: (1) a subjective cognitive complaint; (2) independence in basic activities of daily living; (3) memory performance significantly lower than expected based on age and education level; (4) normal performance in other cognitive domains; and (5) no dementia. The entity

described by this original set of criteria has since become known as *MCI-amnestic* or *amnestic MCI* because it specifies the need for an objectively-measured memory deficit.

Other MCI subtypes have since been proposed to capture the varying patterns of cognitive impairment that occur in cardiovascular patients and other clinical groups. These include *MCI-single non-memory domain*, where non-memory cognitive functions such as attention or visuo-spatial processing are affected, and *MCI-multiple domain*, where more than one cognitive function is affected (Petersen, et al., 2001). A review of population-based studies from developed western countries reports that between 11% and 17% of people aged over 60 or 65 years are affected by some form of MCI (Mariani, et al., 2007), and comparative research suggests that multiple-domain MCI occurs more frequently than amnestic MCI (Busse, Bischkopf, Riedel-Heller, & Angermeyer, 2003).

In many cases, people affected by MCI go on to experience further decline in cognitive function, ultimately deteriorating to the level of dementia. A recent meta-analysis concluded that around 22% of people in the community who display amnestic MCI deteriorate to dementia (any form) over a period of four to five years (Mitchell & Shiri-Feshki, 2009). This equates to a dementia risk that is more than 15 times higher than for people who are free of MCI (Mitchell & Shiri-Feshki, 2009). Other research has shown that dementia conversion rates are higher for people who have deficits in multiple cognitive domains than for those who have isolated memory deficits (Alexopoulos, Grimmer, Perneczky, Domes, & Kurz, 2006; Bozoki, Giordani, Heidebrink, Berent, & Foster, 2001; Di Carlo, et al., 2007). While the pattern of early cognitive deficits varies from individual to individual (Fischer, et al., 2007), overall, patients who show early deficits in executive functions are more likely to develop Vascular Dementia and those who show early deficits in memory are more likely to develop

Alzheimer's Disease (Hayden, et al., 2005; Ingles, Boulton, Fisk, & Rockwood, 2007; Zanetti, et al., 2006).

Detection and measurement of MCI

To diagnose MCI, multiple cognitive domains must be assessed using structured tests, and the test results must be interpreted against age-based norms. This process is time consuming and requires specialised expertise and therefore may not be practical in some circumstances. For example, in research that is designed to determine whether a drug or other intervention is effective in preventing or reducing cognitive decline, both the cost and the burden on study participants may prohibit a full neuropsychological examination. Similarly, in clinical settings, cognitive information may be a useful adjunct to clinical data for determining treatment approaches and support plans for cardiovascular patients. However, cost and time constraints may preclude a comprehensive assessment when other clinical issues also require attention. Thus, a brief cognitive screening tool that is sensitive to the types of deficits that are seen in non-demented people with vascular-related cognitive impairment would be valuable.

Unfortunately, most existing brief cognitive measures are not well suited for use with people who have CVD or CVRFs. Current diagnostic criteria for dementia emphasise the presence of memory deficits (e.g. American Psychiatric Association, 2000; Roman, et al., 1993; World Health Organization, 2004). This has meant that most brief cognitive tests were developed to detect memory deficits but fail to adequately assess deficits in executive functions and information processing speed (Lonie, Tierney, & Ebmeier, 2009), which commonly occur in vascular-related cognitive impairment (Saxton, et al., 2000; van Exel, et al., 2002; Wiederkehr, et al., 2009). In addition, many available cognitive screening tools are insensitive to mild forms of cognitive impairment.

The Mini Mental Status Exam (MMSE) (Folstein, Folstein, & McHugh, 1975) is the most commonly used cognitive screening tool in clinical practice (Shulman, et al., 2006) and it provides a specific illustration of the problems associated with many existing cognitive screening tools. The MMSE was originally developed to detect early Alzheimer's disease. Consequently, it does not include items designed to measure executive functions or information processing speed and has a ceiling effect that can impede detection of mild cognitive deficits (Diniz, Yassuda, Nunes, Radanovic, & Forlenza, 2007). Indeed, the MMSE fails to detect most cases of MCI, making it unsuitable for use with non-demented patients (Lonie, et al., 2009). When the MMSE has been used in studies designed to test whether antihypertensive medications reduce vascular-related cognitive decline, treatment effects have not been detected (Lithell, et al., 2003; Peters, et al., 2008; Prince, Bird, Blizard, & Mann, 1996; SHEP Cooperative Research Group, 1991). However, similar studies that have used cognitive tests that are more sensitive to mild deficits in non-memory domains have reported that these medications do reduce the incidence of dementia (Forette, et al., 1998; Tzourio, et al., 2003) and cognitive decline (Bosch, et al., 2002; Tzourio, et al., 2003), raising the possibility that the former studies failed to detect a treatment effect due to test insensitivity. Research focusing on lipid-lowering medications is affected by the same issue. Only two published trials have examined whether statin medications have a protective effect on cognition (Heart Protection Study Collaborative Group, 2002; Shepherd, et al., 2002) and neither study observed a significant treatment effect. However, both studies relied on the MMSE, so it is possible that a treatment effect went undetected. Debate about the potentially protective effect that these drugs may have on cognition is ongoing and the uncertainty raised by these measurement issues has major clinical implications (Sparks, 2009).

Montreal Cognitive Assessment (MoCA) Test

The Montreal Cognitive Assessment (MoCA) (Nasreddine, et al., 2005) is a recently-developed screening test that was designed to address the problems described above. It assesses a range of cognitive domains, including executive functions, and was designed to be more challenging than the MMSE, and therefore more sensitive to subtle impairments. The MoCA was provisionally recommended for use in research focusing on vascular-related cognitive impairment by The National Institute for Neurological Disorders and Stroke and the Canadian Stroke Network (Hachinski, et al., 2006), however validity testing is still ongoing.

The MoCA has the potential to be useful both as a measure of global cognitive function (i.e. functioning across multiple cognitive domains) and as a screening tool for the detection of MCI. The available evidence generally supports its validity as a measure of global cognitive function. Specifically, it shows moderate to strong correlations with other brief tests of global function including the MMSE (r = .62 to .87) (Lee, et al., 2008; Nasreddine, et al., 2005; Smith, Gildeh, & Holmes, 2007) and the Clinical Dementia Rating Scale (r = -.62) (Lee, et al., 2008), and is sensitive enough to detect differences in the rates of cognitive decline in people with different cardiovascular risk factor profiles over a six month period (Popovic, Seric, & Demarin, 2007).

In terms of its validity as a screening tool for MCI, previous research has established that it has good sensitivity (.83 to .97) and moderate specificity (.35 to .89) in the detection of amnestic MCI (Luis, Keegan, & Mullan, 2009; Nasreddine, et al., 2005; Smith, et al., 2007). However, its capacity to detect multiple-domain MCI, which is the most relevant form of MCI in populations with CVD or CVRFs, has not yet been examined. Furthermore, its validity as a screening tool has not been examined in a population with a high cardiovascular burden.

AIMS OF STUDY 1:

Study 1 was therefore designed to examine the validity of the MoCA as a screening tool in a population at risk of vascular-related MCI. The specific aims were to determine the sensitivity and specificity of the MoCA for detecting MCI in a cohort of people affected by cardiovascular pathology. Using a cross-sectional design, the study examined sensitivity and specificity for both amnestic MCI and multiple-domain MCI. Participants were recruited from patients visiting hospital-based cardiovascular and endocrine outpatient clinics.

1.4 Vascular-related cerebral pathology

Vascular-related cognitive impairment develops through a range of pathophysiological processes. One major substrate is large vessel disease, which is caused by atherosclerotic disease in a major cerebral artery, and typically manifests as occlusive cortical stroke. The other major form is small vessel disease, which results from pathology in the cerebral arterioles and manifests as small subcortical infarcts (lacunae) and/or white matter ischaemic lesions (O'Brien, et al., 2003) (both described in more detail in section 1.4.1). Cognitive impairment arising from large vessel disease is the most readily identified because onset is abrupt and is often accompanied by neurological signs, such as muscle weakness or speech difficulty (Staekenborg, et al., 2008). In contrast, cognitive impairment resulting from small vessel disease usually develops gradually over years and decades, and is not typically marked by discrete changes in cognition or by the abrupt onset of other clinical symptoms (Schmidtke & Hull, 2005).

Although large vessel cerebrovascular disease is more easily recognised in a clinical setting, emerging evidence suggests that small vessel disease may be more common.

Epidemiological research has demonstrated that silent strokes (ie those that are not accompanied by neurological signs and usually result from small subcortical lacunes) are 10 to 20 times more common than overt strokes (Longstreth, 1998). Consistent with this, a recent study that reviewed MRI scans from more than 700 people who had been diagnosed with Vascular Dementia revealed that 74% had small vessel disease, 18% had large-vessel disease, and the remaining 8% were mixed (Staekenborg, et al., 2008). Despite the higher prevalence of cerebral small vessel disease, this subtype of cerebrovascular disease was not well recognised in research or clinical settings prior to the 1980s, largely because the brain imaging technology needed to identify the underlying pathology was not widely available (Babikian & Ropper, 1987). Consequently, small vessel disease is comparatively less well understood and was therefore chosen as the focus of the current research.

1.4.1 Pathological processes involved in cerebral small vessel disease

The brain regions that are most frequently damaged in cerebral small vessel disease are the subcortical white matter, particularly in the frontal lobes, and subcortical grey matter nuclei, particularly the thalamus, basal ganglia and brainstem (Artero, et al., 2004; de Leeuw, et al., 2001; Kalaria, et al., 2004). These brain regions are most vulnerable to cerebral small vessel disease because they are the areas that receive their blood supply via very small vessels. These arterioles are long and narrow, extending from the pial surface and terminating in the subcortical tissue. They increase in tortuosity (i.e. become elongated and twisted) at around the 5^{th} decade of life (Pantoni & Garcia, 1997). Due to these structural factors, blood flow through these small vessels may be compromised during periods when perfusion pressure drops, leaving the surrounding tissue vulnerable to episodes of ischemia (Pantoni & Garcia, 1997).

The vulnerability of subcortical brain tissue is further increased by a number of pathological processes affecting the small vessels, which are caused or exacerbated by CVRFs. These include: arteriolosclerosis, where changes in the cells in the vessel walls lead to thickening and hardening of the vessels; vasculitis, where cells in the vessel walls become inflamed; and cerebral amyloid angiopathy, a condition marked by the accumulation of amyloid proteins in the cells of the vessel walls (Munoz, 2003; Pantoni & Simoni, 2003). These pathological processes, in combination with the structural distortion of the cerebral vessels that occurs as a result of age-related tortuosity, can ultimately lead to ischemia (insufficient supply of oxygen), micro-haemorrhages (rupture of the vessel walls under pressure), or alterations to the blood brain barrier and associated leakage of fluid and molecules that are toxic to the white matter (Munoz, 2003, 2006; Pantoni & Simoni, 2003). It is believed that the pathological processes affecting the small cerebral vessels all result in similar forms of damage to the surrounding subcortical brain tissue, most notably diffuse white matter ischaemic lesions and lacunar infarcts (Munoz, 2003; Pantoni & Simoni, 2003). [1]

White Matter Hyperintensities (WMHs)

The first of these forms of tissue damage, diffuse ischaemic lesions in the white matter, are visible on brain imaging films as patchy areas with indistinct borders (Munoz, 2006). More specifically, on computed tomography (CT) images, they appear as hypodense (gray) areas, and on T2 and FLAIR sequence MRI they appear as hyperintense (white) areas (Munoz, 2003, 2006). These areas of damage are commonly referred to as white matter hyperintensities

[1] A meta-analysis of randomised controlled trials has established that treatment with antihypertensive medications results in a decrease in the incidence of dementia (Peters, et al., 2008). Different classes of antihypertensive medications reduce blood pressure via different mechanisms. If it could be shown that one class had a greater protective effect on cognition than another, then this would provide further insight into the mechanisms through which hypertension detrimentally impacts

(WMHs) (Munoz, 2003, 2006). Histopathology examinations of WMHs reveal that they are not typically characterised by outright neuronal death. Instead, they are associated with multiple forms of damage, including myelin loss, axonal loss, and dilatation of perivascular spaces (Udaka, Sawada, & Kameyama, 2002).

Population-based screening studies suggest that WMHs are present in up to 92% of people who are aged over 65 (de Leeuw, et al., 2001). They increase in severity and frequency with age (Breteler, van Swieten, et al., 1994; de Leeuw, et al., 2001), and are associated with multiple CVRFs (Breteler, van Swieten, et al., 1994; Jeerakathil, et al., 2004). In large-scale studies of people drawn from the general community, the total volume of WMHs is negatively associated with cognitive performance (Au, et al., 2006; Dufouil, et al., 2003; Kramer, et al., 2002; Longstreth, et al., 1996; Mosley, et al., 2005; Prins, et al., 2005; Söderlund, et al., 2006; van der Flier, et al., 2005). Although a large proportion of people with WMHs remain free of cognitive dysfunction, particularly when the pathology is mild, when cognitive deficits do occur, they are more likely to affect executive function, attention, and information processing speed than learning and memory (Boone, et al., 1992; de Groot, de Leeuw, Oudkerk, Van Gijn, et al., 2000; Kramer, et al., 2002; Lucchi, Bellelli, Magnifico, Guerini, & M., 2005; Mosley, et al., 2005; O'brien, et al., 2002; Prins, et al., 2005; Sachdev, Wen, Christensen, & Jorm, 2005; Söderlund, et al., 2006).

Lacunar Infarctions

Lacunar infarctions, the other major pathological substrate of cerebral small vessel disease, are small areas of complete cell death that are less than 2cm in diameter (Fisher, 1965). Approximately 25% to 31% of people over the age of 60 or 65 have at least one lacunar infarct on MRI examination and the risk increases with age (Longstreth Jr, et al., 1998;

Vermeer, Koudstaal, Oudkerk, Hofman, & Breteler, 2002). In around 85% of cases, lacunar infarcts are not accompanied by clinical signs such as speech difficulty or muscle weakness (Longstreth Jr, et al., 1998; Vermeer, et al., 2002). Moreover, they tend to co-occur with WMHs (Chen, Wen, Anstey, & Sachdev, 2009), and a higher number of subcortical lacunes is associated with lower cognitive performance (Carey, et al., 2008; Chen, et al., 2009; Vermeer, et al., 2003; Wright, et al., 2008). As with WMHs, lacunar infarcts are more closely associated with deficits in executive functions than in memory (Carey, et al., 2008; Prins, et al., 2005). Examples of MRI films showing lacunar infarcts (http://www.radiologyassistant.nl/en/484b8328cb6b2) and areas of WMHs (http://www.radiologyassistant.nl/en/43dbf6d16f98d) can be viewed online (Barkhof & Smithuis, 2007; Smithuis, 2008)

1.4.2 Fronto-subcortical circuits

Cerebral small vessel disease causes damage to subcortical regions of the brain, and this is the reason that it is more likely to result in deficits in executive function and information processing speed than are cerebral large vessel disease (Jokinen, et al., 2006) or Alzheimer's Disease (Graham, et al., 2004; Reed, et al., 2007) where the damage predominantly occurs in cortical regions. Subcortical white matter is comprised of the long mylelinated axonal fibres that link anatomically distant brain regions, and facilitate communication and co-ordination between them (Kail, 2000; Turken, et al., 2008). When these fibre tracts are disrupted via WMHs or lacunes, the efficiency of communication and co-ordination between brain regions is compromised, providing an explanation for the reduction in information processing speed.

One series of white matter tracts link subcortical grey matter nuclei, including the basal ganglia and thalamus, to pre-frontal regions of the cortex via a series of closed circuits, and are referred to as the fronto-subcortical circuits (Royall, et al., 2002; Tekin & Cummings, 2002). Each fronto-subcortical circuit follows a similar path, which begins in the frontal lobes and then passes through the striatal areas of the basal ganglia (i.e. the caudate, putamen or ventral striatum), projects to the globus pallidum and substantia nigra, and finally through the thalamus and back to the frontal cortex (Cummings, 1995). One of these circuits, *the dorsolateral circuit*, supports executive functions. Disruption at any point along this circuit may cause executive dysfunction, which manifest as concrete reasoning, perseveration, reduced mental flexibility, and a diminished capacity to maintain and redirect attention (Royall, et al., 2002). This explains why executive functions are particularly vulnerable to cerebral small vessel pathology.

In addition to the dorsolateral circuit, four other fronto-subcortical circuits have been identified, three of which are associated with behaviour and cognition (Tekin & Cummings, 2002). Disruption to the *orbito-frontal circuit* may lead to personality changes, such as behavioural disinhibition and emotional lability, which may involve irritability or aggression, inappropriate responses to social cues, or a lack of interpersonal sensitivity (Tekin & Cummings, 2002; Ylikoski & Hanninen, 2003). It has been suggested that dysfunction in this circuit may predispose people to depression (Ebmeier, Donaghey, & Steele, 2006; Frangou, 2006). A detailed discussion of this hypothesis is provided in Section 2.3. Damage to the third frontal-subcortical circuit, the *anterior cingulate circuit*, is associated with apathy, decreased motivation and difficulty with response inhibition. Each of these three circuits is anatomically distinct. Consequently, a person may experience damage to a single circuit and display a single set of symptoms. However, because the circuits are located in close anatomical

proximity at the deep subcortical level (as depicted in Figure 4), a single lesion in this region may affect more than one circuit, thereby producing a mixed set of symptoms (Royall, et al., 2002; Tekin & Cummings, 2002).

1.4.3 Role of vessel dilation capacity in cerebral small vessel disease

Although it has been established that a number of CVRFs (e.g. hypertension, diabetes and smoking) increase the risk of small vessel brain disease and cognitive impairment (McManus & Stott, 2005), the exact mechanisms that mediate these relationships are not well understood (Black, Gao, & Bilbao, 2009; Ince & Fernando, 2003). As discussed (refer to Section 1.4), evidence from histopathology studies suggests that multiple pathological processes such as arteriolosclerosis, vascalitis and cerebral amyloid angiopathy, are involved (Black, et al., 2009). One factor that may play a role in the development of cerebral small vessel disease, which would not be evident in histopathology studies, is a deterioration in the capacity of blood vessels to dilate.

Under normal circumstances, blood vessels dilate *(vasodilation)* and contract *(vasoconstriction)* in response to chemical or physiological stimuli in order to maintain optimal blood flow under varying systemic blood pressures (Deanfield, Halcox, & Rabelink, 2007). Blood vessel dilation is achieved via relaxation of the smooth muscle in the vessel walls. This muscle relaxation is triggered by a number of different processes, one of which involves the endothelium (the innermost layer of cells in blood vessel walls), and one that does not (Boron & Boulpaep, 2009). In *endothelial-dependent vasodilation*, a physical or chemical trigger causes the endothelial cells to synthesise nitric oxide, which in turn causes the smooth muscle cells to relax, thus dilating the vessel (Furchgott & Zawadzki, 1980). In contrast, during the process of *non-endothelial-dependent vasodilation,* a different set of stimuli trigger

smooth muscle relaxation without the involvement of the endothelium. The aging process itself, as well as the development of CVRFs, both have detrimental effects on the capacity of vessels to dilate (Hashimoto, et al., 2000; Lakatta, 2002). It has been hypothesised that a reduction in vessel dilation capacity may impede the delivery of blood to the brain tissue (Munoz, 2006) which, over time, could cause or exacerbate cerebral ischemia, leading to permanent tissue damage and ultimately cognitive decline (Roman, et al., 2004). The steps in this hypothesised process are summarised in Figure 4.

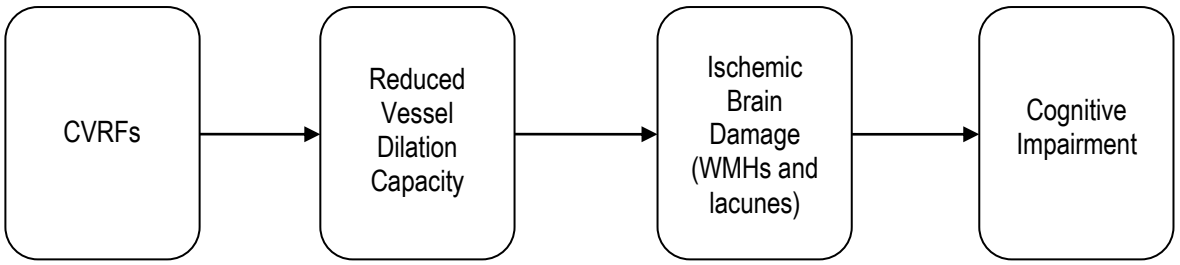

Figure 4. Summary of processes that are hypothesised to link reduced vessel dilation to cognitive impairment.

It is possible to measure the degree of vessel dilation response in an individual in real time. To do this, a single vessel is identified, and a measure is taken, either of blood flow or vessel diameter. Following this, a stimulus known to trigger vasodilation is administered and the measurement taken for a second time. If the vessel has dilated, a greater flow of blood (or an increase in vessel diameter) will be observed. The magnitude of the change in blood flow or vessel diameter between the first and second measurements is then calculated to provide an estimate vessel dilation (Verma, Buchanan, & Anderson, 2003).

Consistent with the model depicted in Figure 4, several cross-sectional studies have demonstrated that, in people with established CVD, poorer non-endothelial-dependent

vasodilation response is associated with poorer cognitive performance (Forman, et al., 2008; Moser, et al., 2004; Moser, et al., 2008; Moser, et al., 2007). However, the role of endothelial-dependent vasodilation is less clear. In one study, a poorer endothelial-dependent response was related to poorer performance on tests of executive function and attention but not to performance on other cognitive tasks, which is a pattern that might be expected in cerebral small vessel disease (Forman, et al., 2008). In contrast, another study found that endothelial-dependent vasodilation was not related to any aspect of cognitive functioning (Moser, et al., 2008; Moser, et al., 2007).

Importantly, none of the above studies incorporated brain imaging to measure brain tissue pathology (i.e. the third of the four variables summarised in Figure 4). Therefore, it is not clear whether subcortical ischaemic damage mediated the observed associations between vasodilation and cognition. However, in another study focusing on elderly people with established cardiovascular disease, which examined brain tissue pathology but not cognition (i.e. the first three but not the fourth variable shown in Figure 4), poorer endothelial-dependent vessel dilation was associated with an increased volume of WMHs on MRI (Hoth, et al., 2007). Non-endothelial-dependent vasodilation was not related to brain pathology in this study. The findings of this study are consistent with the suggestion that ischaemic brain damage may act as an intermediary mechanism linking poor vasodilation and cognitive impairment. However, no study has yet examined all four of the variables set out in Figure 4.

AIMS OF STUDY 2

Study 2 was designed to determine whether vessel dilation response is associated with cognitive performance and whether this relationship can be explained by the presence or severity of WMHs and/or subcortical lacunes. Both endothelial-dependent and non-endothelial-dependent vasodilation processes were measured using a cross-sectional study

design. In order to access brain imaging data, participants were drawn from a list of people who had recently undergone MRI for any reason at a participating public hospital.

1.5 Impact of mild forms of cognitive impairment on daily activities

The recent surge in research interest in MCI originally stemmed from a desire to identify people who are at risk of developing dementia. However, mild cognitive impairments also have the potential to negatively impact on people's lives prior to the onset of dementia. The importance of evaluating the impact of MCI on functional capacity is underscored by the fact that while up to 17 percent of the elderly population is affected by MCI (Mitchell & Shiri-Feshki, 2009**),** only a fifth of this group will go on to develop dementia over a 5 to 10 year period (Mitchell & Shiri-Feshki, 2009). This leaves a large pool of people who will experience MCI on a long-term basis. It is therefore important to determine whether MCI has a measurable impact on their lives.

Two types of cross-sectional study designs have been used to examine whether mild cognitive impairments are associated with problems completing complex day-to-day tasks, such as shopping, preparing meals or managing medications. Tasks of this type are referred to as instrumental activities of daily living (IADLs). The first group of studies has examined people from the general population, using an epidemiological approach to determine whether cognitive function is independently associated with the ability to perform IADLs after controlling for other factors that have the potential to impact on IADL performance, such as age and co-morbid illness. The results of these studies have consistently shown that cognition is an independent predictor of ability to perform IADLs (Barberger-Gateau, Fabrigoule,

Rouch, Letenneur, & Dartigues, 1999; Blaum, Ofstedal, & Liang, 2002; Burton, Strauss, Hultsch, & Hunter, 2006; McGuire, Ford, & Ajani, 2006).

Analogous findings have also been reported in studies using a case-control design, which compare the functional capacity of people who meet the criteria for MCI to that of people who have normal levels of cognitive function. With the exception of some small-scale studies (Binegar, Hynan, Lacritz, Weiner, & Cullum, 2009; Pereira, Yassuda, Oliveira, & Forlenza, 2008), most findings indicate that people with MCI are more likely to require assistance with IADL tasks (Allaire, Gamaldo, Ayotte, Sims, & Whitfield, 2009; Burton, Strauss, Bunce, Hunter, & Hultsch, 2009; Kim, et al., 2009; Mariani, et al., 2008; Schmitter-Edgecombe, Woo, & Greeley, 2009). While the results from some other studies indicate that people with MCI are able to complete common IADLs, they have been found to be slower (Wadley, Okonkwo, Crowe, & Ross-Meadows, 2008) or to make more errors when completing these tasks (Jefferson, et al., 2008). Taken together, these studies provide strong evidence that people who are affected by mild cognitive impairments experience more difficulties on a day-to-day basis, which could potentially affect their quality of life and increase their dependence on family caregivers and community services.

Because the criteria for dementia emphasise memory deficits (American Psychiatric Association, 2000; World Health Organization, 2004), the studies reviewed above have tended to focus on memory function and, thus, the impact of problems in cognitive domains other than memory is less well understood than the impact of memory deficits. However, several recent studies have examined the relative importance of memory and executive functions in relation to IADL performance. These studies have either reported that executive functions are *as* important (Cahn-Weiner, et al., 2007; Farias, et al., 2009; Royall, Palmer, Chiodo, & Polk,

2005) or *more* important (Burton, et al., 2006) than memory in predicting whether people experience difficulties with IADLs. Furthermore, in some studies, executive functions are associated with IADLs but memory does not appear to play any clear role (Insel, Morrow, Brewer, & Figueredo, 2006; Okonkwo, Wadley, Griffith, Ball, & Marson, 2006; Plehn, Marcopulos, & McLain, 2004). Given that executive dysfunction is one of the most frequently occurring forms of cognitive impairment in people with CVD (Saxton, et al., 2000; van Exel, et al., 2002; Wiederkehr, et al., 2009), the results of these studies suggest that patients with CVD may be particularly vulnerable to functional decline.

The potential impact of cognitive impairment on functional capacity has not yet been examined in people with cardiovascular pathology. Any relationship between cognition and functional capacity in this group is complicated by the fact that CVRFs and CVD can cause physical symptoms (e.g., pain, fatigue, or shortness of breath) that may also impair functional capacity (Brach, et al., 2008; Ettinger Jr, et al., 1994; Groll, To, Bombardier, & Wright, 2005; Pinsky, Jette, Branch, Kannel, & Feinleib, 1990; Richardson, 2003). The relative contributions of cognitive impairment and physical impairment to declines in functional capacity are not currently well understood.

AIMS OF STUDY 3

The third study examined patients with CVD to determine whether cognitive function is independently associated with ability to complete IADLs after controlling for potentially confounding factors, including cardiovascular burden, age, education and medical co-morbidity. Participants for this study were recruited from cardiovascular and endocrinology outpatient clinics. People with a diagnosis of dementia were excluded. Cognition was measured with the MoCA test because of its sensitivity to executive deficits.

Chapter 2: Review of Literature Examining Associations between Cardiovascular Pathology and Depression

2.1 Aetiology of Depression

In addition to having a higher risk of developing cognitive impairment, people with CVD or antecedent risk factors also have a higher risk of developing clinical depression. Depression is an episodic mood disorder with the core symptoms of depressed mood or loss of pleasure or interest in activities (American Psychiatric Association, 2000; World Health Organization, 2004). Twin studies indicate that the heritability of Major Depressive Disorder is 31 to 42 per cent (reviewed by Sullivan, Neale, & Kendler, 2000). Several specific genes have been examined, and one in particular, the serotonin transporter gene, has been linked to depression risk. People who have the short-short allele variant for this gene have a higher risk of developing depression (Gutierrez, et al., 1998; Ogilvie, et al., 1996).

One of the major explanations for the aetiology of depression is provided by the catecholamine model, which contends that depression results from net deficiencies of specific neurotransmitters, particularly norepinephrine and serotonin (Schildkraut, 1965). When patients with depression have been examined, changes in the concentration of these neurotransmitters (measured indirectly via their metabolites), and changes in the receptors and reuptake sites (measured post mortem) have been identified, providing support for this model (reviewed in Lange & Farmer, 2007; Nemeroff, 2002). This widely accepted model is further supported by the fact that pharmacological agents targeting serotonergic and noradrenergic systems are effective in ameliorating depressive symptoms in a high proportion of cases

(Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines Team for Depression, 2004).

Environmental factors and, in particular, stressful life events, also have a strong influence on whether someone will develop depression (Kraaij, Arensman, & Spinhoven, 2002; Paykel, 2003). One influential explanation for the link between environmental stress and depression is provided by the glucocorticoid model (Dinan, 1994). According to this model, stressful life events trigger the release of cortisol which, under normal circumstances, is an adaptive biological response that helps the individual respond to the stressors. However, in cases where the stress is severe or prolonged, or the individual has a genetic or dispositional vulnerability, the system that regulates cortisol levels, the Hypothalamic-Pituitary-Axis, may become dysregulated, leading to chronically high levels of circulating cortisol (de Kloet, Joels, & Holsboer, 2005; Dinan, 1994). According to this model, hypercortisolaemia affects the hippocampus and other limbic structures involved in emotional processing, which, in turn, leads to depression (Dinan, 1994). The model is supported by repeated observations of elevated cortisol levels, and changes in the levels of other hormones and neurotransmitters involved in the cortisol regulation process in people suffering from depression, and by a wide body of experimental research that has manipulated the levels of these hormones and neurotransmitters to produce changes in mood and behaviour (reviewed in Alexander, et al., 2009; Holsboer & Ising, 2008; Müller & Holsboer, 2006; Nestler, et al., 2002; Plotsky, Owens, & Nemeroff, 1998; Tafet & Bernardini, 2003) .

Recent perspectives on the aetiology of depression emphasise the interaction between environmental and biological factors (Ebmeier, et al., 2006). For example, a number of studies have now demonstrated that stressful life events confer a higher risk of depression for people

who carry the short-short allele variant of the serotonin transporter gene (see Uher & McGuffin, 2010 for a review and meta-analysis). Similarly, experimental studies have shown that people with the short-short variant of this gene show a stronger cortisol response to stressors (Gotlib, Joormann, Minor, & Hallmayer, 2008; Mueller, Brocke, Fries, Lesch, & Kirschbaum, 2010). Although the causal factors and exact mechanisms involved in the development of depression are still debated, it is generally agreed that both biological and environmental factors play a role (Ebmeier, et al., 2006; Lange & Farmer, 2007).

Studies that have employed structural and functional brain imaging or autopsy examination provide further insight into the aetiology and neurological processes involved in depression. Such studies have reported that people experiencing depression are characterised by abnormalities in brain regions known to be involved in emotional processing in healthy subjects. More specifically, changes are concentrated in circuits involving the prefrontal cortex, particularly ventromedial regions, and subcortical areas including the thalamus, basal ganglia, and limbic structures (reviewed by Carlson, Singh, Zarate, Drevets, & Manji, 2006; Ebmeier, et al., 2006; Frangou, 2006; Mayberg, et al., 1997). These regions correspond to the fronto-subcortical circuits outlined by Tekin and Cummings (2002) (described in section 1.4.2), in particular, the orbitofrontal circuit, as well as another circuit not previously discussed, involving limbic, thalamic and cortical regions (Carlson, et al., 2006). Functional MRI studies have revealed a general pattern of decreased activity in frontal cortical areas, and increased activity in limbic and other subcortical structures during depressive episodes (Stone, Lin, & Quartermain, 2008).

2.2 Explanations for the association between depression and CVD/CVRFs

Recent reviews have reported that depression affects approximately 33 percent of people with cerebrovascular disease (Hackett, Yapa, Parag, & Anderson, 2005), 14 to 20 percent of people with ischemic heart disease (Jiang, Glassman, Krishnan, O'Connor, & Califf, 2005), and 20 percent of people with diabetes (Anderson, Freedland, Clouse, & Lustman, 2001). These estimates are much higher than the prevalence of depression in the overall population, which is estimated to be around 3.2 to 6 percent in western countries (Patten, 1999; Wilhelm, Mitchell, Slade, Brownhill, & Andrews, 2003).

Three main models have been proposed to explain the association between CVD and depression (see reviews by Camus, Kraehenbuhl, Preisig, Bula, & Waeber, 2004; Kales, Maixner, & Mellow, 2005) (summarised in Figure 5):

1. a single factor may cause both depression and CVD;
2. depression may cause or exacerbate CVD; or
3. CVD may cause or exacerbate depression.

While the research in this thesis focuses on the third of these models, the other two major models are described briefly for contextual purposes, and to demonstrate that, in fact, all three models are supported by research and the aetiology of depression may be multifaceted and bi-directional.

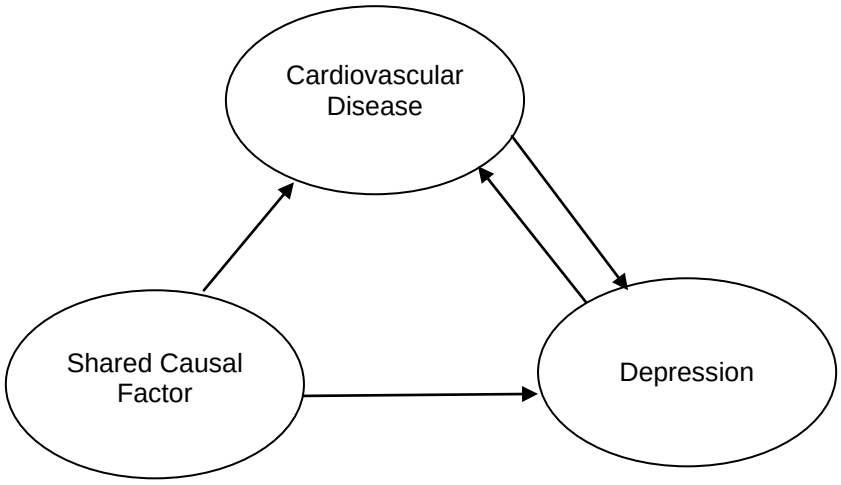

Figure 5. Summary of three models explaining the link between cardiovascular disease and depression.

According to the first model, depression and CVD both arise as a consequence of a shared causal factor (Scherrer, et al., 2003). Potential candidates for this shared causal factor include low levels of essential fatty acids or increased cholesterol levels (Skala, Freedland, & Carney, 2006; Tiemeier, van Tuijl, Hofman, Kiliaan, & Breteler, 2003). For example, low omega-3 levels may affect cardiovascular health by increasing inflammation, which, subsequently, increases the risk for thrombosis (Pischon, et al., 2003), and may simultaneously potentiate the risk for depression by altering neuronal membranes, thereby affecting the transmission of serotonin (Mullen & Martin, 1992). Consistent with this explanation, low levels of omega-3 fatty acids are associated with both coronary heart disease and with depression in epidemiological studies (reviewed in Skala, et al., 2006).

The second model proposes that depression causes or exacerbates CVD. This model provides an explanation for the consistent finding that, amongst patients with CVD, those who have depression are at greater risk of adverse clinical outcomes, including serious cardiac

events (Frasure-Smith & Lesperance, 2008; van Melle, et al., 2004), stroke (Thomas, Kalaria, & O'Brien, 2004), failed revascularisation surgery (Cherr, Wang, Zimmerman, & Dosluoglu, 2007), need for rehospitalisation (Stewart, et al., 2003; Sullivan, Levy, Crane, Russo, & Spertus, 2004), and death (Glassman, Bigger, & Gaffney, 2009; Sullivan, et al., 2004; van Melle, et al., 2004). Depression may influence these health outcomes via behavioural mechanisms. For example, it has been shown that depression adversely affects health-related behaviours, such as smoking and medication compliance (Glassman, et al., 2009; Gonzalez, et al., 2007). These unhealthy behaviours may in turn increase the risk of CVD. Alternately, depression may contribute to the development of CVD via biological pathways. For example, it has been shown that depression is associated with platelet activation and inflammatory responses, which are linked to thrombosis (Ataoglu & Canan, 2009; Morel-Kopp, et al., 2009). It is possible that depression triggers these responses, which could exacerbate cardiovascular illness (Frasure-Smith, et al., 2007; Ziegelstein, Parakh, Sakhuja, & Bhat, 2009).

The third model suggests that CVD causes or exacerbates depression, either through environmental stress or via direct biological mechanisms. The environmental stress explanation is based on the fact that CVD causes physical disability, which reduces quality of life, thus acting as an environmental stressor. This stress may contribute to the development of depression, possibly through associated cortisol elevation (Chiu, Chen, Huang, & Mau, 2005; Lyness, Duberstein, King, Cox, & Caine, 1998). In contrast, the biological explanation proposes that cardiovascular pathology causes damage to cerebral structures involved in emotional regulation and in this way increase a person's vulnerability to depression (Camus, et al., 2004; Kales, et al., 2005).

2.3 Vascular depression model

This final explanation has become known as the vascular depression model (Alexopoulos, Meyers, Young, Campbell, et al., 1997; Krishnan, Hays, & Blazer, 1997), and is discussed in more detail in the remainder of the chapter. The central tenant of this model is that vascular-related subcortical pathology contributes to the development of depression by disrupting the fronto-subcortical brain circuits involved in mood regulation (Alexopoulos, Meyers, Young, Campbell, et al., 1997; Krishnan, et al., 1997). As described previously, a vascular-related lesion occurring at any point along one of these circuits has the potential to affect the function of that circuit, disrupting the communication between cortical and subcortical areas. More specifically, it may impede the capacity of prefrontal areas to regulate the processes of subcortical structures, or for the regions to function in synchronicity (Royall, et al., 2002).

Two variants of the vascular depression model were published in the same year by independent research groups (Alexopoulos, Meyers, Young, Campbell, et al., 1997; Krishnan, et al., 1997). The model proposed by Alexopoulos et al (1997) is broader than the one advanced by Krishnan et al (1997) because, in addition to small vessel pathology (WMHs and lacunes), it encompasses pathology resulting from stroke and from metabolic or microanatomical changes associated with vascular risk factors. However, both models share the same underlying assumption that subcortical vascular pathology located in fronto-subcortical neural circuits contributes to depression, and are collectively referred to as the vascular depression model.

The vascular depression model can be distinguished from the *post stroke depression* model (Robinson, Kubos, Starr, Rao, & Price, 1984), which proposes that cortical strokes

affecting left anterior regions trigger depression (in contrast to the subcortical pathology emphasised by the vascular depression model). The post stroke depression model has not been consistently supported by research (see reviews by Bhogal, Teasell, Foley, & Speechley, 2004; Carson, et al., 2000; Hackett & Anderson, 2005).

The vascular depression model represents a major deviation from the dominant glucocorticoid and monamine models discussed at the beginning of Section 2.1. Importantly, the vascular depression model does not challenge those two etiological models. Rather, it contends that a subset of depression cases arise from vascular causes. The model is particularly relevant to older individuals because CVD typically affects people later in life.

2.4 Commonalities between models of vascular depression and vascular-related cognitive impairment

As depicted in Figure 6, the vascular depression model mirrors the major pathological processes that are understood to cause vascular-related cognitive impairment. More specifically, it has been hypothesised that cerebral small vessel disease plays a critical role not only in the development of cognitive impairment but also depression, through disruption to fronto-subcortical circuits (Fish & Bayer, 2004; Pugh & Lipsitz, 2002). Based on the assumption that depression and cognitive impairment arise from the same pathological processes, some commentators in the field view the two problems as central features of a frontal-subcortical syndrome (Alexopoulos, 2001; Fish & Bayer, 2004; Pugh & Lipsitz, 2002).

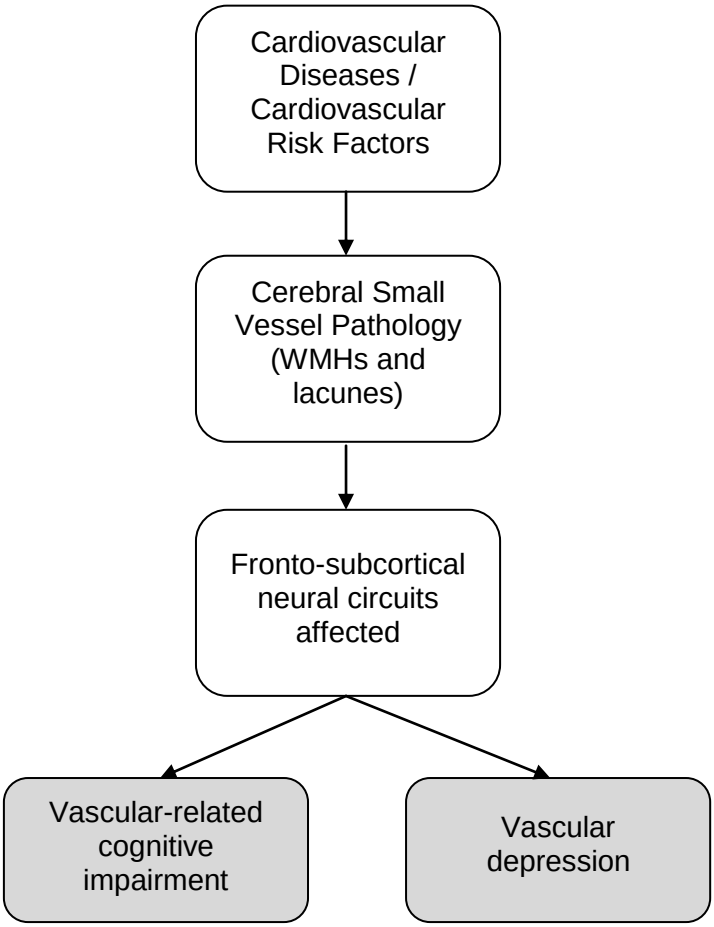

Figure 6. Proposed mechanisms involved in the development of vascular-related cognitive impairment and vascular depression.

Several lines of research have produced results that are consistent with the idea that depression and cognitive impairment arise from similar biological processes. Large epidemiological studies have demonstrated that cognitive impairment and depression often co-occur in old age (Biringer, et al., 2005; Stek, et al., 2004) and people with more severe executive problems tend to have more severe depression symptoms (Airaksinen, Larsson, Lundberg, & Forsell, 2004; Butters, et al., 2000; Cervilla, Prince, & Rabe-Hesketh, 2004; Ganguli, Du, Dodge, Ratcliff, & Chang, 2006; Rainer, et al., 2006; Sanders, et al., 2006; Sheline, et al., 2006). Similarly, longitudinal research has shown that people who are affected by depression are at a greater risk of later developing cognitive impairments (Barnes, et al.,

2006; Fuhrer, Dufouil, & Dartigues, 2003; Gabryelewicz, et al., 2007; Geda, et al., 2006; Sachs-Ericsson, Joiner, Plant, & Blazer, 2005), although not all findings have been consistent (Ganguli, et al., 2006).

This area is conceptually complex because cognitive impairment is considered to be a symptom of depression in a number of currently used diagnostic systems, raising the risk of tautology (American Psychiatric Association, 2000; World Health Organization, 2004). There is evidence to suggest that memory impairment arises as a result of the depressive episode (as opposed to being caused by cerebral small vessel disease). Several meta-analyses have confirmed that hippocampal atrophy is observed in depressed patients (Campbell, Marriott, Nahmias, & MacQueen, 2004; Videbech & Ravnkilde, 2004) and it appears to be ameliorated by treatment with Selective Seratonin Reuptake Inhibitors (SSRIs) (Sahay & Hen, 2007). This suggests that memory impairment may be a secondary outcome of the depressive episode, perhaps triggered by the neurotoxic effects of hypercortisolemia (Holsboer, 2003).

However, other forms of cognitive impairment also occur within depressive episodes, including executive dysfunction and attentional difficulties (Airaksinen, et al., 2004; Ganguli, et al., 2006; Rainer, et al., 2006; Sheline, et al., 2006), and it is possible that these deficits are caused by underlying cerebral small vessel disease rather than by processes specific to the depressive episode. Although findings vary across studies, a recent review showed that in older cohorts, deficits in executive functions and attention tend to endure after successful treatment of depression symptoms, whereas other forms of cognitive impairment more commonly diminish after remission from depression (Douglas & Porter, 2009). The persistence of executive dysfunction after resolution of a depressive episode suggests that rather than being a secondary outcome of the depressive episode, it could be attributable to

permanent structural damage associated with cerebral small vessel disease. Consistent with this, a recent longitudinal study demonstrated that cognitive deficits that persisted after a depressive episode in older patients were associated with WMHs but not with hippocampal atrophy or cortisol levels (Kohler, et al., 2010). Although they are not definitive, taken together, these findings support the idea that some cognitive deficits (particularly memory deficits) arise as a secondary outcome of the depressive episode, whereas others (particularly executive dysfunction) are more persistent, and may therefore be associated with permanent underlying structural damage. This interpretation is consistent with the idea that both vascular-related cognitive impairment and vascular depression result from the shared aetiological processes depicted in Figure 6.

2.5 Evidence for the validity of the vascular depression model

The remainder of the chapter reviews research that has examined the validity of the vascular depression model. The validity of the model has been examined using two main approaches. The first approach uses epidemiological methods to determine whether people with a higher burden of cardiovascular pathology (quantified on the basis of either clinical or radiological signs) have a higher risk of depression than people with a lower burden of cardiovascular pathology. The second approach involves studying people who are already depressed to determine whether those who show evidence of cardiovascular pathology (i.e. are assumed to have vascular depression) display a unique clinical presentation or illness course compared to other depressed people.

2.5.1 Epidemiological research

Association between clinical markers of cardiovascular pathology and depression

Studies adopting the epidemiological approach have, in most cases, reported that a higher burden of clinically diagnosed cardiovascular pathology (i.e. a higher number of CVD diagnoses) is associated with a higher risk of depression. Although some early large-scale epidemiological studies based on clinical samples failed to find an association between the total number of CVRFs or CVD diagnoses and the presence or severity of depression (Lyness, Caine, et al., 1998; Lyness, Caine, King, & al., 1999), more recent studies using clinical cohorts have reported that people who have a higher number of CVRFs or CVD diagnoses are indeed more likely to experience depression (Holley, et al., 2006; Mast, MacNeill, & Lichtenberg, 2004; Mast, et al., 2008; Sanders, et al., 2006). Several large community-based cohorts have also been examined. One of these reported non-significant results (Vinkers, et al., 2005) but four others reported that the prevalence of depression increases in line with the total number of CVRFs or CVD diagnoses (Barnes, et al., 2006; Luijendijk, Stricker, Hofman, Witteman, & Tiemeier, 2008; Stek, et al., 2004; Stewart & Hirani, 2009).

The few negative findings may be due to differences in study populations, or may reflect the fact that it is difficult to quantify the burden of vascular pathology using clinical indicators. A single diagnosis like ischaemic heart disease may vary widely in severity from one patient to the next, making it an insensitive proxy measure of vascular pathology. Significant associations between depression and cardiovascular burden have been reported in large studies that have quantified cardiovascular burden using direct physiological measures of vessel disease, such as vessel wall thickness, the degree of vessel calcification, or arterial stiffness (Elovainio, et al., 2005; Tiemeier, Breteler, van Popele, Hofman, & Witteman, 2003; Tiemeier, et al., 2004), providing further support for the model.

Association between radiological markers of cardiovascular pathology and depression

Brain imaging offers a more direct method for measuring vascular-related brain pathology and, therefore, for assessing the validity of the vascular depression model. Several large-scale cross-sectional epidemiological studies have examined whether elderly people who have a greater burden of WMHs and/or lacunes have a higher risk of depression. Consistent with the vascular depression model, five studies have reported that people with more severe WMHs are more likely to experience depression (de Groot, de Leeuw, Oudkerk, Van Gijn, et al., 2000; Ikram, et al., 2010; Jorm, et al., 2005; O'Brien, et al., 2006; Steffens, Helms, Krishnan, & Burke, 1999). A sixth failed to find an association but the people in this study were the highly selected participants of a drug trial, and overall rates of WMHs and of depression were much lower than for the other studies (Versluis, et al., 2006). Three of these studies also examined basal ganglia lesions. Two reported an association between the number of basal ganglia lesions and depression (O'Brien, et al., 2006; Steffens, et al., 1999), but a third failed to detect a significant relationship (Jorm, et al., 2005). Overall, the results of these large studies are mainly consistent with the vascular depression model.

Several longitudinal studies have also been carried out. Results of two such studies showed that patients without a depression diagnosis at baseline had a higher risk of developing depression two to four years later (Godin, et al., 2008; Teodorczuk, et al., 2010) if they had a higher burden of WMHs, although the relationship was not seen after 10 years in another cohort (Ikram, et al., 2010). Other studies have examined whether a worsening of WMHs over time predicts the onset of depression. One reported that increasing severity of WMHs predicted incident depression (Teodorczuk, et al., 2010). Another study failed to find a relationship but this was the study that used the highly selected participants from a drug trial

(Versluis, et al., 2006). Overall, the majority of the longitudinal studies support the vascular depression model.

Many other studies have examined the relationship between depression and brain pathology using case-control designs (i.e. comparing depressed to non-depressed patients). These studies have been relatively small and have produced mixed findings, possibly due to inadequate statistical power. However, a recent review and meta-analysis of thirty case-control studies confirmed that elderly people suffering from depression had a greater volume of WMHs than those who were depression free (Herrmann, et al., 2008), which is also consistent with the vascular depression model.

In addition to considering the total volume of WMHs, a number of other case-control studies have examined whether brain pathology is concentrated in frontal-subcortical neural circuits in people with depression, as would be predicted by the vascular depression model. Several imaging studies have reported that elderly people with depression are more likely to have lacunes or ischaemic lesions in the basal ganglia (Santos, et al., 2009; Steffens, et al., 1999; Tupler, et al., 2002) and WMHs or other microscructural changes in white matter tracts projecting from the frontal lobes (Dalby, et al., 2009; Dotson, Davatzikos, Kraut, & Resnick, 2009; Greenwald, et al., 1998; MacFall, Payne, Provenzale, & Krishnan, 2001; Taylor, et al., 2004; Taylor, et al., 2007; Thomas, et al., 2003; Tupler, et al., 2002). Although these findings do not demonstrate that the cerebral pathology located in these circuits played a causal role in the development of depression, as the vascular depression model asserts, they are consistent with this idea.

An alternate explanation for the association between cardiovascular pathology and depression

Even though clinical and radiological measures of cardiovascular pathology are associated with depression in most of the studies reviewed above, these results do not definitively demonstrate that CVRFs or CVD cause depression via biological mechanisms, and therefore don't provide unequivocal support for the validity of the vascular depression model. An alternative explanation for the observed associations between CVD and depression is that the functional disability caused by CVD reduces quality of life, thus increasing stress and triggering depression, perhaps via cortisol elevation. For example, angina pectoris associated with ischaemic heart disease or claudication pain associated with peripheral vascular disease may impede employment or self-care, both of which are stressful life events. In addition to the stress generated by the clinical symptoms of CVD, WMHs are directly associated with neurological problems, including gait and balance disturbance (Baezner, et al., 2008; Rosano, Brach, Longstreth, & Newman, 2006), difficulties with urinary control (Kuchel, et al., 2009; Poggesi, et al., 2008) and general disability (Inzitari, et al., 2009; Sachdev, et al., 2005). These disabling neurological symptoms of cerebral small vessel disease may also contribute to a reduction in quality of life and an increase in stress. Indeed, many chronic medical conditions such as arthritis and asthma, which do not directly affect the brain, are associated with depression (Begum, Tsopelas, Lindesay, & Stewart, 2009; Chapman, Perry, & Strine, 2005; Mills, 2001; Penninx, et al., 1996) and these associations can largely be explained by the functional disability that is inherent to them (Begum, et al., 2009). Therefore, illness in general, rather than cardiovascular disorders specifically, may explain the observed associations between CVD and depression, and thus subcortical ischaemic damage may not play a direct role in the development of depression.

It should be possible to resolve the question of whether cardiovascular pathology is directly associated with depression, or whether the relationship is medicated by physical disability or quality of life, by employing research designs that measure and control for these potentially mediating factors. Most of the aforementioned studies that focused on clinical indicators of CVD (as opposed to radiological indicators) did not control for physical disability or quality of life. Of the six that did, three reported that the association between cardiovascular burden and depression remained significant even after controlling for functional capacity (Holley, et al., 2006; Mast, et al., 2008; Mast, Neufeld, MacNeill, & Lichtenberg, 2004). However, the functional measures that were used in these studies were relatively insensitive (e.g. tests of walking capacity, or a checklist of basic activities of daily living, such as showering and feeding, which are only likely to have been sensitive to very severe functional impairments). A fourth study found that the relationship failed to reach significance after controlling for medical burden (Sanders, et al., 2006). The final two studies found that associations were substantially attenuated after adjustment for general health status (Stewart & Hirani, 2009) or co-morbidity (Lyness, et al., 2006). It is therefore possible that psychological stress may at least partially explain the relationship between CVD and depression via psychological stress and associated cortisol elevation.

In the case of the brain imaging research, most of the case-control studies failed to examine physical disability or quality of life. However, three of the five large-scale cross-sectional epidemiological studies discussed above used regression modelling to examine whether associations between subcortical brain pathology and depression remained significant after controlling for these factors. The association between WMHs and depression failed to reach significance in two of these studies when health status (Jorm, et al., 2005) or functional status (Steffens, et al., 1999) were controlled, but was significant in a third when these two

variables were controlled (O'Brien, et al., 2006). In the two longitudinal studies that reported positive results, the results remained significant when IADL function was controlled in one study (Godin, et al., 2008) but the relationship between WMHs and depression was no longer significant when transition to disability was controlled in the other (Teodorczuk, et al., 2010). The association between basal ganglia lesions and depression also failed to reach significance after quality of life was controlled in one study (O'Brien, et al., 2006) but was significant when functional status was controlled in another study (Steffens, et al., 1999). These results are equivocal, at best, and suggest that at least some of the association between brain pathology and depression may be explained by these psychosocial factors.

Future epidemiological research that examines the validity of the vascular depression model should ideally incorporate newer imaging techniques with better spatial resolution than the visual rating scales used in previous studies (de Groot, de Leeuw, Oudkerk, Hofman, et al., 2000; Jorm, et al., 2005; O'Brien, et al., 2006; Steffens, et al., 1999) to increase measurement sensitivity. Similarly, it would be helpful to identify whether lesions that occur in the fronto-subcortical circuits, rather than whole brain lesion load, predict depression. As discussed, it will also be necessary to include sensitive measures of disability and/or health-related quality of life.

Consideration should also be given to the possibility that previous approaches to testing the vascular depression model might be overly simplistic. Alexopoulos et al (1997) originally proposed that vascular factors may "predispose, precipitate, or perpetuate" depression. This conceptualisation allows for the possibility of an interaction between vascular disease and other causal factors. It is well established that stressful life events contribute to depressive illness (Kraaij, et al., 2002; Paykel, 2003). Rather than searching for independent

relationships between vascular pathology and depression, future epidemiological studies might consider the possibility that biological and environmental factors interact. If pathology in the fronto-subcortical circuits reduces a person's capacity for emotional regulation, as hypothesised, then a stressful life event, which may have otherwise been manageable, may trigger depression in the presence of cerebral pathology. Consistent with this idea, Holley et al (2006) reported that stressful life events conferred a greater risk of depression for people who had more severe WMHs.

2.5.2 Clinical research

The second major approach to assessing the validity of the vascular depression model has involved determining whether people who meet the diagnostic criteria for vascular depression are characterised by differences in symptom profile, illness course or treatment response than other patients with depression. One difficulty with this approach is that vascular depression is a hypothetical construct and, as such, its diagnostic criteria are not fixed. Notwithstanding these complexities, research examining the presentation and course of vascular depression has the potential to supplement other approaches to testing the validity of the vascular depression model.

Three sets of diagnostic criteria for vascular depression have been proposed and are summarised in Table 1. The criteria proposed by Krishnan et al (1997) are based primarily on MRI findings. In contrast, the criteria developed by Alexopoulos et al (1997) are broader, and accept clinical evidence of CVD as an alternative to MRI evidence. The third set of criteria, referred to as the Depression Executive-Dysfunction (DED) syndrome (Alexopoulos, 2001), is based on neuropsychological test performance and on the assumption that poor executive function reflects the presence of underlying pathology in the frontal-subcortical circuits. In

other words, a person who presents with executive dysfunction is assumed to be affected by pathology in fronto-subcortical regions and, thus, executive dysfunction acts as a proxy marker for cerebral pathology. It should be noted that this final set of criteria allow for pathology arising not only from vascular damage but also pathology resulting from non-vascular causes, such as aging or other degenerative brain disorders.

Table 1. Diagnostic Criteria for Vascular Depression

MRI-defined Vascular Depression (Krishnan, et al., 1997)

- Significant deep WMHs or subcortical gray matter ratings on MRI (modified Fazekas visual classification system score ≥ 2)

Vascular Depression (Alexopoulos, Meyers, Young, Campbell, et al., 1997)

Cardinal Features (expected in all patients)

- Vascular disease or vascular risk factors (either clinical manifestations e.g. stroke or transient ischaemic attack, focal neurologic signs, atrial fibrillation, angina, myocardial infarction, carotid bruit, hypertension and hyperlipidemia, or laboratory findings e.g. significant white matter hyperintensities at the territory of the perforating arteries, infarcts, or evidence of carotid occlusion or stenosis of the Willis Circle arteries)
- Depression onset after 65 years of age or change in the course of depression after the onset of vascular disease in patients with early-onset depression
- Development of more frequent and persistent depressive episodes

Secondary Features (expected in most but not all patients)

- Cognitive impairment consisting of but not limited to disturbance of executive functions (i.e. planning, organisation, sequencing, and abstracting)
- Psychomotor retardation
- Limited depressive ideation (e.g. guilt)
- Poor insight
- Disability
- No family history of mood disorders

Depression Executive Dysfunction (DED) Syndrome (Alexopoulos, 2001)

- Occurs in late life
- Executive dysfunction

Other suggested clinical features

- Psychomotor retardation
- Limited depressive ideation
- Prominent disability

MRI = Magnetic Resonance Imaging; WMHs = White Matter Hyperintensities

Alexopolous et al (1997) suggested that people with vascular depression may display a distinct cluster of depressive symptoms associated with frontal lobe pathology, including greater psychomotor retardation, less agitation, less guilt, and a lack of insight. This proposition has been examined in multiple studies by comparing the depression symptom profiles of people meeting one of the sets of diagnostic criteria for vascular depression (see Table 1) to those of other depressed patients. A recent review of 13 such studies showed that the findings have been mixed and none of these depressive symptoms is consistently linked to clinically or radiologically defined CVD (McDougall & Brayne, 2007). However, these findings do not definitively preclude the existence of vascular depression. It may be the case that the presentation of vascular depression resembles other forms of depression. Alternatively the diagnostic criteria may need further refinement to produce reliable case selection.

Vascular depression and treatment response

Even if the clinical presentation of people with vascular depression does not differ from that of people with other forms of depression, patients with vascular depression may differ in their treatment response (Steffens, 2004). Based on the assumption that the depressive symptoms in people with vascular depression develop as a result of a different etiological process than other patients with depression, Alexopoulos et al (2001) and others (Stahl, Zhang, Damatarca, & Grady, 2003) have argued that this group of patients may respond poorly to traditional antidepressant medications. This assertion is based on the fact that the function of the fronto-subcortical circuits is modulated by several neurotransmitters, including GABA, dopamine and acetylcholine (Alexopoulos, 2001), but most traditional antidepressants, such as tricyclics and SSRIs, do not primarily target these neurotransmitter systems (Alexopoulos, 2006); instead acting on serotonin and noradrenaline receptor sites (Richelson, 2001).

A large number of studies have evaluated the validity of the vascular depression model by examining whether depressed patients who respond poorly to antidepressant treatment are characterised by abnormalities in fronto-subcortical circuits, identified either using radiological data or cognitive performance. Most of the studies that have employed brain imaging technology to examine this issue have reported that structural (Alexopoulos, Kiosses, Choi, Murphy, & Lim, 2002; Alexopoulos, et al., 2008; Hickie, et al., 1995; Simpson, Baldwin, Jackson, & Burns, 1998; Steffens, et al., 2001; Taylor, et al., 2003) and functional (Mayberg, et al., 1997; Navarro, et al., 2004; Pizzagalli, et al., 2001) abnormalities in pre-frontal and subcortical brain regions are more common in depressed patients who fail to respond to antidepressant medication than in those who respond, although, non-significant findings have also been reported (Baldwin, et al., 2004; Navarro, et al., 2004; Renshaw, et al., 1997; Salloway, et al., 2002). The predominantly positive results are consistent with the contention that structural or functional abnormalities in these circuits are associated with poor treatment outcomes and lend support to the validity of the vascular depression model.

Of the studies that have relied on cognitive performance as a proxy measure of fronto-subcortical dysfunction, several have reported that people who fail to respond to antidepressant treatment exhibit poorer pre-treatment executive function than people who respond (Alexopoulos, et al., 2005; Dunkin, et al., 2000; Kalayam & Alexopoulos, 1999; Kampf-Sherf, et al., 2004; Majer, et al., 2004; Sneed, et al., 2007), which is consistent with the vascular depression model. However, such findings have not always been replicated (Alexopoulos, et al., 2007; Gallagher, Robinson, Gray, Porter, & Young, 2007; Potter, Kittinger, Wagner, Steffens, & Krishnan, 2004; Story, Potter, Attix, Welsh-Bohmer, & Steffens, 2008; Taylor, et al., 2006), making it difficult to draw any overall conclusions. These mixed findings may, in part, be explained by the large number of executive function tests that

have been employed, as well as difference in the study samples, and by the fact that many studies had small samples (less than 30 people), and may therefore have lacked statistical power.

AIMS OF STUDY 4

Study 4 was designed to evaluate the validity of the vascular depression model by focusing on cognitive performance as a predictor of antidepressant treatment response, because the research in this area is particularly unclear and difficult to interpret. The study was designed to address some of the problems affecting the existing research in this area, such as small sample sizes and the wide variety of assessment methods, by using meta-analytic techniques to pool and analyse the data from existing studies. Thus, the fourth study used a meta-analysis to assess the level of evidence for the hypothesis that people who respond to antidepressant treatment exhibit better executive functioning than people who don't respond.

2.5.3 Further evaluation of the vascular depression model using a case-control study design to examine treatment response

A major limitation of research that has focused on cognitive test performance as a predictor of antidepressant treatment response is that it does not directly test the hypothesis that people meeting the DED criteria for vascular depression (i.e. depression *and* executive dysfunction) will fail to respond to treatment. This is because these studies do not examine the *specific* outcomes of people who meet the DED criteria. Part (a) of Figure 7 illustrates this problem. In previous studies, participants were dichotomised into medication-responders (shown on the right) and medication-non-responders (shown on the left). Assuming that the predictions of the vascular depression model are valid, and that people with executive

dysfunction fail to respond to antidepressant treatment, these vascular depression patients (represented by the dark shaded box) are grouped together with other depressed patients who fail to respond to treatment for other reasons. If the non-responder group contains a large proportion of people with vascular depression (labelled DED participants), then the low executive function scores of these vascular depression subjects will pull down the average level of executive function for the non-responder group, and a significant difference between responder and non-responder groups is likely to be observed (see Figure 7a). However, if the study sample contains relatively few people with vascular depression, then the mean level of executive function in the non-responder group will not be as low, and a significant between-group difference is less likely to be detected (see Figure 7b). In other words, even if all of the vascular depression participants in a study fail to respond to medication, as the model predicts, non-significant results may still be produced if only a small proportion of DED participants was included in the study sample.

A more definitive way to examine the predictions of the model would be to identify, at baseline, the participants who meet the DED criteria. The rate of treatment response in this group could then be compared to the rate of treatment response in the remaining participants (Figure 7c). Using this approach, the proportion of DED patients included in the study sample would have no bearing on the effect size when the two groups are compared.

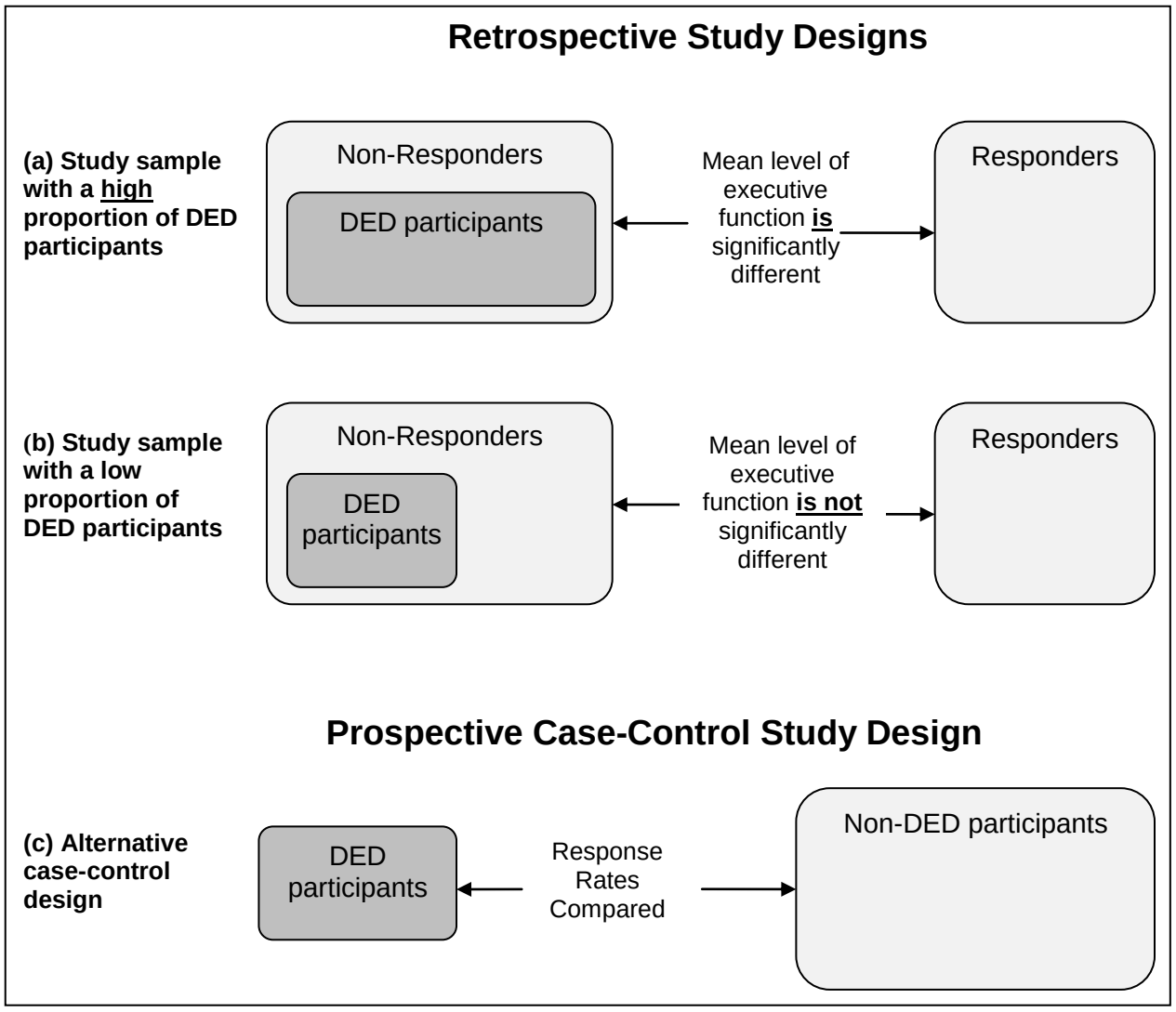

Figure 7. Alternative Study Designs for Testing the Treatment-Response Predictions of the DED Model. **The likelihood of finding a significant difference in the mean level of executive function in Responders vs Non-Responders is influenced by the proportion of people with the DED syndrome included in the study sample in retrospective study designs (a and b). The proportion of DED participants included in a study sample is less important in prospective case-control study designs (c).**

AIMS OF STUDY 5

Using the alternative case-control study design depicted in Figure 7c, the fifth study examined whether depressed patients who exhibited the DED syndrome (i.e. depression and

executive dysfunction) would be less likely to respond to antidepressant treatment than other depressed patients. Participants were drawn from a sample of people with diagnosed CVD because this group has a higher risk of cerebral pathology and associated executive dysfunction (Breteler, van Swieten, et al., 1994; Jeerakathil, et al., 2004), and is therefore likely to include a relatively high proportion of people meeting the DED criteria, thus maximising the power of the study to detect significant results.

2.6 Summary of the research reviewed in Chapters 1 and 2

To summarise the literature reviewed in Chapters 1 and 2, advances in brain imaging technology have revealed that small vessel brain pathology is common (Breteler, van Swieten, et al., 1994; de Leeuw, et al., 2001; Longstreth Jr, et al., 1998; Vermeer, et al., 2002) , and typically affects frontal and subcortical brain regions (Artero, et al., 2004; de Leeuw, et al., 2001; Kalaria, et al., 2004). Consistent results from large epidemiological studies have demonstrated that CVD and CVRFs are associated with an increased risk of cerebral small vessel disease (Breteler, van Swieten, et al., 1994; Jeerakathil, et al., 2004). There is also strong epidemiological evidence indicating that small vessel pathology contributes to cognitive impairment, particularly in the domains of executive function and information processing speed (Nordlund, et al., 2007; Saxton, et al., 2000; van Exel, et al., 2002; Wiederkehr, et al., 2009). Furthermore, well-designed experimental studies have demonstrated that the treatment of hypertension, a central CVRF, can reduce cognitive decline, providing strong evidence for a direct causal relationship between CVRFs/CVD and cognitive impairment (Bosch, et al., 2002; Forette, et al., 1998; Tzourio, et al., 2003).

Evidence for the role of small vessel disease in depression is less conclusive. Epidemiological research has generally reported that people with clinical or radiological

indicators of CVD have higher rates of depression (Barnes, et al., 2006; Holley, et al., 2006; Luijendijk, et al., 2008; Mast, et al., 2008; Mast, Neufeld, et al., 2004; Sanders, et al., 2006; Stek, et al., 2004; Stewart & Hirani, 2009). However, the available evidence fails to definitively rule out the possibility that the relationships are mediated, at least in part, by poor quality of life and associated psychological stress. Findings from clinical studies have also been equivocal. Relatively few studies have examined the clinical presentation of vascular depression cases and overall have failed to show that people meeting criteria for vascular depression consistently show a unique symptom profile disease (reviewed in McDougall & Brayne, 2007). Of the clinical studies that have examined treatment outcomes, the majority of those using radiological information to classify vascular depression cases have reported that poor treatment outcomes are associated with cerebral pathology in the front-subcortical areas but the influence of potentially confounding variables, such as disability or quality of life, has not been adequately assessed. Studies relying on cognitive data to predict treatment outcomes have produced mixed findings, which are difficult to interpret. Taken together, this body of research is generally consistent with the vascular depression model but does not provide definitive support.

Although research in the areas of vascular-related cognitive impairment and depression has developed in parallel and shares overlapping etiological models, the research into vascular-related cognitive impairment is relatively more advanced. Consequently, the gaps in knowledge and, therefore, the areas most in need of further research, differ for these two fields. In the case of vascular-related cognitive impairment, some of the most immediate concerns relate to establishing the validity of specialised measurement tools, examining specific biological mechanisms in the development of the problem, and quantifying the impact

of the problem. In the case of vascular depression, establishing the validity of the aetiological model is of primary concern.

2.7 Summary of the thesis aims

The research presented in this thesis was designed to address each of these gaps. As previously stated, the specific aims of the thesis are:

- To determine the sensitivity and specificity of the Montreal Cognitive Assessment (MoCA) to detect MCI in a population at risk of vascular-related MCI (Study 1).
- To examine whether poor vasodilation is associated with ischaemic brain damage and/or cognitive impairment (Study 2).
- To investigate whether cognitive impairment is independently associated with disability in day-to-day activities in patients with CVD (Study 3).
- To conduct a meta-analysis to determine whether existing research supports the hypothesis that people who fail to respond to medication have significantly lower levels of executive function (Study 4).
- To examine whether cardiac patients who exhibit executive dysfunction are less likely to respond to antidepressant treatment (Study 5).

Chapter 3: Study 1

The following chapter is a manuscript that has been accepted for publication in the Journal of Geriatric Psychiatry and Neurology (http://jgp.sagepub.com/).

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3.1 Title Page

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

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Declaration of Conflicting Interests: No author has a conflict of interest to declare.

3.2 Abstract

While rates of Mild Cognitive Impairment (MCI) are relatively high in populations with cardiovascular diseases and risk factors, screening tests for MCI have not been evaluated in this patient group. This study investigated the sensitivity and specificity of the Montreal Cognitive Assessment (MoCA) tool for detecting MCI in 110 patients (mean age 67.9 ±11.7 years; 60% female) recruited from hospital cardiovascular outpatient clinics. Mean MoCA performance was relatively low (22.8 ± 3.8) in this group, with 72.1% of participants scoring below the recommended cut-off for cognitive impairment (< 26). The presence of MCI was determined using the Neuropsychological Assessment Battery Screening Module (NAB-SM). Both Amnestic MCI and Multiple-Domain MCI were identified. The optimum MoCA cut-off for detecting MCI in this group was < 24. At this cutoff, the MoCA's sensitivity for detecting Amnestic MCI was 100% and for Multiple-Domain MCI it was 83.3%. Specificity rates were 50.0% and 52.0% respectively. The poor specificity of the MoCA suggests that it will have limited value as a screening test for MCI in settings where the overall prevalence of MCI is low.

Key words: Mild Cognitive Impairment, cardiovascular, Montreal Cognitive Assessment, MoCA, MCI, vascular cognitive impairment, vascular dementia.

3.3 Introduction

Mild Cognitive Impairment (MCI) is a state characterised by a deterioration in cognitive functioning greater than expected for a person's age and education level that does not affect basic activities of daily living and, therefore, does not meet the criteria for dementia (Gauthier et al., 2006). The major categories of MCI are Amnestic MCI, where the cognitive impairment is restricted to memory function, and Multiple-Domain MCI, where several other domains such as attention or executive function are affected.(Gauthier et al., 2006) Between 3% and 5% of the general elderly population is affected by Amnestic MCI and up to 17% is affected by MCI involving a broader range of cognitive domains (Mariani, Monastero, & Mecocci, 2007). People affected by MCI are more likely to experience difficulties managing the complex aspects of their self-care, such as using transportation and managing medications and home finances (Kim et al., 2009; Mariani et al., 2008; Pereira, Yassuda, Oliveira, & Forlenza, 2008). They are also at increased risk for developing dementia in the future (Panza et al., 2005).

The risk of MCI is higher for people who have cardiovascular diseases (Barnes, Alexopoulos, Lopez, Williamson, & Yaffe, 2006) or cardiovascular risk factors (Kivipelto et al., 2001), making MCI a particularly pertinent consideration for health care professionals working with this patient group. The early detection of MCI provides an opportunity to implement secondary medical prevention measures, such as the aggressive management of cardiovascular risk factors and ongoing monitoring of cognitive decline. As a first step, a simple screening test that is sensitive to MCI in cardiovascular populations could identify people who would benefit from referral to specialist clinics for comprehensive neuropsycholgical assessment. The Montreal Cognitive Assessment (MoCA) (Nasreddine et

al., 2005) is a brief paper-and-pencil test that may be suitable for this purpose. In contrast to other screening tools (Lonie, Tierney, & Ebmeier, 2009), the MoCA was designed to assess a broad range of cognitive skills, including executive function. This is particularly important in cardiovascular populations because multiple cognitive domains may be affected in the early stages of vascular-related cognitive impairment (Ingles, Boulton, Fisk, & Rockwood, 2007; Nordlund, Rolstad, Klang, & Lind, 2007; Zanetti et al., 2006).

Previous research has shown that the MoCA is sensitive to MCI in memory clinics where Alzheimer's pathology is likely to predominate (Luis, Keegan, & Mullan, 2008; Nasreddine et al., 2005; Smith, Gildeh, & Holmes, 2007). However, the MoCA's capacity to accurately detect MCI in populations at specific risk of vascular-related cognitive impairment has not yet been assessed. Furthermore, previous studies have only focused on the MoCA's ability to detect isolated memory deficits. Although mild memory impairments predict the later development of Alzheimer's Disease, deficits in other cognitive domains are better predictors of Vascular Dementia (Ingles et al., 2007; Zanetti et al., 2006). Moreover, people with multiple cognitive deficits show higher rates of conversion to dementia overall (Alexopoulos, Grimmer, Perneczky, Domes, & Kurz, 2006; Di Carlo et al., 2007). It is not yet known how well the MoCA can detect Multiple-Domain MCI. The present study was therefore designed to investigate the sensitivity and specificity of the MoCA for detecting Amnestic MCI and Multiple-Domain MCI in a sample with a high level of cardiovascular pathology.

3.4 Method

3.4.1 Recruitment

Participants (n = 110) were recruited on a prospective basis from cardiac and diabetic/endocrine outpatient clinics at a large tertiary-referral hospital in South Australia. These clinics are supervised by consultant cardiologists and endocrinologists, and typically complete around 2,600 and 1,700 patient appointments per annum respectively. Patients are referred to these clinics because they have a pre-established cardiovascular disease that requires ongoing management or one or more cardiovascular risk factors, such as hypertension or diabetes. Consecutive eligible patients were invited to participate. Those who could be contacted, who consented, and were available for interview during the study period, were recruited.

The present study was nested within a larger study that was designed to examine the prevalence of undiagnosed Peripheral Arterial Disease (PAD) (unpublished). Patients were eligible for that study if they had attended one of the specified clinics within the 8-month study period; were aged over 45; had one or more cardiovascular diseases or risk factors (smoking, diabetes, hypertension or dyslipidemia); had not previously been diagnosed with dementia; had the capacity to provide informed consent; and could speak English. Patients were excluded if they had a documented diagnosis of PAD or had participated in a screening test for PAD involving dopplar in the preceding three months, had undergone major surgery in the previous three months, or were dependent on a wheelchair. In addition to these criteria, patients had to have spoken English before the age of five to be included in the current study (because English proficiency could affect test performance).

The research complied with the ethical guidelines for human experimentation stated in the Declaration of Helsinki, and was approved by the relevant Hospital and University research ethics committees.

3.4.2 Clinical and demographic data collection

Each participant was assessed at the hospital in a single session. A study nurse used a standardised set of questions to gather demographic and medical history, and to confirm that participants were able to independently perform six basic activities of daily living (bathing, dressing, toileting, transferring, continence, and feeding) (Katz, Ford, Moskowitz, Jackson, & Jaffe, 1963).

The presence of cardiovascular diseases (ischaemic heart disease, stroke/transient ischaemic attack, atrial fibrillation, peripheral arterial disease) and major risk factors for these diseases (e.g. hypertension, diabetes, smoking status) was determined on the basis of self-report and a review of hospital records. Height, weight, blood pressure and ankle-brachial index were measured during the interview, and participants were asked to submit a sample of blood (fasting) within 3 months of the assessment to measure lipid levels and hemoglobin A1c (HbAIc) to supplement information available from medical records.

3.4.3 Cognitive testing

Following the clinical assessment, the same nurse administered the MoCA. The MoCA is a paper and pencil format test that takes 10 to 20 minutes to administer. It includes items designed to assess visuospatial abilities (clock drawing and cube copying), memory (5-word list learning and delayed recall), executive functioning (abbreviated trails-B, phonemic

fluency, and similarities tasks), attention, concentration and working memory (target detection using finger tapping, serial subtraction, and digits forward and backward) language (picture naming and sentence repetition), and orientation (time and place). Scores range from zero to 30, with higher scores indicating better performance. The scoring guidelines recommend adding an additional point for people with less than 13 years of education (Nasreddine et al., 2005). An initial validation study concluded that an education-adjusted score below 26 is likely to indicate MCI (Nasreddine et al., 2005).

Classification of MCI based on gold standard testing

In the final phase of the assessment, a registered psychologist (SNM) who was blinded to the MoCA result and clinical status of the patient, conducted an assessment to establish the presence of MCI. First, subjective cognitive decline was assessed using a semi-structured interview. The following two opening questions were used: "have you noticed a change in your memory, concentration or other mental skills over the last 1 to 2 years?" and, if 'yes', "have the changes been severe enough to impact on your day-to-day activities or are they barely noticeable?". Participants who had noticed a change (decline) and reported the severity as greater than 'barely noticeable', were classified as having a subjective cognitive complaint.

Following the interview, participants were administered the Neuropsychological Assessment Battery Screening Module (NAB-SM) (Stern & White, 2003). The NAB-SM is a neuropsychological battery comprised of 14 subtests, which takes around 45 minutes to administer. The NAB-SM battery was chosen over a battery of stand-alone tests because each subtest was normed on the same demographically-corrected population, making them directly comparable. Subtests were grouped into cognitive domains and an overall domain score

calculated according to the guidelines in the scoring manual (Stern & White, 2003). Subtests included in the Attention Domain were digit repetition (forward and backward) and letter cancellation (single and duel tasks). The Memory Domain included shape learning (immediate and delayed) and paragraph learning (immediate and delayed) tasks. The Visuo-Spatial Domain included a visual discrimination task and a three dimensional design construction task. The final domain, Executive Function, included maze completion and word generation (anagram) subtests.

Each domain score is adjusted for sex, age and education. The mean normative score for each domain and for global performance is 100 (SD = 15) (Stern & White, 2003). The presence of MCI was determined using the four domain scores rather than the 12 individual subtest scores to reduce the likelihood of over-diagnosing MCI through Type 1 error.

Two classification systems for MCI were applied. Amnestic MCI was defined according to the Peterson criteria(Petersen et al., 1999) and required: (1) a subjective cognitive complaint; (2) independence in basic activities of daily living; (3) a NAB-SM Memory Domain score that was at least 1SD below the published mean for a person's sex, age and education; and (4) a normal level of performance in the other 3 cognitive domains (ie Attention, Executive Function, and Visuo-Spatial Skills not less than 1SD below the published mean). Various criteria for Multiple-Domain MCI have been proposed in the scientific literature. We applied the criteria used in a large population based study by Busse, Bischkopf and colleagues (2003). This definition was selected because the items and cut-off points were analogous to those of the Peterson criteria, thus allowing a direct comparison of the results for Amnestic and Multiple-Domain MCI. Specifically, Multiple-Domain MCI required: (1) a subjective cognitive complaint; (2) independence in basic activities of daily living; and (3)

performance in at least two NAB-SM domains (Memory, Attention, Executive Function or Visuo-Spatial Skills) that was 1SD below the sex, age and education-matched test norms.

3.4.4 Statistical analysis

All analyses involving the MoCA used education-adjusted MoCA scores (Nasreddine et al., 2005). The NAB-SM was used to establish the presence of MCI and was therefore considered the gold standard measure for the purpose of this study. The MoCA was the screening test being evaluated in terms of its sensitivity and specificity. Sensitivity was defined as the percentage of participants who met the MCI criteria who scored below 26 on the MoCA. Specificity was defined as the percentage of participants who did not meet the criteria for MCI who scored 26 or higher on the MoCA. For the purpose of providing descriptive data, correlations between the MoCA and age, education, and NAB-SM scores were generated. Some of the variables had slightly non-normal distributions, so Spearman's Rank Order correlations (rs) were used..

3.5 Results

3.5.1 Participants

In total, the participating clinics completed 2,481 patient appointments during the study period for patents that had hospital files available for review. Of these, 1,399 (56%) met the inclusion criteria. Eighty two could not be contacted but the remaining 1,317 were invited to participate. Of those, 992 (75.3%) declined to participate, and a further 31 failed to attend scheduled appointments. Ultimately, 375 attended a clinical assessment. Of these, 262 had learned English prior to the age of five and were therefore eligible for cognitive testing. Due to scheduling restrictions, 152 could not be booked for a clinical assessment. The remaining 110 completed the cognitive assessment and were included in the present study sample.

3.5.2 Clinical and demographic profile

Table 1 summarises key demographic and cognitive data for the sample (n = 110). Participant ages ranged from 41 to 91 years and years of education from 5 to 24. Table 2 provides information on the cardiovascular profile of the study sample. Sixty eight participants (62%) had an overt cardiovascular disease (predominantly ischaemic heart disease), while the remainder had one or more risk factors, confirming a high cardiovascular burden in the study cohort.

Table 1: Demographic and Cognitive Characteristics of the Study Sample (n = 110)

	Mean (SD)	% (n)
Socio-demographic Information		
Male Sex		40% (44)
Age (years)	67.9 (11.7)	
Education (years)	10.5 (3.2)	
MoCA		
MoCA Score, Raw	22.0 (3.9)	
MoCA Score, Education Adjusted	22.8 (3.8)	
NAB-SM		
NAB-SM Global Scaled Score	100.2 (17.4)	
NAB-SM Attention Scaled Score	91.5 (17.2)	34% (37)[a]
NAB-SM Memory Scaled Score	97.9 (14.8)	18% (20) [a]
NAB-SM Executive Scaled Score	106.7 (15.9)	8% (9) [a]
NAB-SM Spatial Scaled Score	99.4 (17.6)	18% (20) [a]
MCI Diagnoses		
Amnestic MCI Based on Gold Standard Testing		2.7% (3)
Multiple-Domain MCI Based on Gold Standard Testing		10.9% (12)
Any MCI Based on Gold Standard Testing		13.6% (15)

Note. MCI = Mild Cognitive Impairment; MoCA = Montreal Cognitive Assessment; NAB-SM = Neuropsychological Assessment Battery Screening Module; [a] proportion >1SD below the population mean

Table 2: Cardiovascular Profile of the Study Sample (n = 110)

	Mean (SD)	% (n)
Cardiovascular Diseases		
Ischaemic Heart Disease		36% (38)
Peripheral Arterial Disease		20% (22)
Atrial Fibrillation		19% (21)
Stroke or Transient Ischaemic Attack		15% (16)
Chronic Heart Failure		6% (7)
Cardiovascular Risk Factors		
Hypertension		76% (84)
Diabetes Mellitus		37% (41)
Family History of Ischaemic Heart Disease		66% (73)
Family History of Diabetes		33% (36)
Past/Present Cigarette Smoking Habit		56% (62)
Obesity		50% (55)
Haemoglobin A1c	7.0 (1.8)	
Creatinine	88.3 (24.1)	
Total Cholesterol (mmol/L)	4.6 (1.1)	
HDL Cholesterol (mmol/L)	1.3 (0.3)	
LDL Cholesterol (mmol/L)	2.5 (0.9)	

3.5.3 Cognitive profile

The average MoCA performance was relatively low (mean = 22.8, SD = 3.8), with 72.1% (n = 66) of participants scoring below the recommended cut-off for cognitive impairment (< 26). As expected, MoCA performance declined with age (r_s = -.36, p < .001). The internal reliability of the test was low (Cronbach's Alpha = .55), probably reflecting the broad nature of the test content.

The mean Global Scaled Score for the NAB-SM was 100.2 (SD = 17.4), indicating that the general cognitive performance of the study sample was comparable to that of the published normative sample (Stern & White, 2003). The MoCA showed a moderate positive correlation with the NAB-SM global score (Rho =.49, p <.001) and with each of the NAB-SM domain scores: Attention (r_s = .34, p < .001); Memory (r_s = .25, p =.007); Spatial (r_s = .48, p < .001); and Executive (r_s = .41, p < .001).

3.5.4 Sensitivity/Specificity of the MoCA for detecting Mild Cognitive Impairment

Based on the gold standard criteria, only three participants met the criteria for Amnestic MCI. Using the recommended cut-off (< 26), the MoCA detected all of these cases (sensitivity = 100%) but failed to screen out 70.8% of the people who were free of Amnestic MCI (specificity = 29.2%). The positive predictive value under these circumstances was .03 and the negative predictive value was 1.0. Alternative cut-off points were also examined. As shown in Table 3, a lower cut-off of < 24 would have provided improved overall diagnostic accuracy with 100% sensitivity and 50% specificity. At this cut-off, the positive predictive value was .05 and negative predictive value was 1.0.

Table 3: Sensitivity and specificity of the MoCA for detecting MCI

	Amnestic MCI		Multiple-Domain MCI	
MoCA cut off	Sensitivity	Specificity	Sensitivity	Specificity
<22	66.7%	70.8%	75.0%	75.3%
<23	66.7%	62.3%	75.0%	66.3%
<24	**100.0%**	**50.0%**	**83.3%**	**52.0%**
<25	100.0%	39.6%	83.3%	40.8%
<26	**100.0**%	**29.2**%	**83.3**%	**29.6**%
<27	100.0%	18.9%	91.7%	19.4%
<28	100.0%	8.5%	91.7%	8.2%

Note. MoCA = Montreal Cognitive Assessment; MCI = Mild Cognitive Impairment

Twelve people (10.9%) met the gold standard criteria for Multiple-Domain MCI. Using the recommended cut-off for the MoCA (< 26) the sensitivity for detecting MCI was 83.3% and the specificity was 29.6%, equating to a positive predictive value was of .13 and a negative predictive value of .94. At a lower MoCA cut-off (< 24), sensitivity remained at 83.3% but specificity increased to 52.0% (Table 3). At this cut-off, the positive predictive value was .18 and the negative predictive value was 0.96.

3.6 Discussion

This study was designed to assess the validity of the MoCA by examining its diagnostic accuracy in detecting MCI in a group of people at risk of vascular-related cognitive impairment.

The MoCA demonstrated excellent sensitivity for detecting MCI in this patient group. Using the recommended cut-off of < 26, it detected all of the Amnestic MCI cases and 83.3% of Multiple-Domain MCI cases. These findings are similar to previous studies that examined the MoCA's utility for detecting Amnestic MCI in memory clinic settings, where sensitivity was reported at 90% (Nasreddine et al., 2005), 83% (Smith et al., 2007), and 97% (Luis et al., 2008) and to findings from a study of elderly Korean hospital outpatients, where the sensitivity was 100% (Lee et al., 2008). However, this is the first study to examine the MoCA's capacity for detecting Multiple-Domain MCI. This form of MCI is particularly relevant in this setting because it more closely reflects the typical pattern of deficits seen in people with cardiovascular pathology (Ingles et al., 2007; Nordlund et al., 2007; Zanetti et al., 2006) and is a better predictor of a future diagnosis of Vascular Dementia than isolated memory impairment (Ingles et al., 2007; Zanetti et al., 2006).

Conversely, we found that the MoCA's specificity was poor. The test failed to screen out more than two thirds of the participants who were free of Amnestic MCI and Multiple-Domain MCI. This sits at the lower end of previously reported specificity rates for the MoCA, which were 89% (Nasreddine et al., 2005), 50% (Lee et al., 2008; Smith et al., 2007), and 35% (Luis et al., 2008). A lower MoCA cut-off point (< 24) resulted in an improved specificity of around 50% for both Amnestic and Multiple-Domain MCI without a compromise in

sensitivity. This alternative cut-off is similar to the optimal cut-off of < 23 reported in two earlier studies (Lee et al., 2008; Luis et al., 2008).

The performance of the MoCA in detecting MCI compares favourably with other available screening tools. For example, the sensitivity rates for the Mini Mental Status Examination (MMSE), which is the most commonly used cognitive screening test (Shulman et al., 2006), are much lower, ranging from 1% to 49% for Amnestic MCI (Lonie et al., 2009). Other brief screening tests, such as the Memory Alternation Test (Rami et al., 2007) and the Alzheimer's Disease Assessment Scale for Cognition (ADAS-Cog) (Pyo, Elble, Ala, & Markwell, 2006), have shown better diagnostic accuracy for Amnestic MCI (Lonie et al., 2009), but the fact that they don't adequately assess cognitive domains other than memory suggests that they not may not be as useful in detecting Multiple-Domain MCI. One test that is comparable to the MoCA in terms of its comprehensiveness is the Consortium to Establish a Registry for Alzheimer's Disease (CERAD). In a community sample, the CERAD demonstrated sensitivity and a specificity rates for Amnestic MCI of 81% and 73% respectively (Chandler et al., 2005), which are higher than those reported in most previous studies of the MoCA (Lee et al., 2008; Luis et al., 2008; Smith et al., 2007). However, these results have not yet been replicated and it is not known if the test performs equally well in the detection of Multiple-Domain MCI or in cardiovascular populations. Few other screening tools have been assessed for their sensitivity to MCI and none have been validated in cardiovascular populations (Lonie et al., 2009).

Although the available research suggests that the MoCA is amongst the best available tools for the detection of MCI, the influence of low base rates need to be taken into account when considering how it might be applied in a clinical setting. Consistent with population-

based studies (Mariani et al., 2007; Zanetti et al., 2006), the prevalence of MCI in this cohort was very low, particularly for Amnestic MCI. The combination of a low base rate and poor test specificity resulted in a large number of false positive results. Even using the optimal cut-off point (< 24), the positive predictive value of the MoCA test for Multiple-Domain MCI was only .17, indicating that a person from this population who 'failed' the test only had a 17% chance of having MCI. In unselected clinical settings, where the prevalence of MCI is likely to be similar to that observed in this cohort, the low negative predictive value means that the MoCA will have limited value as a screening test.

Setting aside the difficulties associated with screening for MCI in low prevalence populations, the process for actually diagnosing MCI is time consuming and expensive and, therefore, the value of the MCI construct itself in a clinical setting should be carefully considered. In most cases of vascular-related cognitive decline, the degenerative process is gradual and continuous, with patients typically moving through periods of milder cognitive impairment in the years preceding a diagnosis of dementia (Hayden et al., 2005; Ingles et al., 2007; Waite, Broe, Grayson, & Creasey, 2001). Therefore, the application of discrete diagnostic categories to distinguish different levels of cognitive impairment provides little value in planning patient care. That is, a patient whose cognitive symptoms fall just outside the diagnostic boundaries for MCI will benefit from a similar approach to risk factor management and patient care as that of a patient whose symptoms fall squarely within the diagnostic criteria. These issues have prompted a conceptual shift within the field, which has lead to the introduction of the term Vascular Cognitive Impairment (VCI) to refer to the whole spectrum of vascular-related cognitive impairments from mild through to dementia (O'Brien et al., 2003). This perspective de-emphasises the discrete categories of MCI and dementia, and recognises that similar pathological processes are involved at all stages of VCI. Against this

background, there is little to be gained from pursuing a diagnosis of MCI and thus the MoCA will add little clinical value when used as a screening tool. However, the test may still be useful in a clinical setting as a continuous measure of global cognitive function. In support of this, preliminary research has shown that performance on the MoCA is moderately correlated with performance on other global measures, including the Clinical Dementia Rating Scale (Lee et al., 2008) and the MMSE (Lee et al., 2008; Nasreddine et al., 2005; Smith et al., 2007), and is sensitive to differences in vascular risk profiles and changes in cognitive function over a 6-month period (Popovic, Seric, & Demarin, 2007).

Two limitations of the study should also be considered when interpreting the results. First, the study sample was not randomly selected and is therefore unlikely to be representative. Given that the testing session took up to two hours, people who had poorer cardiovascular health or poorer cognitive function may have been less inclined to participate. In addition, patients with diagnosed PAD were excluded as part of the procedures of the parent study. As such, the prevalence of MCI in this cohort may have been lower than the prevalence in the clinical population it was drawn from. A second issue is that our sample size was relatively small. When base rates are low, individual cases can have a large impact on sensitivity/specificity calculations, so replication of this research in a larger population is now required to confirm the findings.

In summary, this is the first study to examine the MoCA's ability to detect MCI in a non memory clinic population. The results of this study concur with previous research conducted in other populations to suggest that the MoCA has good sensitivity for detecting MCI but relatively poor specificity. This combination of attributes means it will be of limited use in clinical settings where MCI has a low prevalence. Given that the MCI diagnosis itself

will be of limited relevance in many clinical settings, future studies should broaden their focus and consider assessing the MoCA's validity as a continuous measure, rather than simply a screening tool for MCI.

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Chapter 4: Study 2

The following chapter is an unpublished manuscript that was submitted to the International Journal of Stroke.

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Details of this study were subsequently accepted for publication in the format of a letter to the editor in the International Journal of Stroke.

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4.1 Title Page

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

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Key Words: cardiovascular disease; small vessel disease; cognitive impairment; magnetic resonance; endothelium

4.2 Abstract

Background: Deterioration in the capacity of blood vessels to dilate may contribute to the development of small vessel brain disease and associated cognitive impairments. It has previously been shown that, in elderly populations with established cardiovascular disease, vasodilation response is associated with cognitive performance.

Aims: The present study aimed to determine whether a similar relationship exists in a broader-based cohort.

Methods: A cross-sectional study design was employed. Participants (n = 51) were recruited from consecutive hospital patients who had undergone brain magnetic resonance imaging for any reason. Those with brain pathology other than small vessel disease were excluded. Cognition was measured using a battery of neuropsychological tests. Vessel dilation was induced by administering salbutamol (triggering dilation via the endothelium) and glyceryl trinitrate (triggering dilation via smooth muscle). Maximum dilation after each pharmacological agent was measured using applanation tonometry and pulse wave analysis. Subcortical brain pathology on MRI was graded using a modified version of the Fazekas visual rating scale.

Results: Participants were relatively young (mean age = 50.3, SD = 11.5). Twelve percent had a cardiovascular diagnosis, and only 6.3% had significant ischemic damage on magnetic resonance imaging. None of the cognitive measures was significantly associated with endothelial or smooth muscle vessel dilation.

Conclusions: The absence of an association between vasodilation and cognition in this group suggests that impaired vasodilation may not have detrimental effects on brain structure or function in the absence of old age or severe cardiovascular pathology.

4.3 Introduction

A high proportion of vascular dementia cases develop as a result of cerebral small vessel disease (SVD) (Chui, 2001), and there is a strong link between small-vessel related brain pathology and cognitive impairment more generally (van der Flier et al., 2005; van Dijk et al., 2008). Although cardiovascular risk factors such as hypertension, diabetes and smoking are known to increase the risk of SVD and cognitive impairment (McManus & Stott, 2005; van Dijk et al., 2008), the exact biological mechanisms that mediate these relationships are still debated (Ince & Fernando, 2003). A better understanding of these processes would provide direction for the development of strategies to treat or prevent SVD and associated cognitive impairment.

Cardiovascular risk factors and the aging process both have detrimental effects on vessel distensibility, raising the possibility that vessel dilation capacity may play a role in the development of SVD (Hashimoto et al., 2000; Lakatta, 2002). Impaired vessel responsiveness may impact on oxygen delivery to surrounding tissue (Munoz, 2006), culminating in chronic hypoperfusion and ultimately cognitive decline (Roman et al., 2004).

Consistent with this proposition, it has been shown that, in people with established cardiovascular diseases, poorer smooth muscle mediated vasodilation response is associated with poorer cognitive performance (Forman et al., 2008; Moser et al., 2004; Moser et al., 2008; Moser et al., 2007). The role of endothelial mediated vasodilation is less clear, with one study reporting an association between endothelial response and aspects of cognitive function (Forman et al., 2008), but another failing to observe a relationship (Moser et al., 2008; Moser et al., 2007).

These studies did not directly measure brain pathology. However, in an elderly cohort with established cardiovascular disease, poorer endothelial dependent (but not smooth muscle dependent) vessel dilation was associated with an increased volume of ischemic tissue damage visible as White Matter Hyperintensities (WMHs) on MRI (Hoth et al., 2007). This finding is consistent with the suggestion that ischemic brain damage may be the intermediary mechanism linking poor vasodilation and cognitive impairment.

Although the sequence of events involving reduced vasodilation, cardiovascular/cerebrovascular disease, and cognitive decline has not been established, experimental animal studies have demonstrated that vessel responsiveness deteriorates early in the process of atherosclerotic vascular disease (Lopez, Armstrong, Piegors, & Heistad, 1989). In humans, atherosclerotic vessel changes begin in childhood (Berenson et al., 1998; Tanaka et al., 1988), and associations between cardiovascular risk factors and vessel response are evident from the first few decades of life (Sorensen et al., 1994; Tounian et al., 2001). Other research has shown that some aspects of cognitive function, most notably information processing speed, begin to decline from the mid 20's (see Hedden & Gabrieli, 2004 for a review). It is therefore possible that a deterioration in vasodilation capacity might affect cognition even before cardiovascular and/or cerebrovascular disease becomes symptomatic and clinically detectable. The only study that has examined people selected on the basis of cardiovascular risk (hypertension), rather than established cardiovascular disease, failed to find an independent association between cognition and either endothelial dependent or smooth muscle dependent vasodilation (Kearney-Schwartz et al., 2009). However, a blood plasma marker for more general endothelial health *was* associated with cognition in this group, suggesting that some aspect of endothelial function may play a role in cognitive deterioration.

4.3.1 Aims

In the present study, vessel dilation capacity was examined in people who are not affected by advanced cardiovascular disease to determine:

1. whether vessel dilation response was associated with cognitive performance; and
2. whether such a relationship could be explained by the presence or severity of WMHs.

4.4 Methods

4.4.1 Participants and recruitment

The present study was nested within a larger study examining other aspects of vasodilatory response (Lam et al., 2009). Participants of the larger study (n = 141) were aged between 18 and 75 and had recently undergone brain Magnetic Resonance Imaging (MRI) for any reason at major public metropolitan hospitals in South Australia. Potential participants were excluded from this larger study if they showed brain pathology other than small vessel disease including: other forms of dementia; large vessel ischemic stroke; tumour; primary demyelination; or another central nervous system condition. They were also excluded if they were unable to provide informed consent, had undergone or were currently undergoing radiotherapy of the head, or were already participating in another research study. Of the 1184 people who had an MRI scan during the study period and who were invited to participate via mail, 376 (31.8%) agreed to participate. Of these, 141 were eligible, and were able to travel to the study hospital to participate in the study.

Potential participants were excluded from the present study if they were affected by other factors that may influence performance on cognitive tests; namely:

1. non-English-speaking background;
2. history of significant head injury (loss of consciousness > 10 minutes);
3. previous diagnosis of a learning disorder (e.g. developmental dyslexia) or educational support services consistent with such a diagnosis; *or*
4. neurological event (such as stroke) subsequent to the initial MRI.

In addition, people were excluded if they were using vasoactive medications (eg angiotensin converting enzyme inhibitor, angiotensin II receptor blockers, calcium channel

blockers, nitrates or beta-blockers) because of their potential to affect the vasodilatory response. Fifty one participants passed all 5 additional exclusion criteria and were recruited to the study.

4.4.2 Procedures

Participants were asked to fast and refrain from consuming caffeine over night. They were interviewed in the morning to collect information about demographics and medical histories. Blood samples were then taken to measure lipid, cholesterol and glucose levels. Following this, height, weight and blood pressure were measured and a 12-lead echocardiogram was performed to screen for arrhythmias. Participants were then offered a light caffeine-free breakfast and then the cognitive assessment and vasodilation response measures were completed. MRI scans were subsequently reviewed to grade the level of subcortical tissue damage. Cognition, vasodilation response and subcortical tissue damage were assessed by separate researchers, each blinded to the results of the others.

4.4.3 Measures

Vasodilation response was assessed using applanation tonometry and pulse wave analysis using a protocol similar to that described by Hayward et al (Hayward, Kraidly, Webb, & Collins, 2002). This is a less invasive approach than protocols involving intra-arterial administration of agonists (Verma, Buchanan, & Anderson, 2003). It is reproducible (Hayward et al., 2002), and highly correlated with measures of arterial stiffness (McEniery et al., 2006).

Participants were assessed in a supine position in a temperature-controlled room. The tonometer was positioned over the radial pulse, and pulse-wave analysis was carried out using the SphygmoCor® apparatus and software to calculate a baseline aortic augmentation index (AAIx) (ie the ratio of pulse pressure at the second systolic peak to that at the first systolic peak) (Hayward et al., 2002). To induce smooth muscle mediated vessel response, 50mcg of liquid glyceryl trinitrate (GTN) was placed under the tongue. Serial measures were taken for 20 minutes, and the maximum AAIx (the AAIx with greatest deflection from the baseline) was recorded. When AAIx had returned to baseline level, endothelium dependent vasodilation was induced by administering 400mcg of salbutamol sulfate (inhaled under supervision via a spacer). AAIx measures were again taken for 20 minutes, and the maximum AAIx recorded.

A s*mooth muscle vasodilation* score was calculated by subtracting the maximum AAIx measure taken after GTN administration from the baseline AAIx measure. Larger scores indicate greater dilation response. An *endothelium dependent vasodilation score* was calculated by subtracting the maximum AAIx measure taken after salbutamol administration from the baseline AAIx measure. However, smooth muscle dysfunction can impact on response to salbutamol. Therefore, consistent with previous studies (Moser et al., 2008; Moser et al., 2007), the score was corrected for smooth muscle response by calculating a salbutamol response/GTN response ratio. Larger ratios (ie a larger salbutamol response compared to GTN response) indicates larger endothelial response.

To ensure that the measurement protocol was reliable, a test-retest reliability analysis was undertaken in 5 healthy volunteers (1 male, 4 female) aged between 23 and 58 years (m = 36.4) who were not participants in the study. Each person was tested twice, one week apart, using the protocol described above.

Cognitive function was assessed by a registered psychologist (SM) using the Screening Module of the Neuropsychological Assessment Battery (NAB-SM) (Stern & White, 2003). The NAB-SM takes 30 to 45 minutes to administer and consists of 14 subtests. It provides detailed information on separate cognitive domains, and is sensitive to cognitive performance ranging from very high functioning through to the dementia range. Domain scores for Memory, Attention, Executive Function and Visuo-Spatial Skills were calculated and converted to Scaled Scores, which are adjusted for sex, age and education (Stern & White, 2003). The mean normative Scaled Score for each domain and for Overall NAB-SM Performance is 100 (SD = 15).

The Color-Word Interference Test from the Delis Kaplan Executive Function System (Delis, Kaplan, & Kramer, 2001) was administered to gather additional information about executive functioning and information processing speed. These cognitive skills are particularly vulnerable to deterioration in people with WMHs (Rabbitt et al., 2007) and/or subcortical vascular disease (Pohjasvaara et al., 2003; Price, Jefferson, Merino, Heilman, & Libon, 2005), and have been linked to poor vessel responsiveness in prior research (Moser et al., 2008). In the first part of the test, participants are required to name colour patches, and then read colour names (eg "RED") under timed conditions, providing a measure of information processing speed ('Naming plus Reading' Index). In the latter part of the test participants are presented with colour words that are printed in incongruent ink colours (eg "RED" printed in green ink). They are required to switch between reading the word ("red"), and naming the ink colour ("green") under timed conditions. This provided a measure of executive function ('Naming plus Reading versus Switching' Index). Standardised scores adjusted for age were calculated (Delis et al., 2001). The mean normative Scaled Score for each Index Score is 10 (SD = 3).

Two additional screening tests, the Mini Mental Status Examination (MMSE) (Folstein, Folstein, & McHugh, 1975) and the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005), were administered to provide descriptive information regarding general cognitive status.

Finally, the National Adult Reading Test (NART) Second Edition (Nelson & Willison, 1991) was administered to provide an estimate of pre-morbid intellectual function. In this test, participants were required to pronounce words that have irregular phonetic construction such as '*chord'* and '*ache'.* Reading vocabulary is highly correlated with general intelligence and remains stable even in the context of cognitive decline (Crawford, Deary, Starr, & Whalley, 2001). Estimated Full Scale IQ scores were calculated (Nelson & Willison, 1991). For each of the cognitive tests, larger scores indicate better cognitive performance.

The extent of WMHs on MRI was assessed independently by two neuro-radiologists. Visual inspection of axial T2 and FLAIR sequences was carried out, and the proportion of white matter showing WMHs was rated using the same system as Hassan and colleagues (Hassan et al., 2003), which is a modified version of the Fazekas Scale (Fazekas, Chawluk, Alavi, Hurtig, & Zimmerman, 1987). WMHs were rated as *mild* if < 20% of white matter was affected (equivalent to Fazekas periventricular score ≤ 2), *moderate* if 20% to 50% was affected (equivalent to Fazekas periventricular score 3), and *severe* if > 50% was affected. The validity of the original Fazekas Scale is supported by a post mortem study showing correlations between Fazekas visual ratings and white matter pathology (Fazekas et al., 1993).

4.4.4 Statistical analyses

The level of agreement between the applanation tonometry measurements taken at the two time points for the reliability sub-study was assessed using Pearson's correlations (r). Relationships between vasodilation, cognitive measures, and demographic variables, were assessed using Pearson's correlations for normally distributed variables, and Spearman's Rank Order correlations (r_s) for non-normally distributed variables.

4.5 Results

4.5.1 Population characteristics

Participants' (n = 51) ages ranged from 24 to 73 years, and 63% were female. There was a wide spread of education levels (Table 1). All participants had MMSE scores above 25 (m = 28.8, SD = 1.3), indicating that dementia was unlikely (Tombaugh & McIntyre, 1992). Seven participants (13.7%) achieved a MoCA score below 24 (m = 26.0, SD = 2.7), suggesting that they were likely to be suffering from mild cognitive impairment (McLennan, Mathias, Brennan et al, in press). For most NAB-SM subtests, mean performance was slightly higher than the published normative data (Stern & White, 2003), but there was a relatively large spread of scores. Six participants (12%) had a diagnosed cardiovascular disease or a history of Transient Ischemic Attack (TIA), but none had more than one such diagnosis. Almost half were affected by hypercholesterolemia.

The severity of WMHs could not be rated for four participants (7.8%) due to movement artefact on the MRI or unsuitable sequences. Of the remaining 47, 44 (93.6%) had mild or absent WMHs, two had moderate WMHs, and one had severe WMHs.

Table 1: Sample Characteristics (n = 51)

	Mean	SD	Min	Max	N (%)
Demographics					
Age (years)	50.3	11.5	24	73	
Education (years)	12.7	3.2	7	22	
Estimated IQ	103.3	8.3	82	118	
Vessel Dilation					
Smooth Vessel Mediated Dilation	13.61	4.85	2.5	27.0	
Endothelial Dependent Dilation	0.24	0.29	-.28	1.05	
Cognition					
NAB-SM Total (standard score)	106.8	13.7	77	134	
NAB-SM Attention (standard score)	99.5	15.3	63	136	
NAB-SM Language (standard score)	106.5	9.3	78	127	
NAB-SM Memory (standard score)	99.2	13.5	69	122	
NAB-SM Spatial (standard score)	108.4	15.4	75	135	
NAB-SM Executive (standard score)	107.5	13.3	82	138	
DKEFS – Speed (standard score)	10.8	1.9	5	14	
DKEFS – Executive Function (standard score)	9.7	1.8	6	14	
Cardiovascular Profile					
Body Mass Index	27.6	6.4	20	45	
Systolic Blood Pressure (mmHg)	120.6	16.1	78	162	
Diastolic Blood Pressure (mmHg)	77.3	10.8	59.5	110	
Hypercholesterolemia[a]					24 (48%)
Hypertension[b]					5 (10%)
Transient Ischemic Attack[c]					3 (6%)
Diabetes[c]					2 (4%)
Ischemic Heart Disease[c]					2 (4%)
Peripheral Arterial Disease[c]					1 (2%)
Atrial Fibrillation[c]					0 (0%)

Note. NAB-SM = Neuropsychological Assessment Battery Screening Module; DKEFS = Delis Kaplin Executive Function System; [a] total cholesterol >5.5mmol/L and/or a previous diagnosis, and/or lipid-lowering medication use. [b] systolic >140mmHg and/or diastolic >90mmHg and/or previous diagnosis. [c] previous diagnosis

4.5.2 Vasodilation response

Reliability analysis

There was a strong correlation between the first (m = 12.8, SD = 10.13) and second (10.8, SD = 5.81) measures of smooth muscle dilation (r = 0.70, p = 0.056, n = 5) in the reliability sub-study. Similarly, there was a strong correlation between the first (m = 1.16, SD = 1.05) and second (m = 1.18, SD = 1.06) measures of endothelial dependent dilation (r = 0.98, p = 0.003, n = 5), which supports the reliability of the vessel dilation measurement technique.

Measurement issues

In four cases (7.8%) in the main study, applanation tonometry measurements could not be completed because of insufficient signal strength for pulse-wave analysis. Each of these participants was overweight, with a mean Body Mass Index (BMI) of 36.7 (SD = 9.4), which was significantly higher than that of the rest of the group (m = 26.2, SD = 6.8; $t(48) = -2.90$ p = .006). It appears that the increased thickness of transdermal fat at the site of the ultrasound probe interfered with measurement.

Applanation tonometry is a relatively new technique for assessing vessel responsiveness, and normative values have not yet been established. Therefore, it was not possible to determine how many of participants in the current cohort had vessel response scores in the 'abnormal' range.

4.5.3 Associations between vasodilation response and cognition

None of the cognitive measures was significantly correlated with vessel dilation response (smooth muscle or endothelial) (Table 2).

Table 2: Correlations between degree of vasodilation and cognitive performance (n = 47)

	Smooth Muscle Vasodilation Correlation Coefficient (*p*)	Endothelial Vasodilation Correlation Coefficient (*p*)
NAB-SM Attention	-0.02 (0.87)	-0.22 (0.14)
NAB-SM Language[a]	0.01 (0.95)	-0.07 (0.64)
NAB-SM Memory	-0.24 (0.10)	-0.05 (0.73)
NAB-SM Spatial	-0.01 (0.93)	0.05 (0.72)
NAB-SM Executive	-0.04 (0.77)	0.05 (0.74)
NAB-SM Total	-0.07 (0.66)	-0.10 (0.52)
D-KEFS Speed[a]	0.11 (0.46)	0.16 (0.30)
D-KEFS Executive Function[a]	0.06 (0.68)	-0.05 (0.72)

Note. [a]correlations were calculated using Spearmans rank order test rather than Pearson's because of non-normal distributions. NAB-SM = Neuropsychological Assessment Battery Screening Module; DKEFS = Delis Kaplin Executive Function System.

4.6 Discussion

Poor vasodilatory response was not associated with reduced cognitive performance in this cohort. This was the case for both vasodilation mediated by smooth muscle, and endothelial mediated dilation. These results contrast with findings from three prior studies involving people who had overt cardiovascular diseases. In those studies cognitive function was associated with smooth muscle vasodilation (Forman et al., 2008; Moser et al., 2004; Moser et al., 2008; Moser et al., 2007) and in one study, with endothelial mediated vasodilation (Forman et al., 2008). Compared to the prior studies, the present sample was younger and had fewer indications of cardiovascular pathology. The only other study that has examined people who were not selected on the basis of diagnosed cardiovascular or cerebrovascular diseases also failed to detect associations between vasodilation response and cognition (Kearney-Schwartz et al., 2009).

This pattern of results is consistent with the proposition that poor vessel dilation response may not impact on cognitive performance until cardiovascular disease is well established and/or age-related vascular changes have developed. Advanced age (Roman et al., 2004) and cardiovascular risk factors, such as hypertension and diabetes (Rizzoni & Rosei, 2006), lead to stiffening, lengthening and tortuousity of the small cerebral vessels. When vasodilation deteriorates in the context of these morphological changes, deep white matter may be left vulnerable to ischemic damage during periods of low cerebral perfusion pressure (Roman et al., 2004). In younger, healthier individuals, with fewer changes in vessel structure, tissue perfusion may remain sufficient to protect the brain from ischemia when cerebral perfusion pressure falls, even if compensatory vasodilation is impaired. This might explain why vasodilation was not associated with cognition in the present cohort. The fact that only

6% of this study sample showed evidence of moderate or severe WMHs is also consistent with this proposition. Future studies that include participants with a mix of ages and cardiovascular disease states will be needed to confirm this proposed explanation.

Importantly, the failure to find a relationship between vessel function and cognition is unlikely to have resulted from poor test sensitivity or measurement error. The reliability analysis of vasodilation response scores indicated that, in line with previous research (Hayward et al., 2002), the applanation tonometry measures were highly reproducible. In addition, the reliability and validity of the cognitive assessment tests have been tested extensively (Delis et al., 2001; Stern & White, 2003), and the test battery was selected on the basis that it offered greater sensitivity in non-demented people than tests used in previous research (Moser et al., 2004; Moser et al., 2007). The wide range of cognitive scores supports the sensitivity of the tests and indicates that the correlation between dilation response and cognition was not affected by an attenuation of cognitive scores. Given that the study sample was in relatively good cardiovascular health, there was a risk that the range of vasodilation response scores would be restricted to the higher end of the spectrum. However, an inspection of the scores revealed that some participants showed no dilation response to Salbutamol at all, indicating that at least some scores fell at the lowest end of the range.

An additional methodological consideration is that the study sample was recruited from people who had already undergone brain MRI for a variety of reasons. Although we were careful to exclude people showing evidence of other neurological or cognitive disorders, the group can not be considered to be representative of the wider healthy population and, thus the results must be extrapolated with caution. In addition, the sample was relatively small. However, other studies with fewer than 100 subjects have detected significant relationships

between cognition and vascular response (Forman et al., 2008; Moser et al., 2008; Moser et al., 2007) or subcortical brain pathology (Hoth et al., 2007) in patients with confirmed cardiovascular diseases. In contrast, the study focusing on relatively healthy subjects conducted by Kearney-Schwartz and colleagues (Kearney-Schwartz et al., 2009) failed to find a relationship between cognition and vasodilation even with a much larger sample (n = 198). Considered in this context, a lack of power does not appear to be the critical factor in the failure to detect significant relationships. Patient characteristics appear to be more important.

It is also notable that the methods used to measure endothelial function differed between this study and previous studies in this field, which may have contributed to the variability in findings. While we administered salbutamol to induce endothelial mediated dilation, previous studies administered acetylcholine (Moser et al., 2008; Moser et al., 2007) or used a pressure cuff (Forman et al., 2008; Kearney-Schwartz et al., 2009) to induce flow-mediated dilation. Similarly, while we used GTN to induce smooth muscle dilation, verapamil was used in another study (Moser et al., 2008; Moser et al., 2007). Even in the studies that used GTN to trigger smooth muscle dilation (Forman et al., 2008; Kearney-Schwartz et al., 2009), the doses differed from the present protocol. Other aspects of the procedures also differed; some studies (Forman et al., 2008; Kearney-Schwartz et al., 2009) used ultrasound to measure changes in vessel diameter rather than pulse wave analysis, while others used venous occlusion plethysmography (Moser et al., 2008; Moser et al., 2007). Techniques for measuring vessel dilation response are still being refined and tested (Deanfield, Halcox, & Rabelink, 2007), and thus results across studies may not be directly comparable.

Longitudinal research that tracks vasodilation responsiveness, development of WHMs, and cognitive decline would provide more definitive information about the role of vasodilation

response in the development of SVD. A better understanding of these relationships has the potential to lead to therapeutic trials to prevent neurodegeneration. Medications that enhance smooth muscle mediated vasodilation are already in wide use as anti-hypertensive treatments. In addition, several classes of drugs have been shown to improve endothelial function, either by acting directly on the endothelium (Clarkson et al., 1996 ; Verhaar et al., 1999), or via the mitigation of cardiovascular risk factors (Mancini et al., 1996; Treasure et al., 1995).

In summary, vessel dilation response was not related to cognitive performance in the present sample who were in relatively good cardiovascular health and predominantly free from observable subcortical brain pathology. Although not definitive, these results are consistent with the idea that vascular responsiveness is only a relevant predictor of cognitive performance in people who are elderly and are affected by high levels of cardiovascular pathology.

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Chapter 5: Study 3

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5.1 Title page

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

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5.2 Abstract

Background and Research Objective: A high proportion of elderly people with cardiovascular diseases and risk factors suffer from mild forms of cognitive impairment, the functional impact of which is poorly understood. The aim of this study was to determine whether subtle cognitive impairment contributes to limitations in instrumental activities of daily living (IADLs) in this group, and whether this association is independent of physical co-morbidity and other potentially confounding factors.

Subjects and Method: Two hundred and nineteen non-demented patients were recruited from cardiovascular and diabetic hospital outpatient clinics. Functional dependence was assessed using the self-report version of the Instrumental Activities of Daily Living scale. Cognitive ability was assessed using the Montreal Cognitive Assessment (MoCA). Demographic and clinical information was collected via interview and a review of hospital records. Standard logistic regression was performed to identify factors independently associated with functional status.

Results: Five variables (gender, cardiovascular disease burden, non-cardiovascular disease burden, cognitive status, and age) were independently associated with an increased likelihood of requiring assistance with one or more everyday activities. The likelihood of needing assistance increased 2.05 times (95% CI: 1.59 – 2.79) for each additional cardiovascular diagnosis present and 1.12 times (95% CI: 1.01 – 1.27) for every point lower on the MoCA. Thus, in comparison to a person with a perfect MoCA score, a person who scored in the cognitively impaired range (< 23) was 7.7 (CI 7.07 – 8.89) times more likely to report that they required assistance with an everyday activity.

Conclusion: Cognitive impairments appear to reduce the ability to independently carry out routine daily tasks in patients with cardiovascular diseases and risk factors. Cognition

should therefore be considered along with physical symptoms when assessing and responding to the support needs of this group.

5.3 Introduction

Cardiovascular diseases (CVD), particularly those involving atherosclerosis (Elwood, Pickering, Bayer, & Gallacher, 2002; Singh-Manoux, Britton, & Marmot, 2003; Verhaegen, Borchelt, & J., 2003), and cardiovascular risk factors (CVRFs), like obesity and diabetes (Barnes, Alexopoulos, Lopez, Williamson, & Yaffe, 2006; Elias et al., 2004; Llewellyn et al., 2008), increase the risk of developing mild cognitive impairments. For example, in a representative sample of men aged in their 50s and 60s without a history of stroke, the presence of heart disease or peripheral arterial disease was found to be associated with a reduction in cognitive function equivalent in magnitude to the decline associated with 5 years of aging (Elwood et al., 2002). The risk of cognitive impairment increases with the total number of CVD and CVRFs a person has (Barnes et al., 2006; Elias et al., 2004; Llewellyn et al., 2008; Sanders, Lyness, Eberly, King, & Caine, 2006; Verhaegen et al., 2003; Vinkers et al., 2005). Population-based studies from developed western countries report that between 11% and 17% of people aged over 60 or 65 years are affected by mild cognitive impairment (Mariani, Monastero, & Mecocci, 2007). Prevalence rates among people with CVD and CVRFs are likely to be higher than this. The pathological mechanisms behind this association are largely attributed to ischaemic brain injury caused by small vessel pathology, (Ince & Fernando, 2003) but may be compounded by the adverse effects of prescribed cardio-active pharmacotherapy (Han, Agostini, & Allore, 2008; Hilmer et al., 2007), and/or recurrent hypoglycemic episodes in diabetic patients (McNay, 2010).

The severity of cognitive impairment in cardiovascular patients spans a continuum from barely detectable through to dementia. Longitudinal population-based studies have demonstrated that, in most cases, the onset of vascular dementia is slow and gradual, with most people experiencing a period of mild grade cognitive impairment in the 3 to 5 years

preceding the dementia diagnosis (Hayden et al., 2005; Ingles, Wentzel, Fisk, & Rockwood, 2002; Waite et al., 2005). Thus, the distinction between mild cognitive impairment and dementia is somewhat arbitrary. Importantly, the majority of people who experience a mild decline in cognitive function do not go on to develop dementia over the short term (5 to 10 years) (Mitchell & Shiri-Feshki, 2009). Instead the cognitive impairment remains relatively stable, resulting in a large pool of cardiovascular patients who are affected by subtle deficits that may not be immediately obvious in a clinical setting.

In the general elderly population, mild cognitive impairment is associated with a reduction in the ability to carry out complex daily tasks (Barberger-Gateau, Fabrigoule, Rouch, Letenneur, & Dartigues, 1999; Bell-McGinty, Podell, Franzen, Baird, & Williams, 2002; Blaum, Ofstedal, & Liang, 2002; Burton, Strauss, Hultsch, & Hunter, 2006; Cahn-Weiner et al., 2007; Farias et al., 2009; McGuire, Ford, & Ajani, 2006; Plehn, Marcopulos, & McLain, 2004; Royall, Palmer, Chiodo, & Polk, 2005). Although the functional impact of cognitive impairment has not been studied in populations with cardiovascular pathology, it is likely that subtle cognitive impairments affect functional capacity in this group as well. However, the picture in this clinical group is complicated by the fact that CVD (Brach, Solomon, & Naydeck, 2009; Ettinger Jr et al., 1994; Groll, To, Bombardier, & Wright, 2005; Pinsky, Jette, Branch, Kannel, & Feinleib, 1990; Richardson, 2003) and CVRFs (Groll et al., 2005) can cause physical symptoms (e.g., pain, fatigue, shortness of breath), which additionally limit functional capacity. The relative contribution of physical and cognitive problems to functional limitations in this group is currently poorly understood. More information about the relationship between cognitive impairment and functional capacity in patients with CVD and CVRFs would provide health care professionals who are involved in their management and rehabilitation with a better understanding of their potential functional

difficulties and needs. A cohort of patients with a range of CVD and/or CVRFs factors was therefore examined to determine whether cognitive performance was related to limitations in daily activities, and whether this relationship was independent of overall cardiovascular burden and other potentially confounding demographic variables and co-morbid illnesses.

5.4 Method

5.4.1 Participants

The research was approved by the Queen Elizabeth Hospital (2005080) and University of South Australia (P153/05) Human Research Ethics Committees. Participants (n = 219) were recruited on a prospective basis from cardiac and diabetic/endocrine outpatient clinics at a large tertiary-referral hospital in South Australia. Patients were initially referred to the clinics because they had pre-established CVD that required ongoing management or CVRFs such as hypertension or diabetes. Consecutive eligible patients were invited to participate, and those who consented and were available for interview were recruited. This study sample represented a subset of patients recruited for a larger study that investigated the prevalence of Peripheral Arterial Disease.

Patients were eligible to participate in the current study if they were aged over 18; had the capacity to provide informed consent; had attended one of the specified clinics within the 18 month recruitment period; and English was their first language (because English proficiency could affect cognitive test performance). People with a diagnosis of dementia that was documented in hospital records were excluded.

5.4.2 Measures

Level of independence in daily activities

All the patient measures were taken during a single assessment session. Participants' level of independence in daily activities was assessed using the self-rated version of the Instrumental Activities of Daily Living (IADL) Scale from the Multilevel Assessment Instrument (Lawton, Moss, Fulcomer, & Kleban, 1982). This 9-item measure has been used

extensively in geriatric populations. In a similar cohort, scores on the self report version were strongly correlated with those of the informant-report version (r = .69) (Burton, Strauss, Bunce, Hunter, & Hultsch, 2009). Instrumental activities were measured rather than basic activities of daily living, like eating, dressing, or using the toilet, because instrumental activities require a greater level of skill and judgment (Lawton, 1988), and are therefore more likely to be sensitive to mild changes in cognitive capacity (Mariani et al., 2008; McGuire et al., 2006).

Participants were required to rate, on a three-point scale, how much help they would require to perform each of nine tasks (using the telephone, shopping, food preparation, housekeeping, laundry, transportation, managing medications, handyman chores and home finances). A score of 0 was assigned for a response indicating "no help", one point for a response indicating "some help", and two points for a response indicating "complete dependence".

Scores for each item were tallied to generate a total IADL score, ranging from zero (no help) to 18 (complete dependence in all activities). Scores were also dichotomized to produce a group that required no help (total IADL score = 0) and a group that required some help with at least one activity (total IADL score $\geq$ 1).

Cardiovascular and non-cardiovascular diagnoses

The burden of co-morbid diseases was measured using the Functional Comorbidity Index (FCI) (Groll et al., 2005). The FCI is comprised of a list of eighteen diagnoses. One point is assigned for each diagnosis present. The FCI was developed to include items that are associated with physical function, thus distinguishing it from other co-morbidity indexes such

as the Charlson (Charlson, Pompei, Ales, & McKenzie, 1987), which reflects the risk of mortality. Its construct validity has been confirmed in a number of studies (Fortin et al., 2005; Groll, Heyland, Caeser, & Wright, 2006; Tessier, Finch, Daskalopoulou, & Mayo, 2008).

The individual effects of both cardiovascular and non-cardiovascular diagnoses were of interest, so they were tallied separately to create two total scores. There were seven CVD and CVRFs (stable angina, congestive heart failure, past myocardial infarct, stroke or TIA, peripheral arterial disease, diabetes, and obesity), resulting in a cardiovascular score ranging from zero to seven. There were 11 non-cardiovascular diagnoses (arthritis, osteoporosis, asthma, chronic obstructive pulmonary disease/acquired respiratory distress syndrome/emphysema, neurological disease, upper gastrointestinal disease, depression, anxiety or panic disorders, visual impairment, hearing impairment, and degenerative disc disease), resulting in a non-cardiovascular score ranging from zero to 11.

The presence of each diagnosis was established via interview and a comprehensive review of patient hospital files. In the case of peripheral arterial disease, the results of a clinical assessment conducted as part of a larger study were also considered, and in the case of depression, the Centre for Epidemiological Studies Depression (CES-D) (Radloff, 1977) scores were also used. The CES-D is a widely used paper-and pencil depression screening tool. It has been validated in the elderly (Hertzog, Van Alstine, Usala, Hultsch, & Dixon, 1990) and those with cardiovascular diseases (Parikh, Eden, Price, & Robinson, 1988) and other co-morbidities (Berkman et al., 1986). It has adequate test-retest reliability and high internal consistency (Eaton, Smith, & Muntaner, 2004). In line with scoring guidelines (Radloff, 1977), participants who recorded a score higher than 15 were classified as depressed.

Cognitive Performance

Cognition was assessed using the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005), which is an individually administered paper and pencil format test that takes 10 to 20 minutes to complete. It includes items designed to assess visuospatial abilities (clock drawing and cube copying), memory (5-word list learning and delayed recall), executive functioning (abbreviated trails-B, phonemic fluency, and similarities tasks), attention, concentration and working memory (target detection using finger tapping, serial subtraction, and digits forward and backward) language (picture naming and sentence repetition), and orientation (time and place). Scores range from zero to 30, with higher scores indicating better performance.

Previous validation studies suggest that an education-adjusted score below 23 is likely to indicate Mild Cognitive Impairment (MCI) (Lee et al., 2008; Luis, Keegan, & Mullan, 2008). MCI is a formal diagnosis applied to non-demented individuals that is established using comprehensive neurological testing, and denotes a level of cognitive impairment that is at least one standard deviation below what is expected given the person's age and level of education (Gauthier et al., 2006).

The MoCA has good test-retest reliability (r =.92) (Nasreddine et al., 2005) and internal consistency (alpha = .83 to .86) (Lee et al., 2008; Nasreddine et al., 2005), and shows moderate to strong correlations with other brief tests of global function including the MMSE (r= .62 to r = .87) (Lee et al., 2008; Nasreddine et al., 2005; Smith, Gildeh, & Holmes, 2007), and the Clinical Dementia Rating Scale (r = -.62) (Lee et al., 2008). It is sensitive to differences in cardiovascular risk factor profiles (Popovic, Seric, & Demarin, 2007) and is more sensitive to mild levels of cognitive impairment than other screening tools, such as the

MMSE (Lee et al., 2008; Luis et al., 2008; Nasreddine et al., 2005), and covers a wider range of cognitive skills (Lonie, Tierney, & Ebmeier, 2009).

Although the scoring guidelines recommend adjusting the total score for people with low education (Nasreddine et al., 2005), this was not done because education was treated as a separate variable in regression analyses.

Statistical Analysis

To provide descriptive data, exploratory analysis was conducted using Spearmans correlations (r_s) to examine relationships between IADL scores, MoCA scores and other variables.

Participants were then dichotomised into those who needed help with IADLs (43.8%) and those who did not need help (56.2%). Standard logistic regression (entry model with calculation of adjusted odds ratio (OR) and 95% confidence intervals (95% CI)) was used to identify variables that were independently associated with help status (help needed vs no help needed).

Age, education, sex, cardiovascular illness and non-cardiovascular illness were identified as potential predictors of functional difficulty based on the findings of existing research (Albert et al., 2006; Burton et al., 2009; McGuire et al., 2006; Plehn et al., 2004). To select which of these variables should be entered into the model, univariate group comparisons were carried out. The group that needed help was compared to the group that did not need help, and variables that differed at a .05 level of significance level were entered into the model. Mann-Whitney U tests were used for non-normally distributed variables (education,

cardiovascular diagnoses, and non-cardiovascular diagnoses), and are presented as the median (Mdn) and interquartile range (IQR). A t-test was used for the normally distributed variable (age), and is presented as the mean (m) and standard deviation (±). A chi-square test was used for the categorical variable (sex).

After generating the initial model, cases with large standardized residuals (z) were identified. These outliers, for whom the model did not fit well, were investigated and removed from the dataset where appropriate.

5.5 Results

5.5.1 Descriptive information

Descriptive data are set out in Table 1, and show that there were approximately equal numbers of men and women. Participants' ages ranged from 41 to 91 (m = 67.6, SD = 11.7). Education levels ranged from 5 to 27 years (Mdn = 10, IQR = 8 - 12). The number of CVD/ CVRFs and non-cardiovascular diagnoses each ranged from 0 to 6.

Table 1: Demographic and Clinical Features of the Study Sample

	Whole Group (n=219) Mdn (IQR) / %	Need IADL Help (n = 96) Mdn (IQR) / %	Do Not Need IADL Help (n = 123) Mdn (IQR) / %
Demographics			
Female	49.8%	59.0%	28.0%
Age	67.1 ± 11.7[1]	71.7 ± 11.0[a]	63.5 ± 10.9[a]
Education	10 (8 - 12)	9 (8 - 11)	11 (9 - 13)
Cognition			
MoCA Total Score	23 (20 - 25)	22 (18 - 24)	24 (21 - 26)
MoCA < 23	37.4%	49.0%	28.5%
IADL Help Needs			
IADL Total Score	0 (0 - 1)	2 (1 - 4)	0 (0 - 0)
Diagnoses			
Total Non-CVD Diagnoses	2 (1 - 3)	2 (1 - 3)	1 (1 - 2)
Total CVD Diagnoses	2 (1 - 2)	2 (1 - 3)	1 (1 - 2)
Chronic Heart Failure	5.0%	6.3%	4.1%
Myocardial Infarction	28.8%	37.5%	22.0%
Diabetes	42.5%	40.6%	44.7%
Peripheral Arterial Disease	16.4%	26.0%	8.9%
Angina	37.0%	52.1%	25.2%
Stroke or TIA	14.6%	24.0%	7.3%
Body Mass Index > 30	43.4%	43.8%	43.1%

Note. CVD = Cardiovascular Disease, IADL = Instrumental Activities of Daily Living, MoCA = Montreal Cognitive Assessment, TIA = Transient Ischaemic Attack; [a] mean and standard deviation

Total MoCA scores ranged from 11 to 29. Poorer cognitive performance was associated with older age (r_s = -.45, p < .001), fewer years of education (r_s = .43, p <.001), and a greater number of CVD states (r_s = -.21, p = .002), but was not associated with the number

of non-CVD diagnoses (r_s = -.11, p = .105). More than a third of participants (37.4%) recorded a MoCA score below 23, suggesting MCI (Lee et al., 2008; Luis et al., 2008).

The total IADL score ranged from 0 to 10. Greater independence, as measured by the total IADL score, was associated with younger age (r_s = .35, p<.001), more years of education (r_s = -.26, p< .001), fewer CVD/CVRFs (r_s = .32, p <.001), fewer non-cardiovascular diagnoses (r_s = .26, p < .001), and better cognitive performance (r_s = -.27, p < .001). Almost half the participants (43.8%) reported requiring help on at least one IADL item. As displayed in Table 2, of all the tasks, people were most likely to report needing help with handyman work, followed by housework and shopping. Women reported needing help more often than men on most items.

Table 2. Proportion of Participants Requiring Help for each IADL Item

IADL Item	Whole Group (n = 219)	Women (n = 109)	Men (n = 110)
Handyman work	40.4% (n = 88)	58.7% (n = 64)	21.8% (n = 24)
Housework	16.8% (n = 36)	18.3% (n = 20)	14.5% (n = 16)
Shopping	15.5% (n = 34)	23.9% (n = 26)	7.3% (n = 8)
Transport	8.7% (n = 19)	15.6% (n = 17)	1.8% (n = 2)
Meal preparation	4.1% (n = 9)	5.5% (n = 6)	2.7% (n = 3)
Money management	4.1% (n = 9)	5.5% (n = 6)	2.7% (n = 3)
Laundry duties	3.7% (n = 8)	2.8% (n = 3)	4.5% (n = 5)
Managing medications	2.7% (n = 6)	0.9% (n = 1)	4.5% (n = 5)
Telephone use	0.9% (n = 2)	0% (n = 0)	1.8% (n = 2)
Any Item	43.8% (n = 96)	59.6% (n = 65)	28.2% (n = 31)

Note. IADL = Instrumental Activity of Daily Living

5.5.2 Logistic regression

Identification of variables to enter into the regression model

Compared to the group that did not need help with IADLs, the group needing help was older ($t(217) = -5.48$, $p < .001$), had fewer years of education ($U = 4224.0$, $z = -3.56$, $p < .001$), a greater number of CVD/CVRFs ($U = 3955.0$, $z = -4.34$, $p < .001$), more non-cardiovascular diagnoses ($U = 4337.0$, $z = -3.45$, $p = .001$), and performed more poorly on the MoCA ($U = 4088.5$, $z = -3.92$, $p < .001$). In addition, a significantly higher proportion of women than men reported needing help (X^2 (1) = 22.0, p<.001). Thus, all of these variables were entered into the regression model.

Three extreme outliers were identified ($z \pm 3.9$ in all cases). All were from the group that needed help with IADLs. All three participants were relatively young, had few disease diagnoses and, in two cases, had relatively high cognitive scores. All had a rare diagnosis with the potential to impact on functional capacity that was not captured by the FCI (psychotic illness, genetic abnormality associated with intellectual impairment, and unexplained fatigue). These cases were thought to be unrepresentative of the current patient group and were therefore excluded from further analysis, leaving 216 cases.

The resulting full model was statistically significant X^2 (6, n = 216) = 78.54, p <.001, indicating that it was able to distinguish between those who needed help and those who did not. It correctly classified 76.3% of cases. The model as a whole explained between 35.1% (Cox and Snell R square) and 47.0% (Nagelkerke R squared) of the variance.

With the exception of education, all variables made a unique statistically significant contribution to the model (Table 3). The association between cognition and needing help was negative (ie poorer cognition was associated with a greater likelihood of needing help), so for ease of interpretation, the odds value was inverted. The inverted odds ratio was 1.12 (CI 1.01 – 1.27), indicating that a decrease by one point on the MoCA (i.e., decline in cognitive performance) was associated with a 1.12 times greater likelihood of a person reporting functional impairment controlling for other factors in the model. By extrapolation, in comparison to a score of 30, which indicates an absence of cognitive impairment, a person who scored below 23 (the suggested cut-off for Mild Cognitive Impairment) (Lee et al., 2008; Luis et al., 2008) was 7.7 (CI 7.07 – 8.89) times more likely to report that they required some assistance with one or more everyday activities.

Table 3. Independent Correlates of Needing Help with an IADL

							95% CI for Odds Ratio	
	B	S.E.	Wald	df	*p*.	Odds Ratio	Lower	Upper
Sex	2.135	.425	25.255	1	.000	8.454	3.677	19.438
Cardiovascular Diagnoses	.717	.158	20.547	1	.000	2.049	1.502	2.793
Non-Cardiovascular Diagnoses	.301	.136	4.936	1	.026	1.351	1.036	1.763
Education	.072	.064	1.269	1	.260	1.075	.948	1.219
Age	.072	.018	15.537	1	.000	1.074	1.037	1.113
Cognitive Performance	-.112	.051	4.792	1	.029	.894	.809	.988
Constant	-6.479	2.121	9.330	1	.002	.002		

Note. Nagelkerke R squared = 47%

5.6 Discussion

This study focused on patients without a dementia diagnosis who were receiving ongoing medical management for CVD or CVRFs to gain a better understanding of the factors that impede their ability to carry out day-to-day tasks. Almost half of the participants in the study sample (43.8%) reported that they needed assistance with instrumental activities of daily living such as shopping, using transport, or completing handyman tasks. As predicted, poor cognitive performance was an independent predictor of these problems. A decrease by one point on the MoCA test was associated with a marginally increased likelihood of a person reporting functional limitation. In comparison to a score of 30, which indicates an absence of cognitive impairment, a person who scored below 23 (the suggested cut-off for Mild Cognitive Impairment) (Lee et al., 2008; Luis et al., 2008) was more than seven times more likely to report that they required some assistance with one or more everyday activities. These results suggest that subtle cognitive impairment is not a benign complication of cardiovascular disease. The fact that more than a third of the participants in this cohort of cardiovascular outpatients recorded a cognitive test score in the impaired range highlights the importance of these findings.

In line with previous research (Brach et al., 2009; Ettinger Jr et al., 1994; Groll et al., 2005; Pinsky et al., 1990; Richardson, 2003), the presence of CVD/CVRFs was also an independent predictor of needing help with an everyday activity. The likelihood of a person requiring assistance more than doubled for every additional cardiovascular disease or risk factor present. Likewise, non-cardiovascular diagnoses were also associated with activity limitation, consistent with prior studies (Blaum et al., 2002; McGuire et al., 2006), and older

age was associated with a higher likelihood of needing help (Albert et al., 2006; Burton et al., 2009; McGuire et al., 2006).

The present results concur with previous studies carried out in other non-demented populations, which also reported an association between cognitive impairment and difficulty completing daily tasks (Barberger-Gateau et al., 1999; Bell-McGinty et al., 2002; Burton et al., 2006; Cahn-Weiner et al., 2007; Farias et al., 2009; Plehn et al., 2004; Royall et al., 2005). The finding that cognitive impairment and disease burden make independent contributions to functional disability has also been observed in community-based populations (Blaum et al., 2002; Gill, Williams, Richardson, & Tinetti, 1996; McGuire et al., 2006; Plehn et al., 2004) and a population with diabetes (McGuire, Ford, & Ajani, 2006). However, this is the first time this issue has been examined in patients with CVD and CVRFs.

Through clinical experience, specialists working with patients who have CVD or CVRFs are alert to the fact that elderly people with multiple comorbidities are at increased risk of functional limitations. However, the present results suggest that aging and medical illness may not fully explain the increase in help requirements. Rather, the cognitive impairment that often accompanies old age and cardiovascular disease also appears to play a role. Specialists involved in determining the support requirements of patients with CVD and CVRFs need to consider the cognitive components of tasks alongside the physical components. For instrumental activities of daily living such as banking, arranging transport and shopping, relevant physical components might include walking, transferring, lifting and carrying. Conversely, the relevant cognitive components might include information recall, planning, sequencing, and problem solving in the face of unanticipated events. Strategies that effectively compensate for physical impairments differ markedly from strategies that address

cognitive impairments. Thus, more thorough assessment practices that take account of cognitive performance have the potential to improve quality of life and prolong independence for those experiencing cognitive difficulties. Importantly, mild problems with memory or executive function may not be immediately obvious in a busy cardiovascular clinic and, therefore, formal cognitive testing may be beneficial for high risk patients. In the current study sample, consistent with prior research (Barnes et al., 2006; Verhaegen et al., 2003; Vinkers et al., 2005), people with multiple cardiovascular conditions and older age were at greatest risk of cognitive impairment.

An unexpected finding of this study was that women were more likely to report that they needed help with an activity than were men, and that this difference could not be explained by illness burden or demographic differences between males and females. Higher levels of self-reported activity limitation have been repeatedly reported in prior research (Albert et al., 2006; Merrill, Seeman, Kasl, & Berkman, 1997; Rahman & Liu, 2000). Studies that have used objective lab-based assessments to establish physical capacity have demonstrated that some of this variation can be explained by the fact that older women have inherently poorer physical abilities (e.g. less strength and endurance) (Merrill et al., 1997; Rahman & Liu, 2000), possibly due to differences in bone and muscle composition or fitness levels. However, even controlling for true physical ability, women report their activity limitations to be more severe than men do (Merrill et al., 1997; Rahman & Liu, 2000). It has been suggested that the gender-specific nature of some daily activities may result in response bias (e. g. women feel more able to complete meal preparation, and men feel more able to carry out handyman duties) (Rahman & Liu, 2000). We attempted to minimise this source of bias, by using the version of the IADL questionnaire that asked “could you” rather than earlier versions that asked “do you”. In the present sample women reported needing help more often

than men across most activities, not just those typically associated with male roles. Thus, gender-role stereotyping does not appear to explain the discrepancy. Another possible explanation for the sex difference is that cultural factors may influence men to downplay their level of difficulty or influence women to more readily admit to difficulties at a lower threshold (Merrill et al., 1997; Rahman & Liu, 2000). This form of response bias may well have applied in the present sample.

A limitation of this study is that several of the assessment instruments were brief screening tools. Thus, low sensitivity may have lead to an underestimation of the strength of the observed relationships. Specifically, cognition was measured using the MoCA (Nasreddine et al., 2005). This tool was designed to be a brief screening tool and, although it is more sensitive to mild cognitive impairment than many other screening tools (Lonie et al., 2009), it lacks the sensitivity of a comprehensive neuropsychological assessment.

The IADL Scale (Lawton et al., 1982), which was used to measure functional status, is also very brief and may be less sensitive than other tools (Burton et al., 2009). The fact that the tool relies on self-report rather than direct assessment of functional capacity may also contribute to measurement error. Importantly, these problems are likely to have attenuated the strength of the associations between variables rather than changing the overall pattern of results because there is no reason to suspect that the measurement problems affected the group needing help differently from the group who did not need help. However, replication of this study using more sensitive measures is required to confirm the findings.

In conclusion, the results of this study suggest that subtle cognitive impairment is not a benign complication of cardiovascular pathology, and warrants greater research and clinical attention.

5.7 Summary and implications

Results suggest that cognitive impairment is an independent predictor of functional problems in non-demented patients with cardiovascular disease.

Professionals working with cardiovascular patients need to be alert to the possible impact of cognitive impairment when considering how to best assist them.

Mild cognitive impairments may not be immediately obvious, and thus cognitive screening may be warranted for high risk groups such as those with multiple cardiovascular conditions and advanced age.

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Chapter 6: Study 4

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6.1 Title page

Title: The Depression-Executive Dysfunction (DED) Syndrome and response to antidepressants: A meta-analytic review

Running Head: DED Syndrome and antidepressant response

Authors: S N McLennan, School of Psychology, University of Adelaide

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Key Words: depression; antidepressants; cognition; neuropsychological tests; prefrontal cortex; executive function

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Word Count: 3975

6.2 Abstract

Background: The Depression-Executive Dysfunction (DED) model predicts that cognitive impairment, particularly executive dysfunction, is associated with poor response to antidepressant medication. A meta-analysis was undertaken to assess the evidence for this hypothesis.

Methods: The PsycInfo and PubMed databases were searched to identify studies that examined response to antidepressant treatment in relation to pre-treatment cognitive performance. Systematic screening yielded 17 eligible publications, providing data for 1269 individuals. Ninety cognitive tests and subtests were used by these studies; 30 were used by more than one study. Weighted mean Cohen's *d* effect sizes, 95% confidence intervals, and Fail Safe Ns were calculated for these 30 tests.

Results: Five cognitive tests provided good discrimination ($d_w > .5$) between patients who ultimately responded to antidepressant medication and those who failed to respond. One was a test of executive function but the remainder assessed other cognitive domains. Due to the small number of studies the influence of methodological factors, such as participant age and treatment duration, could not be statistically examined. However, a supplementary analysis restricted to nine studies where SSRIs were the only class of antidepressant revealed a similar pattern of results.

Conclusions: Performance on selected tests of executive function and non-executive cognitive functions is associated with response to anti-depressant medication in some populations. The available evidence does not provide strong support for the DED model.

6.3 Introduction

Although the efficacy of antidepressant medications for the treatment of Major Depression is well established (Williams et al., 2000), a large proportion of patients fail to respond to such treatment (Sneed et al., 2008). If factors could be identified that predict which patients are likely to experience a poor response, then this may advance the understanding of physiological mechanisms relevant to treatment response and ultimately lead to the development of better tailored therapies. More immediately, it may be useful in assisting clinicians who work with depressed patients to anticipate likely treatment outcomes and decide on models of follow-up care.

Differences in aetiology underlying depressive illnesses may account for some of the variance in treatment response rates. The Depression – Executive Dysfunction (DED) model offers one basis for predicting poor response to antidepressant medications (Alexopoulos, 2001). It predicts that, among depressed patients, those who exhibit deficits in executive function are likely to respond poorly to antidepressant medication. The DED model is based on the premise that, in some cases, depression results from abnormalities in the fronto-limbic and fronto-striatal neural circuits, which are critical to both mood regulation and to executive functions (Tekin & Cummings, 2002). This suggestion is supported by a small number of studies showing high rates of structural and/or functional abnormalities in fronto-limbic and fronto-striatal neural pathways in patients with depression (Alexopoulos, Kiosses, Klimstra, Kalayam, & Bruce, 2002; Herrmann, Le Masurier, & Ebmeier, 2008). The DED model is conceptually aligned with the Vascular Depression model (Alexopoulos et al., 1997) and post-stroke depression theories (Robinson, Kubos, Starr, & al, 1984), which suggest that vascular damage to prefrontal circuits may result in depression. Taking a broader perspective, the DED

model encompasses additional non-vascular factors, such as age-related changes and degenerative brain disease as potential causes of neural disruption (Alexopoulos, 2006). Research into all three models has produced mixed findings, and consensus about the existence and mechanisms of these forms of depression has not been reached (Almeida, 2007; Newberg, Davydow, & Lee, 2006).

The pathological mechanisms outlined in the DED model are thought to explain only a small proportion of depression cases, and the model stands in contrast to dominant pathogenic explanations for depression, which emphasise the importance neurotransmitters deficits, particularly serotonin and norepinephrine (Nemeroff, 2002). Consistent with classical models of depression, Selective Serotonin Reuptake Inhibitors (SSRIs), which boost neurotransmission in monomanine pathways, are recommended as first-line medical treatments for depression (National Institute for Health and Clinical Excellence, 2007). Prefrontal processes are supported by multiple neurotransmitters, including dopamine, norepinephrine, histamine and acetylcholine (Stahl, Zhang, Damatarca, & Grady, 2003). For this reason, proponents of the DED model have suggested that widely used antidepressant medications, such as SSRIs and tricyclic antidepressants, may have limited effectiveness for patients experiencing executive dysfunction (Alexopoulos, 2001).

In support of the DED model, several studies have reported that depressed patients who display executive dysfunction are less likely to respond to antidepressant treatment (Alexopoulos et al., 2005; Dunkin et al., 2000; Kalayam & Alexopoulos, 1999; Kampf-Sherf et al., 2004; Majer et al., 2004; Sneed et al., 2007), however such findings have not always been replicated (Potter, Kittinger, Wagner, Steffens, & Krishnan, 2004). Running contrary to the model, other studies have reported that cognitive functions such as memory, which are not

closely associated with frontal-subcortical neural circuits, are also predictive of treatment response (Deuschle et al., 2004; Story, Potter, Attix, Welsh-Bohmer, & Steffens, 2008). Yet, there is inconsistency in these findings as well (Kampf-Sherf et al., 2004; Marcos et al., 2005; Sneed, Keilp, Brickman, & Roose, 2008). A comparison of findings from these studies is further complicated by the large number of neuropsychological tests that have been employed and by differences in study methodology. In many cases, data have been published as incidental or secondary results within studies addressing other research questions and, as such, they may be overlooked when reviewing the literature. Furthermore, many studies are based on cohorts of less than 30 people and may therefore have insufficient statistical power to detect significant relationships. Meta-analytic techniques offer a means for addressing some of these problems through data pooling and the calculation of effect sizes, which provide a means for consolidating and directly comparing the findings from studies that have used different assessment tools.

The current study assessed the treatment-related predictions of the DED model. First, databases were searched to identify all previously published studies that have examined antidepressant treatment response in relation to pre-treatment cognitive function. Following this, a meta-analysis was undertaken to determine whether there is evidence for (a) a large and consistent difference in pre-treatment executive function between medication responders and non-responders and/or (b) an absence of a difference between medication responders and non-responders in other types of cognitive function. Finally, methodological variables were examined to determine the extent to which aspects of study design are likely to have influenced the findings.

6.4 Methods

6.4.1 Literature search

Systematic searches were conducted using the PubMed and PsycINFO databases. A specialist subject librarian assisted in developing the search terms, which included an exhaustive list of variants for "depressive illness", "cognitive assessment", and "drug therapy". A full list of search terms is available on request. Searches were limited to papers published in English before September 2008.

6.4.2 Inclusion and exclusion criteria

To be included in the current analysis, studies had to meet the following criteria:

1) A pharmacological treatment for depression was administered (studies were retained if psychological or electroconvulsive shock therapy (ECT) were also administered to a minority of participants);

2) The severity of depression was assessed before and after treatment;

3) Cognitive performance was assessed before treatment;

4) A published test was used to assess cognitive performance;

5) Participants were categorised as responders or non-responders;

6) Pre-treatment cognitive performance data was presented separately for responder and non-responder groups; *and*

7) Statistical data necessary for the calculation of Cohen's d effect sizes were provided.

In cases where a study met the first six inclusion criteria but failed to provide the necessary statistical data, authors were contacted by email and the information requested. Basic demographic data (age, sex, education, baseline depression scores) was also requested

where necessary but this had no bearing on eligibility. Studies were excluded if participants were selected on the basis that they had a disorder with neurological symptoms, such as HIV, Bi-polar Disorder, Parkinson's Disease, Multiple Sclerosis or Alzheimer's Disease, or if all participants had cognitive screening scores suggestive of a neurological disorder (eg Mini Mental Screening Exam (MMSE) < 24).

The PubMed search identified 8388 titles, and the PsycINFO search 2801. After reviewing all titles, and 243 abstracts, 108 full-text articles were retrieved. Of these, 78 were excluded. In most cases, the studies that were excluded failed to meet more than one criteria, the most common being that they addressed unrelated research questions or examined 'relapse after initial response' or 'time to response' rather than response or remission. Four studies were excluded because data was presented in a format unsuitable for meta-analysis (eg cognition scores were dichotomised) (Bogner et al., 2007; Kampf-Sherf et al., 2004; Sneed et al., 2008; Stoudemire et al., 1991). In two publications (Deuschle et al., 2004; Saghafi et al., 2007) participants had been divided into three groups (full responders, partial-responders, and non-responders); these studies were retained but, to enable comparison with the other studies, data was collapsed into two groups (full-responders, verses partial or non-responders).

Two studies were excluded (Alexopoulos, Kiosses, Murphy, & Heo, 2004; Portella et al., 2003) because they presented data that had already been reported in another publication (Alexopoulos et al., 2005; Marcos et al., 2005). A search of the reference lists of all included studies yielded one additional eligible study (Majer et al., 2004). One further study (Mayberg et al., 2000) was supplied by an author following email contact about another publication. It was not identified in the original search because the neuropsychological data were incidental to the primary focus of the paper. Twenty studies ultimately met all inclusion criteria.

6.4.3 Effect size calculations and analyses

A total of 95 different cognitive tests and subtests were used across the 20 studies. Only 30 of these were used by more than one study, which meant that mean effect sizes could only be calculated for these 30 tests. The remaining 65 cognitive tests were not examined further. Data from three of the 20 eligible studies could not be included in analysis because the cognitive tests in these three studies were not used by any other study (Caligiuri et al., 2003; Deuschle et al., 2004; Garcia-Toro et al., 2003). One used a German list learning test (Deuschle et al., 2004), another used computerised tests of physical reaction time (Caligiuri et al., 2003), and the third used Spanish tests of vocal reaction time, working memory and attention (Garcia-Toro et al., 2003). Consequently, only 17 studies contributed to the final analyses.

The first step in calculating mean effect sizes was to compute a Cohen's *d* effect size for each cognitive test in each study. The Cohen's *d* represented the magnitude of difference in pre-treatment cognitive test scores between the group who ultimately responded to antidepressant treatment and the group that failed to respond. When calculating effect sizes, the scores of responders were always subtracted from the scores of non-responders. For most tests, higher scores represented better performance. Therefore, a positive effect size indicated *that responders performed better than non-responders. For tests that were scored in the opposite direction, such that lower scores indicated better performance (eg tests assessing errors or speed), the direction of the effect sizes was reversed, ensuring that positive effect sizes always indicated that responders performed better than non responders.

For each cognitive test, a weighted mean effect size (d_w) was then calculated. The mean effect size pools information about effect sizes across studies. The reliability of an individual effect size is influenced by sample size, so before individual effects sizes were aggregated, they were weighted to account for the sample size. In line with the recommendations of Lipsey and Wilson (2001), the inverse of the variance was used to weight each mean effect size. In this context, d_w = 0.2 is considered a small effect, d_w = 0.5 medium, and d_w = 0.8 large (32).

Standard Deviations (SDs) were calculated for each mean effect size to provide an indication of the variability in individual effect sizes across studies. Ninety five percent confidence intervals (95% CIs) were calculated (Lipsey & Wilson, 2001) to assess statistical significance. An effect size is significant if the 95% CI does not span zero. Percent overlap (%OL) statistics were also generated to illustrate the amount of overlap in the distribution of cognitive tests scores between responders and non-responders (Zakzanis, 2001).

One problem facing meta-analytic studies is that statistically significant results are more likely to be published and therefore more likely to be included in a meta-analysis. The failure to include unpublished studies with non-significant results increases the risk of a Type 1 error, which may result in an effect size being overestimated. In response to this problem, Fail Safe N's (N_{fs}) were calculated using the method described by Orwin (cited in Zakzanis, 2001). The N_{fs} statistic estimates the number of hypothetical unpublished studies with non-significant results (ie small effect) that would be required to overturn the obtained mean effect size, and result in a relatively meaningless effect, which was set at d = 0.2. The larger the N_{fs}, the more confidence can be placed in a particular finding.

In interpreting the results, cognitive tests were judged to provide good discrimination between responders and non-responders if they met the following criteria: the mean effect size was at least moderately strong ($dw \geq 0.5$); the mean effect size was significant (95% CI did not span zero); and the Fail Safe N was relatively large (Nfs ≥ N Studies).

6.5 Results

6.5.1 Characteristics of study designs

Table 1 summarises key methodological features of the 17 studies and serves to highlight some important differences across studies. Of note, there was considerable variation in the antidepressant drugs administered and in the treatment format. Specifically, in nine studies, a single drug (SSRI) was administered in a standardised format with the same dose or target dose given to all participants. In five other studies, drugs were administered using an algorithm, such that one agent was initially given to all patients and then participants who failed to respond to, or could not tolerate, this initial agent were administered an alternative medication, and so on. Three of these studies used a SSRI as the first line treatment and the remaining two used a Tricyclic antidepressant. Treatment in three additional studies was totally non-standardised and was left to the discretion of the treating physician.

There were also differences in other elements of the study designs. The time between initiation of treatment and reassessment of symptoms ranged from four to 52 weeks. Around half the studies classified responders on the basis that they achieved a specific cut-off score on the assessment instrument (usually referred to as ‘remission’ in the original articles), while the others defined response as a drop of 50% (or similar) in symptom severity from baseline. The proportion of participants who responded to medication according to these various definitions ranged from 21% to 71%. Dropout rates and rates of medication adherence were not reported in most studies.

Table 1. Summary of Study Design Features

Study Reference	N	Age (m)	Male (%)	Age at First Episode (m)	Definition of Response	Weeks of Follow up	Treatment Format	Drug Category	Response Rate (%)
(Alexopoulos et al., 2005)	112	73.2	48		50% Decrease	8	Standardised	SSRI	61
(Alexopoulos et al., 2007)	12	70			Cut-off Score	8	Standardised	SSRI	50
(Dunkin et al., 2000)	14	41.9	21		Cut-off Score	8	Standardised	SSRI	57
(Devanand et al., 2003)	26	76.7	36	63.9	50% Decrease	12	Standardised	SSRI	65
(Saghafi et al., 2007)	175	73	30	57.0	Cut-off Score	6	Standardised	SSRI	31
(Taylor et al., 2006)	37	36.3	54	16.8	Other Decrease	12	Standardised	SSRI	68
(Doraiswamy et al., 2003)	386	67.8	42		Other Decrease	12	Standardised	SSRI	71
(Mayberg et al., 2000)	8	48			50% Decrease	6	Standardised	SSRI	50
(Kalayam & Alexopoulos, 2003)	22	72.1			Cut-off Score	6	Standardised	SSRI	59
(Marcos et al., 2005)	25	70.8	20		Cut-off Score	52	Algorithm	SSRI, then Tricyclic then ECT	72
(Story et al., 2008)	100	69.1	38		Other Decrease	52	Algorithm	SSRI, then Venlafaxine or Buproprion, then Tricyclic or lithium	66
(Potter et al., 2004)	110	73.8	41		Cut-off Score	12	Algorithm	SSRI, then Venlafaxine or Bupropion, then Tricyclic or lithium, then ECT or psychotherapy	21
(de Groot, et al, 1996)	52	49	33		50% Decrease	6	Algorithm	Tricyclic then MAOI	50
(Kalayam & Alexopoulos, 1999)	49	74.7	27	55.7	Cut-off Score	6	Algorithm	Tricyclic, then SSRI or MAOI or Venlafaxine or Bupropion or Trazodone	49
(Majer et al., 2004)	73	45.6	40		50% Decrease	4	Unrestricted	Any	48
(Mayberg et al., 1997)	18	45	83		Other	6	Unrestricted	SSRI or Tricyclic or Bupropion	44
(Gallagher et al., 2007)	25	32.5	32	29.3	Cut-off Score	15	Unrestricted	SSRI or Venlafaxine or Prochlorperzaine	44

Note. m = mean; 50% Decrease = 50% decrease in depression rating scale score between baseline and follow-up; Other Decrease = decrease in depression rating scale score between baseline and follow-up other than 50%; Absolute Score = specific score on depression rating scale at follow-up; Standardised = same drug and target dose for all patients; Algorithm = same sequence of drugs prescribed as first and second-line treatment; Unrestricted = drug chosen by treating physician without restriction; SSRI = serotonin reuptake inhibitor; MAOI = monoamine oxidase inhibitor; ECT = electro convulsive shock therapy.

6.5.2 Participants

Data from 1269 participants were analysed. As shown in Table 1, females outnumbered males in most studies. All 17 studies provided data on age. The mean age of the study cohorts ranged from 32.5 to 76.7 years (m = 62.8, SD = 8.05). Around half the studies recruited relatively young adults and the other half specifically recruited elderly patients. Fifteen papers provided age data separately for the responder and non-responder groups. For these 15 publications, responders were significantly younger (m = 62.4) than non-responders (m = 66.5), (d_w = -0.24, CI: -0.39 to -0.08). Fourteen studies provided information on years of education, which was relatively high (m = 13.5, SD = 3.07). There was no significant difference in education level between responders (m = 14.0) and non-responders (m = 13.6) for the 12 studies that provided this information (d_w = 0.08, CI: -0.07 to 0.25). Thirteen papers provided baseline depression scores separately for responders and non-responders. Of these, patients who ultimately responded to medication were significantly less depressed at baseline than those who did not respond (d_w = -.16, CI: -0.31 to 0.00).

6.5.3 Effect sizes for cognitive tests

The weighted mean effect sizes (d_w) for the tests, broadly grouped according to cognitive category (Lezak, Howieson, & Loring, 2004) and rank ordered by size, are provided in Table 2. Cohen's *d* was positive for most tests, indicating that responders performed better on baseline cognitive tests than non-responders. Five of the 30 tests (identified by bold font in Table 2) showed good discrimination between groups based on the study criteria ($d_w \geq 0.5$; 95% CI $\neq 0$; and $N_{fs} \geq$ N Studies). These were the Mattis Dementia Rating Scale Initiation Perseveration Subtest (DRS-IP), a test of executive function, the Colour and Word trials of the Stroop test, which both measure information processing speed, the Block Design subtest of the

Wechsler Adult Intelligence Scale (WAIS), which draws on visuo-constructional skills and processing speed, and the Delayed Recall trial of the Logical Memory Subtest from the Wechsler Memory Scales. The percentage of overlap (%OL) was relatively large for all cognitive tests. Even for the tests showing the best discrimination between groups, there was still more than 50% overlap in the cognitive scores of responder and non-responder groups.

Table 2. Weighted Mean Effect Sizes for Pre-Treatment Cognitive Differences between Antidepressant Responders and Non-Responders

Cognitive Assessment Tool	N Studies	N Subjects	d_w	SD	95% CI	% OL	N_{fs}	Study References
Executive Function								
WCST: % Perseverative Errors	2	26	0.71	0.66	-0.09 - 1.52	57	5	(Alexopoulos et al., 2007; Dunkin et al., 2000)
DRS IP Subtest (raw)	**3**	**183**	**0.70**	**0.32**	**0.40 - 1.01**	**57**	**8**	**(Alexopoulos et al., 2005; Kalayam & Alexopoulos, 1999, 2003)**
Tower of London	2	47	0.29	0.46	-0.33 - 0.90	79	1	(Gallagher et al., 2007; Marcos et al., 2005)
Stroop Interference	6	247	0.28	0.43	0.02 - 0.53	79	2	(Alexopoulos et al., 2005; Dunkin et al., 2000; Kalayam & Alexopoulos, 2003; Majer et al., 2004; Mayberg et al., 1997; Mayberg et al., 2000)
COWAT	7	272	0.25	0.89	-0.02 - 0.51	79	2	(de Groot et al., 1996; Devanand et al., 2003; Dunkin et al., 2000; Gallagher et al., 2007; Mayberg et al., 2000; Potter et al, 2004; Taylor et al., 2006)
WCST: Perseverative Errors	2	51	0.16	0.71	-0.42 - 0.75	85	0	(Dunkin et al., 2000; B. P. Taylor et al., 2006)
WCST: Categories Completed	2	51	0.10	0.80	-0.48 - 0.69	92	0	(Dunkin et al., 2000; B. P. Taylor et al., 2006)
Category (Animal) Fluency	2	136	0.02	0.07	-0.38 - 0.42	100	0	(Devanand et al., 2003; Potter et al., 2004)
Speed / Reaction Time								
Stroop Colour: Number Completed	**2**	**51**	**0.64**	**0.23**	**0.05 - 1.23**	**62**	**4**	**(Dunkin et al., 2000; B. P. Taylor et al., 2006)**
Stroop Word: Number Completed	**2**	**51**	**0.63**	**0.06**	**0.04 - 1.22**	**62**	**4**	**(Dunkin et al., 2000; B. P. Taylor et al., 2006)**
WAIS Digit Symbol (scaled)	3	76	0.39	0.27	-0.09 - 0.88	73	3	(Dunkin et al., 2000; Marcos et al., 2005; Taylor et al., 2006)
Letter Cancellation: Time	2	99	0.30	0.32	-0.11 - 0.70	73	1	(Devanand et al., 2003; Majer et al., 2004)
Trail Making Test A: Time	5	257	0.11	0.40	-0.16 - 0.39	92	0	(Dunkin et al., 2000; Marcos et al., 2005; Mayberg et al., 2000; Potter et al., 2004; Story et al., 2008)
WAIS Digit Symbol (raw)	3	437	-0.02	0.17	-0.23 - 0.18	100	0	(Devanand et al., 2003; Doraiswamy et al., 2003; Gallagher et al., 2007)
Construction								
WAIS Block Design (scaled)	**2**	**51**	**0.64**	**0.50**	**0.04 - 1.23**	**62**	**4**	**(Dunkin et al., 2000; B. P. Taylor et al., 2006)**

DRS Construction Subtest (raw)	3	183	0.35	0.32	0.05 - 0.65	73	2	(Alexopoulos et al., 2005; Kalayam & Alexopoulos, 1999, 2003)
Attention / Working Memory								
Digit Span Forward (raw)	3	208	0.36	0.22	0.05 - 0.66	73	2	(Majer et al., 2004; Marcos et al., 2005; Potter et al., 2004)
DRS Attention Subtest (raw)	3	183	0.31	0.11	0.01 - 0.60	79	2	(Alexopoulos et al., 2005; Kalayam & Alexopoulos, 1999, 2003)
Trails Making Test B: Time	5	250	0.17	0.52	-0.11 - 0.45	85	0	(Dunkin et al., 2000; Mayberg et al., 1997; Mayberg et al., 2000; Potter et al., 2004; Story et al., 2008)
Digit Span Forward Plus Back	3	77	0.07	0.28	-0.40 - 0.54	92	0	(Devanand et al., 2003; Dunkin et al., 2000; Taylor et al., 2006)
Digit Span Back (raw)	3	208	0.06	0.12	-0.24 - 0.37	92	0	(Majer et al., 2004; Marcos et al., 2005; Potter et al., 2004)
Memory								
WMS LM Delayed Recall	**2**	**125**	**0.50**	**0.30**	**0.12 - 0.88**	**67**	**3**	**(Marcos et al., 2005; Story et al., 2008)**
Word List Recall: Short Delay	4	151	0.23	0.45	-0.11 - 0.56	85	1	(Alexopoulos et al., 2007; Dunkin et al., 2000; Gallagher et al., 2007; Story et al., 2008)
Word List Learning: 5 Trials	3	51	0.29	0.46	-0.11 - 1.02	79	1	(Alexopoulos et al., 2007; Dunkin et al., 2000; Gallagher et al., 2007)
Benton Facial Recognition Test	2	66	0.26	0.42	-0.23 - 0.75	79	1	(de Groot et al., 1996; Dunkin et al., 2000)
DRS Memory Subtest (raw)	3	183	0.14	0.38	-0.16 - 0.43	92	0	(Alexopoulos et al., 2005; Kalayam & Alexopoulos, 1999, 2003)
Global Function / Language / Conceptualisation								
Boston Naming Test	2	40	0.52	1.08	-0.15 - 1.19	67	3	(Devanand et al., 2003; Dunkin et al., 2000)
WAIS Vocabulary (scaled)	3	76	0.39	0.23	-0.10 - 0.87	73	1	(Dunkin et al., 2000; Marcos et al., 2005; Taylor et al., 2006)
DRS Conceptualisation Subtest (raw)	3	183	0.31	0.38	0.01 - 0.60	79	2	(Alexopoulos et al., 2005; Kalayam & Alexopoulos, 1999, 2003)
DRS Total Score (raw)	4	348	0.14	0.52	-0.08 - 0.37	92	0	(Alexopoulos et al., 2005; Alexopoulos et al., 2007; Kalayam & Alexopoulos, 1999; Saghafi et al., 2007)
Mini Mental Status Exam	4	449	-0.03	0.20	-0.23 - 0.17	100	0	(Alexopoulos et al., 2007; Devanand et al., 2003; Doraiswamy et al., 2003; Marcos et al., 2005)

Note. d_w = weighted mean effect size; SD = standard deviation; %OL = percent of overlap between groups; 95% CI = confidence intervals; N_{fs} = Fail Safe N; COWAT = Controlled Oral Word Association Test; DRS = Dementia Rating Scale; IP = Initiation Perseveration; WAIS = Wechsler Adult Intelligence Scale; WCST = Wisconsin Card Sort Test; WMS LM = Wechsler Memory Scale Logical Memory; Raw = unadjusted test score; Scaled = score adjusted for age/education/sex.
Bold text = findings meet study criteria for adequate discrimination ($d_w \geq 0.5$; 95% CI do not span zero; Nfs ≥ N Studies).

For most cognitive measures, there were large differences in effect sizes across the individual studies, which was reflected in the large SDs and the fact that most 95% CIs spanned zero. Finally, most N_{fs} were relatively small, suggesting that only a small number of additional studies with non-significant group differences would be needed to reduce mean effect sizes to a negligible level.

6.5.4 Moderator variables

Given the disparity in study designs, options for assessing the influence of moderating variables were explored. The calculation of Q statistics, which provide information about effect size homogeneity, was considered. However, Q is unreliable when there are a limited number of studies (Lipsey & Wilson, 2001) so this approach was not pursued. The possibility of examining subsets of studies sharing relevant characteristics was also considered. Unfortunately, the pool of available studies was too small and the list of potentially relevant variables too large to enable a breakdown into homogenous groups for most variables. However, there was a sufficient number of studies (n = 9) to allow supplementary analysis restricted to studies that used standardised administration of a SSRI.

The total number of participants in the nine studies that administered a standardised dose of SSRI was 792. The mean age of participants was 68.0 years (SD = 7.94). Responders were significantly younger (m = 65.4) than non-responders (m = 70.1), (d_w = -0.25, 95% CI: -0.46 to -0.04). The mean level of education was 14.0 years (SD = 2.93), with no significant difference between responders (m = 14.6) and non-responders (m = 13.8), (d_w = 0.14, 95% CI: -0.07 to 0.36). Baseline depression was less severe in responders than non-responders, but this difference was not significant (d_w = -0.10, 95% CI: -0.29 to 0.09).

The previous analyses were repeated for this subset of studies. In some cases, fewer than two studies used the same cognitive test, and therefore mean effect sizes could not be generated. However, it was possible to calculate mean effect sizes for 24 of the 30 original tests. Table 3 shows that the pattern of mean effect sizes was similar to that seen in the previous analyses. That is, there was a relatively wide range of effect sizes within each domain of cognitive function, including executive function. Five tests provided adequate group discrimination according to the criteria applied previously. Four of these were the same tests from the former analysis. In addition, a memory test, Delayed Word List Recall, provided adequate discrimination between groups. Similar to the whole group analysis, the SDs remained relatively high, and the 95% CI's relatively wide, indicating that individual effect sizes varied substantially from study to study.

Table 3: Mean Effect Sizes for Pre-Treatment Cognitive Differences Between Antidepressant Responders and Non-Responders - Studies using Standardised Administration of SSRIs.

Cognitive Assessment Tool	N Studies	N Subjects	d_w	SD	95% CI	% OL	N_{fs}	Study References
Executive Function								
WCST: % Perseverative Errors	2	26	0.71	0.66	-0.09 - 1.52	57	5	(Alexopoulos et al., 2007; Dunkin et al., 2000)
DRS IP Subtest (raw)	**2**	**134**	**0.59**	**0.42**	**0.24 - 1.95**	**62**	**4**	**(Kalayam & Alexopoulos, 1999, 2003)**
Stroop Interference	4	156	0.49	0.44	0.17 - 0.82	73	6	(Alexopoulos et al., 2005; Dunkin et al., 2000; Kalayam & Alexopoulos, 2003; Mayberg et al., 2000)
COWAT	4	85	0.42	1.23	-0.05 - 0.89	73	4	(Devanand et al., 2003; Dunkin et al., 2000; Mayberg et al., 2000; Taylor et al., 2006)
WCST: Perseverative Errors	2	51	0.16	0.71	-0.42 - 0.75	85	0	(Dunkin et al., 2000; B. P. Taylor et al., 2006)
WCST: Categories Completed	2	51	0.10	0.80	-0.48 - 0.69	92	0	(Dunkin et al., 2000; B. P. Taylor et al., 2006)
Speed / Reaction Time								
Trail Making Test A: Time	2	157	0.78	0.03	-0.09 - 1.65	53	6	(Dunkin et al., 2000; Mayberg et al., 2000)
Stroop Colour: Number Completed	**2**	**51**	**0.64**	**0.23**	**0.05 - 1.23**	**62**	**4**	**(Dunkin et al., 2000; Taylor et al., 2006)**
Stroop Word: Number Completed	**2**	**51**	**0.63**	**0.06**	**0.04 - 1.22**	**62**	**4**	**(Dunkin et al., 2000; Taylor et al., 2006)**
WAIS Digit Symbol (scaled)	2	51	0.45	0.38	-0.14 - 1.03	67	2	(Dunkin et al., 2000; Taylor et al., 2006)
WAIS Digit Symbol (raw)	2	412	-0.02	0.17	-0.23 - 0.20	100	0	(Devanand et al., 2003; Doraiswamy et al., 2003)
Construction								
WAIS Block Design (scaled)	**2**	**51**	**0.64**	**0.50**	**0.04 - 1.23**	**62**	**4**	**(Dunkin et al., 2000; Taylor et al., 2006)**
DRS Construction Subtest (raw)	2	134	0.12	0.16	-0.22 - 0.47	92	0	(Alexopoulos et al., 2005; Kalayam & Alexopoulos, 2003)
Attention / Working Memory								
Trails Making Test B: Time	2	22	0.75	0.82	-0.14 - 1.64	53	6	(Dunkin et al., 2000; Mayberg et al., 2000)
DRS Attention Subtest (raw)	2	134	0.28	0.16	-0.07 - 0.63	79	0	(Alexopoulos et al., 2005; Kalayam & Alexopoulos, 2003)
Digit Span Forward Plus Back	3	77	0.07	0.28	-0.40 - 0.54	92	0	(Devanand et al., 2003; Dunkin et al., 2000; Taylor et al., 2006)

Memory								
Word List Recall: Short Delay	**2**	**26**	**0.86**	**0.09**	**0.05 - 1.66**	**48**	**7**	**(Alexopoulos et al., 2007; Dunkin et al., 2000)**
Word List Learning: 5 Trials	2	26	0.43	0.41	-0.36 - 1.21	73	2	(Alexopoulos et al., 2007; Dunkin et al., 2000)
DRS Memory Subtest (raw)	2	134	0.05	0.54	-0.30 - 0.40	92	0	(Alexopoulos et al., 2005; Kalayam & Alexopoulos, 2003)
Global Function, Language, and Conceptualisation								
Boston Naming Test	2	40	0.52	1.08	-0.15 - 1.19	67	3	(Devanand et al., 2003; Dunkin et al., 2000)
WAIS Vocabulary (scaled)	3	76	0.39	0.23	-0.10 - 0.87	73	1	(Dunkin et al., 2000; Marcos et al., 2005; Taylor et al., 2006)
DRS Conceptualisation Subtest (raw)	2	134	0.12	0.16	-0.22 - 0.47	92	0	(Alexopoulos et al., 2005; Kalayam & Alexopoulos, 2003)
DRS Total Score (raw)	3	299	0.03	0.33	-0.21 - 0.27	100	0	(Alexopoulos et al., 2005; Alexopoulos et al., 2007; Saghafi et al., 2007)
Mini Mental Status Exam	3	424	-0.05	0.03	-0.26 - 0.15	92	0	(Alexopoulos et al., 2007; Devanand et al., 2003; Doraiswamy et al., 2003)

Note. d_w = weighted mean effect size; SD = standard deviation; %OL = percent of overlap between groups; 95% CI = confidence intervals; N_{fs} = Fail Safe N; COWAT = Controlled Oral Word Association Test; DRS = Dementia Rating Scale; IP = Initiation Perseveration; WAIS = Wechsler Adult Intelligence Scale; WCST = Wisconsin Card Sort Test; Raw = unadjusted test score; Scaled = score adjusted for age/education/sex.
Bold text = findings meet study criteria for adequate discrimination ($d_w \geq 0.5$; 95% CI do not span zero; $N_{fs} \geq$ N Studies).

6.6 Discussion

The DED model predicts that a person's level of executive functioning at the time they begin antidepressant medication will affect their likelihood of responding to this treatment (Alexopoulos, 2001). Furthermore, the model suggests that other types of cognitive function should be largely unrelated to treatment response. These two predictions are based on the premise that executive dysfunction is a marker for underlying pathology in frontal-subcortical brain circuits, and that this pathology is involved in the pathogenesis of the depressive illness (Alexopoulos et al., 2002). This study set out to review the published literature to assess the level of support for these hypotheses.

The available data provides only limited support for the first prediction. Of the nine executive function tests examined, only performance on the DRS-IP Subtest provided reasonable discrimination between patients who responded and those who failed to respond. The DRS-IP assesses verbal fluency and skills associated with switching between and terminating mental activities without perseveration (Jurica, Leitten, & Mattis, 2001). Other tests such as the Controlled Oral Word Association Test (COWAT), which also assesses verbal fluency, showed much weaker associations with antidepressant response.

The DED model can not easily accommodate the finding that some, but not all, tests of executive function were associated with treatment response. However, because of notable differences in methodologies and patient characteristics across the studies, these results must be interpreted with caution. Factors such as patient age, duration of treatment, severity of the illness, illness history (single versus multiple depressive episodes), and medication status at baseline assessment may have moderated the relationship between executive function and

treatment response. In other words, the model may only have predictive validity for certain patient subgroups or treatment formats. It was not possible to examine statistically the influence of all these variables due to the small number of available studies – a limitation of the current meta-analysis. This said, the DED model, in its current form, does not make specific predictions in relation to patient subgroups.

Amongst the potential moderating variables, the specific type of antidepressant agent used is particularly relevant to the predictions of the model. The model assumes that, in people with the DED syndrome, depression develops as a result of pathological changes to frontal-subcortical brain circuits. It has been argued that traditional antidepressants including SSRIs may be relatively ineffective in this context and that drugs targeting dopamine systems may be more effective (Alexopoulos, 2001). Several of the studies examined in this review incorporated Venlafaxine and Bupropion in their treatment regimens (Dunkin et al., 2000; Gallagher, Robinson, Gray, Porter, & Young, 2007; Kalayam & Alexopoulos, 1999; Mayberg et al., 1997; Potter et al., 2004; Story et al., 2008). These agents, which have effects on dopamine systems, could potentially be more effective in DED patients, thus reducing between-group differences in treatment response (Alexopoulos, 2001). Fortunately, there were sufficient studies within the review to allow a supplementary analysis restricted to those that administered SSRIs. The results for this subgroup of studies mirrored the overall analyses, with a range of mean effect sizes across the different executive function tests. Therefore, the main prediction of the model was not supported, even when the potentially important influence of drug category was examined.

The second prediction stemming from the DED model was that non-executive cognitive skills would fail to show strong associations with antidepressant response. The

findings of this meta-analysis largely failed to support this proposal. Responder and Non-responder groups differed in their performance on specific tests of visuo-spatial construction, memory, and processing speed. While the effect sizes were somewhat smaller than for the DRS-IP, the differences between the executive and non-executive tests were not striking. It is acknowledged that some tests of visuo-spatial construction and memory draw on executive skills, such as planning and strategy use. Thus, it is conceivable that the executive elements of the Block Design and Word List Recall tests accounted for their association with treatment response. However, this pattern was not consistent for all relevant memory and visuo-spatial construction tests. Rather than confirming the role of executive dysfunction as an exclusive marker of poor antidepressant response, the current findings suggest that multiple areas of cognitive performance are relevant to prognosis but that this is not consistent under all circumstances.

The variability in findings is difficult to interpret. Even the large and statistically significant effect sizes need to be interpreted with care due to the possible influence of confounding variables. An examination of the demographic features of the 1269 participants revealed that people who responded to medication were, on average, four years younger than people who failed to respond. Given that many aspects of cognitive function are known to decline with age, the observed associations between cognition and medication response may partially reflect an underlying relationship between age and medication response. Baseline depression severity may also have acted as a confounder. Consistent with other research (Howland et al., 2008; Lyness et al., 2002; Saghafi et al., 2007), participants who responded to medication had milder depression symptoms at baseline. Cognitive impairment is considered a symptom of depression (American Psychiatric Association, 1994). Thus, it may be the case that people with cognitive impairment experienced poorer response rates because they were

more severely depressed to begin with. Thus, the confounding effects of age and baseline depression severity could account for the observed relationships between cognition and medication response.

Another possible explanation for the 'spattering' of significant effect sizes is that they resulted from statistical chance. Table 2 summarises results from 75 separate analyses, and thus some positive findings would be expected by chance alone.

It is important to distinguish the DED concept, which is a description of a putative clinical syndrome, from the wider etiological theory that depression may arise from frontal-subcortical disruption. Studies employing direct measures of frontal-subcortical abnormalities have reported poor response to antidepressant medications in patients with structural (Alexopoulos et al., 2008; Hickie et al., 1995; Simpson, Baldwin, Jackson, & Burns, 1998; Taylor et al., 2003) and functional (Kalayam & Alexopoulos, 1999; Mayberg et al., 1997) abnormalities in prefrontal regions offering support for the validity of the wider theory. Available cognitive tests may be insensitive to this pathology.

The results of this review have clear implications for the clinical setting. The variability in the predictive value of cognitive tests from study to study indicates that cognitive performance does not offer a reliable basis for making clinical judgements about probable illness course. Even the DRS-IP, which provided the best discrimination of all the tests, only correctly classified 43% of patients. It is also notable that the three studies that used the DRS-IP were conducted by the same research group, and study characteristics like patient age, depression severity and treatment duration were similar across each study. It is not known if this test has predictive value under other circumstances. Unless and until relevant moderator

variables can be identified, the evidence indicates that cognitive testing does not provide a reliable basis for predicting depression course in the clinical setting.

In summary, the available evidence indicated that performance on one test of executive skills, and three tests of non-executive skills, was associated with medication response. Because of inconsistencies in individual study findings, and varying results for different tests within the same cognitive domain, the findings of the meta-analysis do not support the treatment-related predictions of the DED model.

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6.7 References for Study 4

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Chapter 7: Study 5

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7.1 Title Page

Title: Response to treatment for depression in cardiac patients with executive dysfunction

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Key Words: depression; antidepressants; cognition; neuropsychological tests; prefrontal cortex; executive function

7.2 Abstract

Objectives: A sub-set of depressed patients also experience impairments in executive functioning, a clinical presentation referred to as the Depression-Executive Dysfunction (DED) syndrome. This study examined the hypothesis that the proportion of people with the DED syndrome who respond to treatment for depression would be lower than the proportion of other depressed patients who respond.

Design: A prospective case-control study design was employed. Participants with the DED syndrome were identified at baseline using neuropsychological testing. Depression status (remitted/depressed) was assessed at 3 and 6 months post treatment in DED and non-DED groups.

Setting: Participants were recruited from nine general practices.

Participants: Participants were depressed patients with chronic ischaemic heart disease (n = 45).

Intervention: Depression was treated by each participants' usual General Practitioner on a case-by-case basis without restriction on treatment mode.

Measurements: Deficits in executive function were identified using the Initiation–Perseveration Index from the Dementia Rating Scale and a Stroop task. Remission status was assessed using the Centre for Epidemiological Studies Depression Scale (remission < 16).

Results: The proportion of participants with the DED syndrome that had achieved remission at three months (0%), was significantly lower than the proportion of non-DED participants who achieved remission (40%), (p = .04, Fischer's Exact Test; phi = .365). At six months, the difference in proportions (11% v 40%), was no longer significant (p = .12) although the effect size was moderate (phi = .308).

Conclusions: If these findings are confirmed in larger cohorts, alternative forms of antidepressant treatment should be explored for patients with the DED syndrome.

7.3 Introduction

A proportion of people suffering from depression are affected by structural or functional abnormalities in pre-frontal regions of the brain or in associated fronto-limbic and fronto-striatal neural pathways (reviewed in Drevets, Price, & Furey, 2008), raising the possibility that these abnormalities play a role in causing or perpetuating some cases of depression. Prefrontal cortical regions and associated fronto-striatal neural circuits are also implicated in a range of high-level cognitive skills, collectively referred to as executive functions (Tekin & Cummings, 2002). Abnormalities in these neural circuits may therefore manifest in the dual problems of depression and executive dysfunction; a clinical presentation that has been labelled the Depression – Executive Dysfunction (DED) Syndrome (Alexopoulos, 2001). Based on the assumption that depressed patients who exhibit executive dysfunction may be affected by an aetiologically distinct form of depression, Alexopolous (2001) predicted that this group is likely to respond poorly to traditional approaches to depression treatment.

Several prior studies have reported that depressed patients who fail to respond to antidepressant treatment display poorer pre-treatment executive function (Alexopoulos et al., 2005; Dunkin et al., 2000; Kampf-Sherf et al., 2004; Majer et al., 2004; Sneed et al., 2007). However, such findings have not always been replicated (Gallagher, Robinson, Gray, Porter, & Young, 2007; Potter, Kittinger, Wagner, Steffens, & Krishnan, 2004). In other studies, baseline performance on certain tests of executive function is lower in non-responders but differences are not seen for other executive tests (Kalayam & Alexopoulos, 2003; Majer et al., 2004; Taylor, Steffens, & Krishnan, 2006). Moreover, a recent meta-analysis that pooled the results of 17 studies found that, for eight out of nine tests of executive function, there was no significant difference in the cognitive performance of people who responded compared to

those who did not respond, thus largely failing to support the treatment-related predictions of the DED model (McLennan & Mathias, 2010).

A problem with the retrospective nature of these studies is that the chance of detecting a significant difference in executive function between treatment responders and non-responders is at least partly dependent on the proportion of the study sample that is affected by the DED syndrome. If a study only includes a small proportion of subjects with the DED syndrome, then even if all these patients fail to respond to treatment as the model predicts, the mean level of executive function in the non-responder group may not differ from the level of executive function in the responder group.

To address this problem, the present study used a prospective case-control design. We hypothesised that a significantly lower proportion of patients with the DED syndrome (i.e. patients with executive dysfunction) would respond to antidepressant treatments than patients with normal executive functioning. A cohort with cardiovascular disease was selected because this patient group has a particularly high risk of ischaemic brain pathology (Jeerakathil et al., 2004) and executive dysfunction (Sanders, Lyness, Eberly, King, & Caine, 2006).

7.4 Methods

The study was nested within the intervention arm of the Take Heart in Primary Care Study, a cluster randomised controlled trial conducted in General Practices in Adelaide, South Australia between 2007 and 2009 (Eckert et al., 2009). Ethics approval to conduct the research was obtained from the relevant participating Universities.

7.4.1 Participants

Participants were eligible for inclusion if they: (1) attended a participating general practice; (2) were depressed, as defined by a score of 16 or higher on the Centre for Epidemiological Studies - Depression (CES-D) scale (Radloff, 1977) (3) were aged between 18 and 85 years; (4) had spoken English since the age of five and could therefore be validly assessed using the neuropsychological testing procedures; (5) had a diagnosis of ischaemic heart disease confirmed by a stress echocardiogram or coronary angiogram, and; (6) had required ongoing management for chronic heart disease in the preceding six months.

Exclusion occurred if a participant had: (1) a psychotic illness or significant communication deficit that precluded effective communication with their general practitioner (GP); (2) been diagnosed with dementia or had a Mini Mental Status Examination (MMSE) Score < 24 at initial screening; (3) planned to have corrective surgery for an underlying cardiovascular disease (eg coronary artery bypass graft), or; (4) an acute cardiovascular-related hospital admission in the previous three months.

7.4.2 Instruments and outcome measures

Data were obtained via clinical assessment at baseline, and self-reported questionnaires completed at baseline, and at three and six months. Questionnaires were scored and data entered by a researcher blinded to the cognitive test results.

Depression

Depression status was assessed using the Centre for Epidemiological Studies - Depression (CES-D) scale (Radloff, 1977). Participants respond to 20 items on a 4-point self-report scale. Possible scores range from zero to 60, with higher scores indicating more severe depressive symptoms. The CES-D has been validated in elderly populations (Hertzog, Van Alstine, Usala, Hultsch, & Dixon, 1990) and those with cardiovascular diseases (Parikh, Eden, Price, & Robinson, 1988). It has acceptable test-retest reliability and high internal consistency (Eaton, Smith, & Muntaner, 2004). Remission at follow-up was defined as a CES-D score < 16.

Cognition

Executive functioning was measured using two neuropsychological tests that provided the best discrimination between treatment responders and non-responders in a previous meta-analysis (McLennan & Mathias, 2010). The Initiation–Perseveration Index from the Dementia Rating Scale, Second Edition (DRS-IP) (Jurica, Leitten, & Mattis, 2001) required participants to generate a series of verbal and graphomotor responses, such as verbally listing items found in a supermarket and copying a sequence of “palm up” “palm down” hand sequences. The DRS-IP is sensitive to problems related to initiating, terminating and switching between tasks, and to perseverations or intrusions from previous activities (Jurica et al., 2001). Raw scores

range from zero to 37, with higher scores indicating better executive function. Age-adjusted Scaled Scores (SS) were also calculated.

The Color-Word Interference Test from the Delis Kaplan Executive Function System (D-KEFS) (Delis, Kaplan, & Kramer, 2001) is a Stroop-format test. The first two trials of the test measure information processing speed. Participants had to name colour patches, and then read colour names. The time taken to complete both trials is reported as a raw score (D-KEFS Speed raw score) and an age-adjusted SS (D-KEFS Speed SS). In the final trial, which measures executive function, participants were presented with colour words printed in incongruent ink colours (eg "RED" printed in green ink), and had to switch between reading the word ("red"), and naming the ink colour ("green") under timed conditions. The task is sensitive to executive difficulties associated with maintaining attention, inhibiting well-learned responses, and switching between different task demands. A Contrast SS was calculated, which adjusts for information processing speed, thus providing a more pure indication of executive function. For each of the DRS-IP and D-KEFS indices, the mean SS in the normative samples is 10 (SD = 3) (Delis et al., 2001; Jurica et al., 2001). Impairment on each index was defined as a SS < 7.

Global cognitive functioning was assessed using the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005). The MoCA is a 30-item paper and pencil test designed to assess visuospatial abilities, memory, executive functioning, attention, concentration, working memory, language and orientation. Scores range from zero to 30, with higher scores indicating better performance. One extra point is allocated for participants with less than 12 years of education. The test is sensitive to vascular-related cognitive impairment (Mclennan, Mathias, Brennan, & Stewart, in press; Popovic, Seric, & Demarin, 2007). A cut-off score of 24 offered

the optimum discrimination for Mild Cognitive Impairment in a previous study that examined a group of patients with cardiovascular diseases recruited from the same city as the present study sample (Mclennan et al., in press). Thus, scores below 24 were considered impaired.

Functional Capacity and Quality of Life

The SF-12 Health Survey, version 2 (SF-12v2) was used to measure health-related functional capacity and wellbeing (Ware, Kosinski, Turner-Bowker, & Gandek, 2002). This self-report questionnaire provides a Physical Component Summary and a Mental Component Summary. Scores range from zero to 100, and higher scores indicate better quality of life. In the normative population, scores have a mean of 50 (SD = 10) (Ware et al., 2002). The reliability and validity of the instrument are well established (Ware et al., 2002), and the tool has been validated in the Australian population (Wilson, Tucker, & Chittleborough, 2002).

Task-specific functional capacity was assessed using the self-rated version of the Instrumental Activities of Daily Living (IADL) Scale from the Multilevel Assessment Instrument (Lawton, Moss, Fulcomer, & Kleban, 1982). Participants were required to rate, on a three-point scale, how much help they would require to perform each of nine tasks (e.g. using the telephone; shopping; food preparation). Scores range from zero (no help required) to 18 (complete dependence in all activities).

Treatment for Depression

Treatment for depression was delivered by each patient's usual GP. In the month prior to the initiation of treatment, each GP participated in an individually-delivered academic detailing session, where they were provided with information about best-practice treatment for depression. Treatment plans were then developed on a case-by-case basis by GPs, without

restriction on treatment mode or intensity. GPs were supported in this process by a study psychiatrist (GS) via telephone. Both the GP and psychiatrist were blinded to the participants' cognitive test results.

7.4.3 Statistical analysis

In order to examine the potential for sample bias two-tailed independent samples *t*-tests (Mann Whittney U tests for categorical variables) were used to examine differences in the demographic characteristics of participants who had missing cognitive data or were lost to follow up. A *p* value of <0.05 indicated statistical significance. As the sample was small, analyses of effect sizes (using Cohen's *d*) were also conducted to further determine the magnitude of differences between groups. A Cohen's *d* of .20 indicates a small effect; .50 a medium effect; and .80 a large effect (Cohen, 1988).

To test the study hypothesis, first, participants were categorised as having impaired executive function if they scored below the pre-defined cut-off point on at least one of the two tests of executive function. The proportion of participants who had achieved remission at three months (CES-D < 16) was then calculated for each group (impaired executive function/normal executive function), and compared using 2-tailed Fischer's Exact Tests. Effect sizes (Phi) are also reported. A Phi of .10 indicates a small effect, .30 a medium effect, and .50 a large effect (Cohen, 1988). Previous research suggests that depressed patients with executive deficits may take longer to respond to treatment (Alexopoulos, Kiosses, Murphy, & Heo, 2004; Murphy & Alexopoulos, 2006). Therefore, all analyses were repeated using CES-D scores collected at six months.

7.5 Results

7.5.1 Missing data

In total, 45 people met study inclusion criteria. Cognitive data was unavailable for three participants, and was incomplete for an additional five, mainly due to scheduling difficulties. These participants were marginally younger (m = 68.1, SD = 14.7), less educated (m = 11.2, SD = 2.4), and less depressed (m = 22.6, SD = 5.3) than the remainder of the group. However, none of these differences were statistically significant, and effect sizes were small (Cohen's *d* = .22, -.22, .18 respectively), indicating that sampling bias due to missing cognitive data was unlikely.

Three people withdrew from the study prior to the follow-up assessment. They were slightly older (m = 75.0, SD = 13.9), less educated (m = 9.3, SD = 2.5), and more severely depressed (m = 25.3, SD = 5.1) than the remainder of the group. All contrasts were non-significant but effect sizes were moderate to large (Cohen's *d* = -.34, .90, -.39 respectively), so the sample available for analysis may over-represent higher-functioning depressed patients.

7.5.2 Study sample characteristics

This left 39 participants available for analysis. Their ages ranged from 47 to 84 years. Depression was mild (CES-D 16 to 26) in 28 cases (72%), and moderate to severe (CES-D 27 – 60) in 11 cases (28%). Other demographic information is presented in Table 1.

Six participants (16.6%) scored in the impaired range on the DRS-IP SS, and four (11.7%) on the D-KEFS Contrast SS. In total, nine participants (23%) scored in the impaired range on at least one executive function test. As shown in Table 1, these participants were

similar to the remaining participants with respect to their age, depression severity, global cognitive function, functional capacity and quality of life, but, on average, had a lower level of education.

Table 1. Demographic features of participants with impaired v normal executive function

	Whole Group (n = 39)	Impaired Executive Function (n = 9)	Normal Executive Function (n = 30)		
	Mean (SD)	Mean (SD)	Mean (SD)	*p*	Cohen's *d*
Age (years)	71.5 (9.8)	70.1 (10.3)	71.9 (9.8)	.647	0.18
Education (years)	11.7 (3.5)	9.9 (1.5)	12.3 (3.7)	**.007**	1.11
Baseline CES-D score	23.4 (6.2)	21.1 (6.7)	23.2 (6.1)	.695	-0.14
Montreal Cognitive Assessment	24.1 (2.8)	23.6 (2.9)	24.2 (2.8)	.695	-0.10
IADL (Median, Range)	2 (0-9)	1 (0 – 7)	2 (0 – 9)	.466	-.25
SF12v2 – Physical Component	33.9 (10.7)	36.8 (12.1)	32.4 (10.1)	.313	-.41
SF12v2 – Mental Component	44.2 (10.4)	46.8 (7.0)	43.3 (11.0)	.470	-.34

Note. CES-D = Centre for Epidemiological Studies Depression; IADL = instrumental activities of daily living; SF12v2 = SF12 version 2.

Twelve participants (30.7%) were in remission from depression at three months, and 15 (38.5%) were in remission at six months. There were no significant differences in demographic characteristics, functional capacity or quality of life between participants who achieved remission and those who remained depressed (Table 2). There were no significant differences between the remitted and non-remitted groups on any of the cognitive measures.

Table 2. Baseline features of participants who were Remitted and Depressed at 3 months

	Remitted (n=12) Mean (SD)	Depressed (n=27) Mean (SD)	Remitted vs Depressed *p*	Cohen's *d*
Demographic Features				
Age (years)	73.5 (9.0)	70.6 (10.2)	.407	.29
Education (years)	12.1 (3.4)	11.6 (3.6)	.694	.14
Baseline CES-D score	21.5 (4.1)	24.2 (6.8)	.211	-.44
Functional Capacity / Quality of Life				
IADL (Median, Range)	2 (0-7)	2 (0-9)	.975	-.08
SF12v2 - Physical Component	32.0 (8.3)	34.8 (11.8)	.504	-.26
SF12v2 - Mental Component	46.2 (11.0)	43.4 (10.3)	.485	.27
Executive Function				
DRS-IP Raw Score	35.7 (1.5)	34.3 (3.7)	.103	.43
DRS-IP SS	10.1 (1.6)	9.0 (3.1)	.063	.41
D-KEFS Contrast SS	10.4 (1.4)	9.5 (4.0)	.490	.27
Mental Processing Speed				
D-KEFS Speed Raw Score	58.7 (10.2)	57.6 (11.3)	.798	.10
D-KEFS Speed SS	10.3 (2.2)	10.5 (2.5)	.876	-.06
Global Cognition				
Montreal Cognitive Assessment	24.7 (3.1)	23.8 (2.6)	.339	.34

Note. CES-D = Centre for Epidemiological Studies Depression; DRS-IP = Dementia Rating Scale Initiation Perseveration Index; D-KEFS = Dellis Kaplin Executive Function System; IADL = instrumental activities of daily living; SF12v2 = SF12 version 2; SS = Scaled Score.

7.5.3 Treatment outcomes of participants with impaired executive function versus normal executive function

As hypothesised, the remission rate (0%) in people with impaired executive function was significantly lower than in people with normal executive function (40%; X^2 =3.49, p = .04, Fischer's Exact Test) (see Figure 1). This difference was moderate in magnitude (Phi = .365). A similar pattern was evident for both tests of executive function when considered individually, although the differences did not reach statistical significance. Classifications based on non-executive cognitive tests did not produce differences in remission rates.

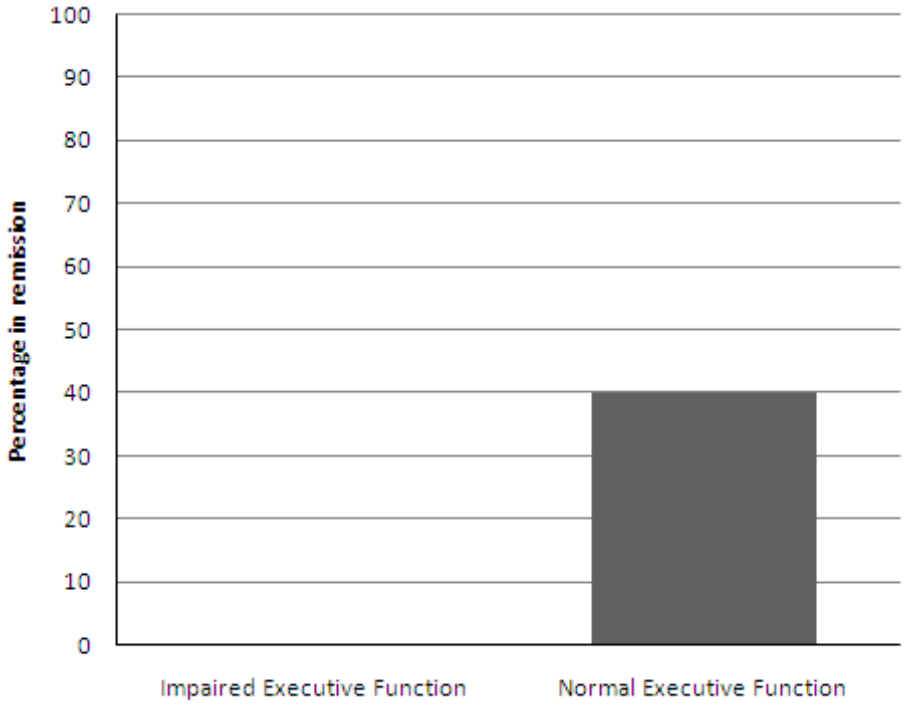

Figure 1. Proportion of Participants who Achieved Remission at Three Months

At six months, one further participant with executive dysfunction and three additional participants with normal executive function had also achieved remission (Figure 2). When the remission rates for the impaired and non-impaired groups were compared (11% v 47%), the

magnitude of the difference remained moderate (Phi = .308), but the difference was no longer statistically significant ($X^2 = 2.35$, p = 0.12, Fischer's Exact Test).

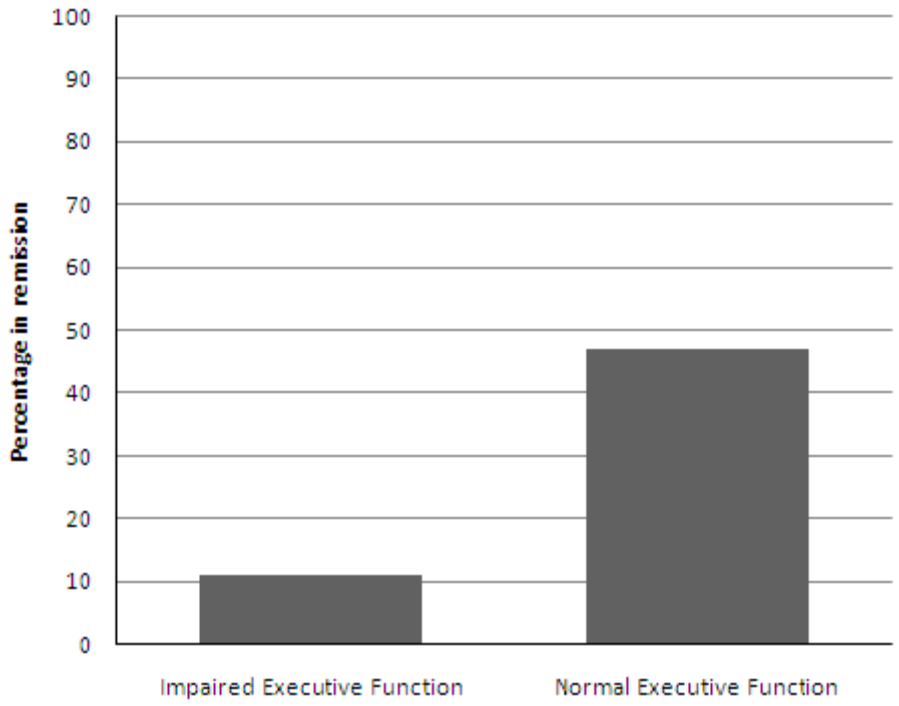

Figure 2. Proportion of Participants who Achieved Remission at Six Months

7.6 Discussion

Rates of remission from depression in cardiac patients who had impaired executive function (0% at 3 months; 11% at 6 months) were lower than the remission rates in patients who had intact executive functioning (40% at 3 months; 47% at 6 months). Moreover, this difference in treatment response rates could not be explained by age, depression severity, functional status or quality of life.

The association between cognition and treatment response appeared to be specific to executive dysfunction because the proportion of participants with global cognitive impairment that failed to respond to treatment was similar to the proportion of those with intact global cognitive function. These findings are consistent with the DED model, which is based on the premise that people exhibiting executive dysfunction are affected by a distinct form of depression, which is triggered and/or maintained by pathology in pre-frontal-striatal neural circuits, and is less responsive to mainstream treatments for depression (Alexopoulos, 2001).

Consistent with our findings, a similar study reported that 11 of the 12 weakest performers on the DRS-IP also failed to achieve remission (Kalayam & Alexopoulos, 1999). We are not aware of any previous studies that have examined the D-KEFS Color Word Interference Test, but one study that used another Stroop-format task showed that participants who scored in the bottom quartile of the study sample experienced weaker treatment responses than other participants, with a large between-groups effect size (Cohen's d = .86) (Sneed et al., 2007). The findings of this small group of studies are consistent with research employing brain imaging techniques, which has shown that poor response to antidepressant treatment is associated with structural (Alexopoulos, Kiosses, Choi, Murphy, & Lim, 2002; Alexopoulos et

al., 2008; Hickie et al., 1995; Simpson, Baldwin, Jackson, & Burns, 1998; Steffens et al., 2001; Taylor et al., 2003) and functional (Mayberg et al., 1997; Navarro et al., 2004; Pizzagalli et al., 2001) abnormalities in pre-frontal and subcortical brain regions. In contrast, studies that have examined the outcomes of people with cognitive deficits in non-executive domains (ie domains not relevant to the DED hypothesis) have not shown clear differences in treatment outcomes (Steffens et al., 2006; Stoudemire et al., 1991). Taken together, these findings are consistent with the proposition that the function of the frontal lobes and their associated circuits are specifically relevant to treatment response.

Our results, if replicated, suggest that different treatment approaches may be needed for patients with the DED syndrome. If dysfunction in prefrontal-striatal circuits is involved in the aetiology and/or maintenance of depression in these patients, then treatments that specifically augment the functioning of these circuits may be more effective than alternative treatments. Thus, psychotherapies that focus on facilitating problem solving skills may be superior (Alexopoulos, Raue, & Arean, 2003) because people with executive dysfunction often have difficulty responding to novel problems (Ylikoski & Hanninen, 2003). Similarly, drugs that act on neurotransmitters such as dophamine, which are specifically involved in regulating prefrontal-striatal circuits, may be more effective than agents that target other neurotransmitter systems (Alexopoulos, 2001).

Given the small sample size, the results of this study require replication. A larger study sample would also allow multivariate analysis to control for the influence of variables such as age, education and depression severity and quality of life. It is important that future research into the treatment-related predictions of the DED model employs prospective case-control study designs. When this approach was used in the present study, a striking difference in the

response rates of DED and non-DED participants was revealed. This pattern would have been obscured (see Table 1) had the data been analysed retrospectively and the cognitive performance of all treatment responders been compared to that of all non-responders, as has occurred in previous studies (Alexopoulos et al., 2005; Dunkin et al., 2000; Gallagher et al., 2007; Kalayam & Alexopoulos, 2003; Kampf-Sherf et al., 2004; Majer et al., 2004; Potter et al., 2004; Sneed et al., 2007; Taylor et al., 2006).

It is notable that a relatively small proportion of participants achieved remission from depression in the overall study sample (30.7%). One possible explanation for the low overall rate of treatment response is that participants could have been undertreated. The study protocol was designed to optimise treatment; the treating GPs received individual training in best-practice treatment, as well as ongoing support in their treatment decision making from the study psychiatrist, strategies that have produced improved treatment outcomes in prior research (O'Brien et al., 2007; Schrader, Cheok, Hordachre, Marker, & Wade, 2005). However, information about the treatment format and about adherence rates was not available for analysis. This leaves open the possibility that GPs did not prescribe optimal treatments to all participants or that a number of participants did not follow recommendations from their doctors, leading to poor response rates. It is also possible that GPs made different treatment decisions for DED participants, perhaps because of differences in their presentation during clinical consultation. Similarly, DED participants may have had more difficulty following prescribed treatment regimens due to their cognitive problems, thus reducing their effectiveness. Future research that incorporates standardised treatment protocols and/or measures adherence rates has the potential to determine the relative importance of these factors. Further research will also be needed to determine whether the same patterns of response are seen in non-cardiac patient groups.

Notwithstanding the above limitations, a strength of the present study is its ecological validity. The DED hypothesis will only have clinical relevance if it can predict treatment outcomes in real-life settings. Participants in this study were treated by their usual GP at their usual clinic, and their treatments were individually tailored to account for their co-morbid illnesses, and their beliefs and preferences relating to treatment. For these reasons, the current findings, if replicated, are likely to have direct relevance to clinical practice.

In summary, participants in this study who exhibited the features of the DED syndrome experienced poor responses to treatments for depression. These findings were obtained from a small and specific patient group, and therefore require replication. However, they are consistent with the DED model, which posits that the aetiology or factors maintaining depressive illness in this group may be linked to abnormalities in fronto-striatal circuits (Alexopoulos, 2001). The findings suggest that alternative treatment approaches may be needed for these patients and that, in the future, cognitive testing may prove useful in treatment planning.

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Chapter 8: Summary and Conclusions

The overlapping fields of vascular-related cognitive impairment and vascular depression are at different stages of development. The studies described in this thesis were designed to examine five key questions to address some of the gaps in the literature. In the case of vascular-related cognitive impairment, where the field is more advanced, these gaps related to screening for vascular cognitive impairment, identifying the biological mechanisms involved in its development, and determining its impact on people's day-to-day function. In the case of vascular depression, where the field is at an earlier stage of development, the important unanswered questions related to establishing the validity of the DED model.

In this chapter the findings from each of the five studies are considered consecutively. For each study, the aims and major results are summarised, and then the methodological strengths and limitations are discussed. Following this, implications of the findings and recommendations for future research are examined. The methodological issues and implications that were discussed in the individual papers are only briefly restated in this chapter to avoid excess repetition. Because each of the original papers was written for different journal audiences, the issues discussed in the papers were restricted to those of direct relevance to each journal's scientific field (e.g. cardiovascular nursing for Study 3, and neuropsychology for Study 1) and professional focus (e.g. clinical practice for Study 3, and theory development for Study 4). Issues pertinent to a wider range of disciplines are discussed here, and broader implications are examined.

8.1 Study 1: Validity of the Montreal Cognitive Assessment (MoCA) as a screening test for Mild Cognitive Impairment (MCI) in a cardiovascular population

8.1.1 Restatement of the aims and main findings

Study 1 was designed to determine the sensitivity and specificity of the Montreal Cognitive Assessment (MoCA) to detect MCI in a population at risk of vascular-related MCI. Results showed that in a sample of people with mixed forms of CVD and CVRFs, a cut off point of 23/24 provided optimal sensitivity/specificity in this cohort (rather than the original recommended cut-off of 25/26). The MoCA had good sensitivity for detecting MCI but relatively poor specificity. Applying the new cut-off, sensitivity and specificity were 100% and 50% for amnestic MCI, and 83.3% and 52% for multi-domain MCI. The study also produced some notable secondary findings. Namely, in univariate analyses, there was a moderate correlation between the MoCA and the NAB scores, and between the MoCA and cardiovascular burden (the number of concurrently diagnosed CVD states in one individual).

8.1.2 Methodological strengths and limitations

Major strengths of the study design were that it extended previous research by testing a sample that was at specific risk of vascular-related cognitive impairment, and examined multiple-domain MCI in addition to amnestic MCI. Moreover, the protocols for defining MCI and the specific analyses were modelled on previous studies, allowing a direct comparison of results. A further strength was the comprehensive clinical assessment of CVD and CVRFs. The descriptive data relating to CVD pathology will allow clinicians to judge the relevance of the study results to their particular settings and will enable the results of future studies conducted in cardiovascular settings to be compared with the current findings.

Importantly, this study also incorporated the Neuropsychological Asessment Battery, Screening Module (NAB-SM) to establish the gold-standard diagnosis of MCI. Each of the tests in the NAB-SM was recently normed on a large representative population (Stern & White, 2003). Furthermore, each subtest was normed on the *same* population, ensuring that performance across subtests was directly comparable. This meant that a person diagnosed with *amnestic* MCI could be compared, in terms of the severity of their cognitive deficit, to a person with *multiple-domain* MCI. This point has rarely been addressed in previous studies because, until now, a comprehensive battery sensitive to both normal and significantly impaired cognitive function across multiple domains has not been available (Hartman, 2006).

A weakness of the study was that it relied on a review of medical records to identify and exclude people with dementia. The medical records may not have been complete and, as a result, some people with undiagnosed dementia may have inadvertently been included in the study sample. If people with early dementia were included, this may have amplified the specificity ratings; a person with severe cognitive impairments will be more likely to 'fail' the screening test than a person with subtle cognitive impairments. On the other hand, a reliance on medical records improves the ecological validity of the study and ensures that the results are directly applicable to a hospital setting. That is, the types of people who are likely to be screened in a real-life cardiovascular clinic are unlikely to have been thoroughly examined to exclude dementia before they are administered the MoCA either.

The most significant weakness of the study was its small sample size. Given that the prevalence of MCI was relatively low (10.9% for multiple-domain MCI, and 2.7% for amnestic MCI), minor differences in the performance of individual participants had the potential to substantially alter the results. A larger sample size would have strengthened the

reliability of the results. Replication of this study using a larger sample is therefore recommended.

8.1.3 Implications and recommendations for future research

Applicability of the MoCA in populations with low base rates

The finding that the MoCA has high sensitivity and low specificity means that it will be of limited use in a non-selected population of cardiovascular patients where the base rate of MCI is likely to be relatively low. Although the low prevalence of MCI in the current study (13.6%) falls within the range of rates reported in other studies (Busse, et al., 2003; Mariani, et al., 2007), low base rates diminish the predictive accuracy of screening tests (McCaffrey, Palav, & O'Bryant, 2003). In previous studies that assessed the validity of the MoCA, base rates ranged from 24.3% to 65.7%, because participants were predominantly drawn from memory clinics where people were self-selected for suspected cognitive impairment (Luis, et al., 2009; Nasreddine, et al., 2005; Smith, et al., 2007). Under these circumstances, the positive predictive value and negative predictive values are higher, and thus the test is more valuable in these settings. In the current study, using the optimum cut-off point (23/24), the positive predictive value for multiple-domain MCI was .18. So, a subject from the cohort who scored below the MoCA cut-off (performed poorly) only had an 18% chance of having MCI. On the other hand, the negative predictive value was high (.96). A person who scored above the cut-off on the MoCA (performed well) had a 96% chance of *not* having MCI.

Given that the base rate in unselected patients with CVD is also likely to be low, the specificity ratings are too low to provide acceptable diagnostic accuracy. Thus, the most important implication of these results is that, although the test was shown to have better

diagnostic accuracy for MCI than alternative tools like the MMSE (Lonie, et al., 2009), it will be of limited clinical value when used in a non-specific population of patients with CVD. It will be more useful in high-risk subgroups where the base rate is higher, such as those who report concerns about their own cognitive function or have multiple risk factors, such as old age and multiple cardiovascular diagnoses, and/or functional difficulties. Even if the MoCA is used in high-risk populations, the low specificity dictates that secondary assessment will still be required to achieve a reliable diagnosis for those people who perform below the cut-off.

As a caveat to these comments, it is important to bear in mind that this is the only study that has examined the diagnostic accuracy of the MoCA in a cohort of patients with CVD, and thus the study should be replicated in a larger sample to confirm the results. However, this is the third study to report a lower optimal cut-off point for detecting MCI (Luis, et al., 2009; Smith, et al., 2007) than was originally recommended (Nasreddine, et al., 2005). Thus, another implication of the study findings is that there is now sufficient evidence to confidently recommend a lower cut-off score for the test.

Use of the MoCA as a continuous measure

Although the primary results indicate that the MoCA will only be useful as a screening test under certain conditions, the secondary findings (significant correlations between MoCA scores and NAB-SM scores, and between MoCA scores and burden of CVD), provide preliminary support for the validity of the MoCA as a continuous measure of global cognitive function. The fact that MoCA performance also predicted functional capacity (see results from Study 3) supports its external validity as well. For example, the MoCA may be useful in research and clinical settings where it is necessary to track cognitive performance in a single

person over time, or in studies where group differences in global functioning are of interest. However, the test-retest reliability, and practice effects of this measure need to be established in future research before its use as a continuous measure can be recommended with confidence.

Adequacy of the education adjustment in cohorts with low education

Another interesting secondary finding of this study was that MoCA scores correlated significantly with both age and education, even after making the recommended adjustment for education (Nasreddine, et al., 2005). A number of other publications have also reported strong positive correlations between MoCA scores and education (Johns, et al., 2008; Luis, et al., 2009; Nasreddine, et al., 2005). This could potentially lead to an overestimation of cognitive impairment in people with low education. In other words, poor performance may partially reflect low education rather than cognitive impairment. To address this problem, the authors of the MoCA recommend adjusting scores by allocating one extra point for people who have less than 13 years education (Nasreddine, et al., 2005). This adjustment was effective in reducing the relationship between education and MoCA scores in the cohort that was used originally to develop the test (Nasreddine, et al., 2005). However, the participants in that study had more years of education (m= 12.3, SD = 3.4 and 13.3, SD = 4.3 in control subjects and MCI subjects, respectively) (Luis, et al., 2009) than participants in the present study (m = 10.5, SD = 3.2). The present findings therefore suggest that the scoring adjustment may not be sufficient to remove the influence of education in cohorts with low levels of education.

Another notable difference between the current and previous studies was that participants in the present study were younger (mean age = 67.9, SD = 11.7) than the previous

three studies (mean ages ranged from 72.8 to 78.9) (Luis, et al., 2009; Nasreddine, et al., 2005; Smith, et al., 2007). In addition, the present sample included a larger range of ages (SD = 11.7), compared to previous studies (SD = 3.7 to 10.0). This is relevant because, in accordance with accepted clinical practice (Lezak, et al., 2004; Petersen, 2004), the presence of MCI was determined with reference to Standard Scores on the NAB-SM subtests (ie scores adjusted for sex, age and education). A larger age range is likely to have attenuated the correlation between the age-adjusted NAB-SM scores and the non-age-adjusted MoCA scores. As an illustration of how adjusted and non-adjusted test results are less congruent at extreme ages, consider a hypothetical participant aged 80. They may fail many items on both the MoCA and on the NAB-SM tests. However, once their NAB-SM score is adjusted for age, the resulting scaled score is likely to fall within the normal range, while the MoCA score will remain in the impaired range, producing a mismatch, reducing whole-group correlations, and ultimately resulting in poor specificity ratings.

Practices for defining abnormal cognitive performance

The issue of adjusting scores for age raises the more fundamental question of whether cognitive test scores *should* be age-adjusted in elderly populations. Many aspects of cognitive function decline with age (Hedden & Gabrieli, 2004). In the discipline of neuropsychology, normality and dysfunction are defined with reference to population-based averages for different age groups. To establish normality/abnormality status, test performance in a large representative population is sampled, and for each age group (usually 10-year blocks) the average score and the range of scores are identified. In this way, a different definition of normal (i.e. average) is assigned to each age group. Abnormality is defined in terms of a statistical difference from the average score for the relevant age group. In clinical settings,

abnormal performance is usually defined as performance that is at 1.5 or 2 standard deviations below the mean for the relevant age group (Lezak, et al., 2004; Petersen, 2004).

There is an inherent assumption in this neuropsychological approach to defining normality/abnormality that some cognitive decline is normal in old age and reflects non-pathological processes. However, if a cognitive disorder were highly prevalent in older age groups in the general population, then impaired cognition would be viewed as 'normal' from a purely statistical standpoint and the practice of applying age adjustments would have the effect masking the problem. Vascular-related neuro-degeneration could potentially be one such high-prevalence disorder. A recent review of research that examined non-pathological ('normal') cognitive aging identified seven factors that contribute to normal aging (Deary, et al., 2009). Of these, four could be considered CVRFs (poor diet and nutrition; smoking; alcohol use; and sub-optimal activity participation and physical fitness). Two others (self-reported health status and physiological markers of health status) are clearly related to CVD and CVRFs, and the final one (education and social class) is also associated with cardiovascular health (Arendt & Lauridsen, 2008; Deary, et al., 2009; Kilander, Berglund, Boberg, Vessby, & Lithell, 2001; Mayer, Simon, Heidrich, Cokkinos, & De Bacquer, 2004; Yan, et al., 2006). Thus, it is possible that much of what we currently consider to be normal age-related cognitive decline is in fact pathological cardiovascular-related cognitive decline. In this context, using age-adjusted scores to define abnormality is less defensible.[2]

[2] It would have been interesting to examine whether the MoCA showed a stronger correlation with raw NAB-SM scores than with age and education adjusted NAB-SM scores. However such analysis was not possible due to the complexities involved in calculating NAB-SM scores. First NAB-SM subscales are adjusted for age and education, and then these adjusted scores are summed to derive the NAB-SM indexes. In other words, raw (unadjusted) NAB-SM index scores are not available.

Mungas, Reed et al (2009) evaluated how the adjustment of test scores affected the relationship between cognitive performance and structural MRI measures in an elderly cohort whose cognitive scores ranged from normal through to the demented range. They found that brain pathology was more strongly correlated with raw scores than with age-adjusted scores. This was the case for four separate cognitive domains (semantic memory, episodic memory, executive function and spatial skills), and for three different forms of brain pathology (brain volume, hippocampal volume and WMHs) (Mungas, Reed, Farias, & DeCarli, 2009). The explanation they offered for these findings was that age is associated with pathology, so applying age-adjustments statistically removes the effects of pathology on cognitive test scores. They concluded that age-adjustment is not appropriate in elderly populations when the objective is to identify potential brain pathology (Mungas, et al., 2009).

This discussion highlights the complexities and fundamental problems embedded in any attempt to test the sensitivity and specificity of a non-normed screening tool (the MoCA in this case) for identifying the clinical entity MCI, which is defined using age-adjusted scores. By definition, the correlation between these two sets of scores is guaranteed to be less than perfect, and by extension, sensitivity/specificity ratings are also destined to be inexact, particularly in a population with a wide spread of ages.

The use of age-adjusted neuropsychological assessment tools is currently accepted clinical practice and, thus, from a pragmatic stand-point the pursuit of establishing the validity of the MoCA as a screening tool should remain a priority for future research. However, consideration should also be given to using age-adjusted screening tools, or to developing an age-adjustment for the MoCA as long as this clinical practice is retained. Research priority should also be assigned to resolving the more fundamental issue of clarifying what ‘normal

aging' is, and re-evaluating the reliance on age-adjusted scores for defining and measuring cognitive impairment in elderly populations, now that the high prevalence and clinical impact of cardiovascular pathology on cognition has been clearly established.

8.2 Study 2: Vasodilation response and cognition in a cohort without advanced cardiovascular disease

8.2.1 Restatement of the aims and main findings

Study 2 examined whether poor vasodilation capacity is associated with ischaemic brain damage and/or cognitive impairment in a sample of people who were free of brain pathology other than small vessel pathology. The study was designed to determine whether this relationship, if it existed, could be explained by the presence of WMHs. Results failed to show a relationship between vessel dilation and cognition, which rendered the second aim redundant. The prevalence of significant WMHs was very low (6.4%) in the study sample.

8.2.2 Methodological strengths and limitations

Methodological strengths

A major strength of the study design was that it measured the four central variables of cardiovascular burden (CVRFs/CVD), vessel dilation, brain pathology *and* cognition in the same sample, which had not been attempted before. As such, the study had the potential to directly examine whether small vessel cerebral pathology played a mediating role in the relationship between vessel dilation and cognition.

The strongest aspect of the methodology was the approach to assessment. The tests selected to assess cognition were more appropriate than in similar studies. The primary

cognitive assessment tool, the NAB-SM (Stern & White, 2003), is sensitive to cognitive function in the normal range, right through to the demented range. The Color-Word Interference Test from the Delis Kaplan Executive Function System (Delis, Kaplan, & Kramer, 2001) was administered as well to ensure that a full range of executive functions were assessed. In comparison, the Repeatable Battery for the Assessment of Neuropsychological Status (R-BANS) battery, which was used in some previous studies (Moser, et al., 2004; Moser, et al., 2007), is insensitive to executive dysfunction (Randolph, 1998). In addition, the National Adult Reading Test (NART; Nelson & Willison, 1991) was administered to provide an estimate of pre-morbid intellectual function, which some previous studies failed to do (Forman, et al., 2008; Kearney-Schwartz, et al., 2009; Moser, et al., 2007). The technique used to measure vasodilation was also a particular strength. More specifically, the high test-retest correlations produced in the reliability sub-study confirmed that this relatively new measurement technique was reliable over time.

Methodological limitations

These methodological strengths are overshadowed by the some notable weaknesses, which predominantly resulted from restrictions imposed by the parent study. As discussed in the paper, even though the assessment of vasodilation was shown to be reliable, it is not known how well applanation tonometry readings correlate with the measurement techniques used in previous studies. A gold standard approach to the measurement of vessel dilation has not been identified (Deanfield, et al., 2007) and therefore the validity of the current measurement technique has yet to be unequivocally established. The measurement technique used in this study was based on the procedures described by Hayward, Kraidly, Webb and Collins (2002). In a previous study, this approach was able to distinguish between people with

coronary artery disease and people without CVD or CVRFs (Hayward, et al., 2002), which supports its validity. However, its sensitivity to more subtle differences in dilation capacity is not known. It is possible that applanation tonometry is less sensitive than the more invasive techniques used in prior studies that reported positive associations between vasodilation and cognition (Forman et al., 2008; Moser et al., 2004; Moser et al., 2008; Moser et al., 2007). Consequently, the failure to find significant associations may, at least in part, have been a product of poor measurement sensitivity.

The demographic and clinical features of the study population also represented a significant problem. The final participants available for assessment were relatively young and healthy. Previous studies in this field have examined older people with established CVD (Forman et al., 2008; Moser et al., 2004; Moser et al., 2008; Moser et al., 2007) because diminished vasodilation and cognitive impairment are both more prevalent in elderly populations with CVD (Hashimoto, et al., 2000). It was anticipated that a significant proportion of the current sample would be elderly and/or would be affected by CVD. However, it was ultimately not possible to recruit a suitable population within the protocol of the parent study and the time available.

The larger parent study was designed to examine genetic determinants of vasodilation response. To optimise the protocol for that purpose the investigators minimised the influence of age and lifestyle factors by excluding people in older age groups (> 75 years). In addition, because the study used applanation tonometry to measure vasodilation, it was necessary to exclude people who were taking vaso-active medications because these drugs have the potential to affect vasodilation response measures. As a consequence, most people with significant hypertension were excluded. Given that hypertension is a common precursor and

concomitant condition for CVD, this effectively resulted in the exclusion of people with more severe forms of cardiovascular illness.

To circumvent the problem of antihypertensive medication effects, other studies have included people who are using these medications but requested that they stop taking them leading up to the assessment (Forman, et al., 2008; Moser, et al., 2008; Moser, et al., 2007). This option was rejected in the current study because of the risk to the participants and a lack of access to physicians who could monitor them and manage potential adverse outcomes. Given that the parent study aimed to recruit several hundred participants, it was anticipated that a sufficient number of older people (aged 55 to 75) who had been untreated for hypertension would be recruited to allow a replication of prior studies. Unfortunately, this was not the case. The parent study did not meet recruitment targets, and therefore, the participants available for the present study were relatively young and healthy in comparison to other studies.

This left the option of replicating the existing studies in a younger cohort with lower levels of cardiovascular pathology. This provided the opportunity to examine a new hypothesis, namely that vasodilation response and cognitive function are associated even in the absence of old age and major cardiovascular pathology. Although the existing literature suggested that vasodilation would be unlikely to play a role in small vessel pathology in young healthy populations, significant findings would have had major implications for theoretical models addressing the role of vasodilation. More specifically, if it could have been shown that cognition was affected even prior to the onset of clinically detectable CVD, this would have demonstrated a pivotal early role for vasodilation, and would have provided a clear target for

early interventions that might prevent or slow small vessel related cognitive impairment and dementia.

8.2.3 Implications and recommendations for future research

Ultimately, a relationship between vasodilation and cognition was not observed in this cohort. The null findings fit with current understandings of the aetiology of CVD. The results suggest that in younger healthier people, whose cerebral vessels have not undergone morphological changes associated with age and CVD (i.e. tortuosity, stiffening and narrowing) poor vessel dilation has minimal negative effects on brain structure and cognitive function. However, this interpretation should be considered speculative for a number of reasons. First, the sample was small and therefore the study may have been statistically underpowered. In addition, the vasodilation measure has not undergone extensive validation, and may therefore be insensitive. Furthermore, the study sample contained a low percentage of people with diagnosed CVD (12%), which may have restricted the range of scores on the vasodilation measure, which would have reduced the size of the relationship, should one have been present. To summarise, due to the methodological problems discussed, it is not possible to determine whether the failure to find an association between vasodilation and cognition reflects the fact that no such relationship exists in young relatively healthy people or whether the methodological problems of low statistical power, poor test sensitivity or an attenuated range of scores prevented the detection of such a relationship. Study 2 did not, therefore, provide an adequate test of whether poor vasodilation is associated with ischaemic brain damage and/or cognitive impairment.

Ideally, the study should be replicated in a larger sample that includes a significant proportion of elderly people and people with a range of cardiovascular severity ratings. Future research should prioritise replication of the studies by Moser et al (2004; 2008; 2007) (i.e. confirm that the relationships exist in older people with cardiovascular pathology) before extending research into other groups, and should incorporate an appropriate cognitive testing protocol, such as the one used here. Further cross-validation of techniques for assessing vasodilation is also needed so that results across studies employing different techniques can be confidently compared.

8.3 Study 3: Cognitive impairment predicts functional capacity in dementia-free patients with cardiovascular disease

8.3.1 Restatement of the aims and main findings

Study 3 investigated whether cognitive impairment is independently associated with disability in day-to-day activities in patients with CVD. The results revealed that cognitive performance predicted whether people required help with everyday activities even when the effects of age and disease burden were controlled.

8.3.2 Methodological strengths

A major strength of Study 3 was its large sample size, which ensured sufficient statistical power to detect a relationship between cognition and functional status and allowed for the control of potentially confounding variables. An additional strength of the study was that participants were drawn from a typical hospital outpatient clinic, which ensured that the results have direct relevance to this setting and provide a firm basis for making clinical decisions using this data. However, it should be noted that participants in the study were all

drawn from a small geographical area in the western suburbs of Adelaide. The socio-demographic profile of this location features low education levels, low income, and a high proportion of migrants (although the exclusion criteria excluded many from non-English-speaking countries to maximise the validity of the cognitive testing), so the results may not be applicable to all populations.

Another strength was the use of the Functional Comorbidity Index (Groll, et al., 2005) to quantify cardiovascular burden and co-morbid disease burden. This tool was developed to only include items that are related to functional capacity. The use of this index distinguishes the present study from others that have attempted to measure the impact of co-morbid disease using unvalidated measures or tallies (Moritz, Kasl, & Berkman, 1995; Plehn, et al., 2004), tools designed for other purposes (Mariani, et al., 2008), or arbitrarily selected individual diagnoses (Barberger-Gateau, et al., 1999)**.** A related strength of the study was that a thorough clinical assessment and review of medical records was undertaken (in addition to information collected during interview), along with specific screening for depression, to ensure that the Functional Comorbidity Index was coded accurately.

8.3.3 Methodological limitations

The primary limitation of the study design (as discussed in the paper) was that the IADL scale (Lawton, Moss, Fulcomer, & Kleban, 1982) used to assess functional status was brief and may therefore have lacked sensitivity, which could have reduced effect sizes. A study similar to the present one found that this IADL scale was less sensitive to MCI than two other self-report tools (Burton, et al., 2009). Other research suggests that informant-rated measures may have been more appropriate in this cohort. Specifically, in a mixed group with

MCI or mild Alzheimer's Disease, *informants* rated functional disability more severely than people's *self-reports* (Onor, Trevisiol, Negro, & Aguglia, 2006). Another study found that the discrepancy between self-reports and informant reports was larger for those with more severe cognitive dysfunction (in the range of probable dementia) than those with milder cognitive impairments (Albert, et al., 2006). Based on this information, an informant-rated scale of functional capacity may have been more sensitive and may have resulted in a greater number of people being classified as impaired, which would have resulted in statistically stronger associations. The MoCA tool, used to measure cognitive function, is also a brief screening tool, which may have further reduced the statistical power because of a lack of sensitivity. Despite these limitations, the study was still able to demonstrate a relationship between cognitive performance and day-to-day function, so, ultimately, the selection of assessment tools was not a major limitation.

8.3.4 Implications and recommendations for future research

Confirmation of the clinical significance of cognitive impairment

Prior to this study, even though there was clear evidence that people with CVD experience increased rates of cognitive impairment, the significance of these cognitive deficits in non-demented populations was not well understood. The functional impact of cognitive impairment in cardiovascular populations had not previously been examined. As a consequence, little information was available to guide staff working with cardiovascular patients in deciding whether and how they should respond to this issue. At present, the vast majority of clinical practice guidelines focusing on people with CVRFs do not stipulate whether cognitive capacity should be assessed, and how and under what circumstances this should be done (Rockwood, Middleton, Moorhouse, Skoog, & Black, 2009). The main

implication of these findings is that mild cognitive impairment is not a benign problem in dementia-free cardiovascular patients. Rather, the results suggest that it may limit people's ability to complete their day-to-day tasks and thus may affect their quality of life. It therefore provides a justification for investigating whether targeted cognitive assessment should be incorporated into the routine clinical management of CVD.

Subtle cognitive impairment may be difficult to recognise in a clinical setting, particularly given that deficits in executive functioning are more common than problems with memory (Saxton, et al., 2000; van Exel, et al., 2002). People with impaired executive functions may experience difficulty with planning and organisation, but may function well in highly structured settings where well-learned routine behaviour is required (Kahokehr, et al., 2004; Ylikoski & Hanninen, 2003). Consequently, formal cognitive testing for high-risk patients may be helpful if it can be shown that there is some potential benefit to the patient in identifying the deficit.

Although pharmacological treatment options for mild vascular-related cognitive impairment are currently limited, it may be possible to improve functional capacity in this group using non-pharmacological interventions. Alexopolous et al (2002) suggested that, for people with mild executive deficits, behavioural interventions may be effective in improving functional capacity. They specifically highlighted the potential benefits of organising patients' activities and providing cues for initiating tasks (Alexopoulos, Kiosses, Klimstra, Kalayam, & Bruce, 2002). Compensation strategies such as calendars and reminder systems used to address memory decline have been used successfully in other groups such as people with traumatic brain injury (Fish, Manly, Emslie, Evans, & Wilson, 2008; Wilson, 2000). More recently, programs employing similar compensation strategies have been shown to improve

functional capacity in people with Amnestic MCI or early Alzheimer's Disease (Greenaway, Hanna, Lepore, & Smith, 2008; Kurz, Pohl, Ramsenthaler, & Sorg, 2008; Londos, et al., 2008). However, such strategies may be less effective for people with executive deficits. In one study, people with executive dysfunction were less likely to continue using a pager reminding device than people with other forms of cognitive impairment (Fish, et al., 2008). This is consistent with other observations that people with executive deficits are less likely to use adaptive devices such as hearing aids or walking frames prescribed to address functional difficulties (Royall, Chiodo, & Polk, 2000). Thus, further research into the efficacy of compensation strategies for vascular-related MCI is needed.

In summary, Study 3 fulfilled its aim by demonstrating that cognitive impairment is independently associated with functional loss in cardiovascular patients. The study needs to be replicated to confirm these findings because little other information about the functional impact of cognitive impairment in cardiovascular populations is available. Further research is also needed to examine more specific aspects of this relationship. First, more information is needed to clarify which specific types of cognitive deficits have the most impact. Available evidence from non-cardiovascular populations implicates executive dysfunction (Cahn-Weiner, et al., 2007; Farias, et al., 2009; Royall, et al., 2005), but it would be interesting to examine the specific role of executive function in cardiovascular patients with CVD where deficits in this aspect of cognition are particularly common (Nordlund, et al., 2007; Saxton, et al., 2000; van Exel, et al., 2002; Wiederkehr, et al., 2009). Cross-sectional study designs like the one used in the present study don't provide information on the direction of causality, so longitudinal research would be useful in determining whether changes in cognition predict functional decline over time in cardiovascular patients. More research is also needed to establish the impact of mild cognitive impairment and functional loss on other sections of the

population. As a starting point, studies might examine the burden that mild cognitive decline has on family members of the person affected and on community support services.

8.4 Study 4: The Depression-Executive Dysfunction (DED) Syndrome and response to antidepressants: A meta-analytic review

8.4.1 Restatement of the aims and main findings

Study 4 was designed to analyse existing research in order to determine whether it supports the hypothesis that depressed patients who fail to respond to medication have significantly lower levels of executive function. A meta-analysis was used to synthesise findings from previous research. Results showed that five cognitive tests discriminated between patients who ultimately responded to antidepressant medication and those who failed to respond. One was a test of executive function but the remainder assessed other cognitive domains. These results largely fail to support the predictions of the DED model. Secondary analysis revealed that people who responded to treatment were significantly younger and were less depressed at baseline.

8.4.2 Methodological strengths and limitations

A major strength of the study was that it incorporated a comprehensive search of the existing literature, which included not only studies that addressed the question of treatment response as a primary research aim, but also studies that looked at unrelated questions and presented relevant data as descriptive statistics or secondary findings. This search approach maximised the data available for analysis.

The main weaknesses of this study were related to the heterogeneity of the individual studies. In many cases, data from different studies could not be statistically pooled because studies used different neuropsychological tests. Different tests, even those falling within a single cognitive domain, are sensitive to different cognitive processes and to pathology in different brain regions. Some brain regions may be relevant to treatment response, while others may not be. If the results of studies that used different cognitive tests had been combined, their meaningfulness would have been reduced. Notwithstanding this, the process of identifying relevant studies, calculating effect sizes, and then collating them in a single table still provided a meaningful summary of findings across studies, and allowed a direct comparison of results. It demonstrated that the results are not as consistently positive, and the hypothesis not as robust, as some narrative reviews suggest (Alexopoulos, 2006; Kales, et al., 2005).

The heterogeneity in participant characteristics was also problematic for similar reasons. Some studies examined relatively young cohorts, while others selected elderly patients. Although the DED model does not make predictions based on age, it is possible that the determinants of treatment response differ across age groups. Thus, pooling data across these studies may have obscured some relationships. Although these differences across studies make it more difficult to interpret the results, it should be remembered that the DED model, in its current form, suggests that poor treatment response should be related to all forms of executive dysfunction (i.e. all executive function tests) and this should be the case for patients of any age. In this respect, a pooling of the data was defensible.

Heterogeneity in the treatment protocols used by the individual studies is a further problem. Drugs that affect dopamine transmission, like Sertraline and Bupropion, may be more effective in treating depression for people with frontal lobe abnormalities than other

medications (Alexopoulos, 2001). If this is the case, then studies employing those agents would be less likely to report differences in the cognitive function of responders and non-responders that studies using other pharmacological agents. Thus, the pooling of results across such studies may have masked drug-specific relationships. In an attempt to address this problem, separate analyses were run, restricted to just those studies that used SSRIs. This analysis produced very similar results.

The total number of available studies was quite small in both the main analysis and the analysis restricted to SSRIs. In most cases, fewer than 3 studies were available for each cognitive test. The small sample size is a further limitation of the study. If a greater number of studies had been available, it would have been possible to perform homogeneity analysis to examine the effect of moderator variables such as age and medication type.

8.4.3 Implications and recommendations for future research

The DED syndrome is believed to be a marker for vascular depression. The failure to find a consistent relationship between executive dysfunction and treatment response is open to a number of interpretations. It may signify that people with the DED syndrome do not differ from other depressed patients with respect to treatment outcomes. An alternative explanation is that executive dysfunction is a poor marker for frontal lobe abnormalities. Direct measures of brain pathology using imaging technology may be more sensitive and have better predictive value.

However, as discussed in detail in Section 1.6.1, the most important consideration, which overshadows the points discussed above, is that the research design adopted by the

individual studies included in the meta-analysis is not optimal for testing the treatment-response hypothesis stemming from the DED model. This is because the likelihood of any one study detecting a significant result is directly influenced by the proportion of the study sample who have the DED syndrome. Thus, the most fundamental implication of the failure to find consistently poorer executive function in non-responsive patients is that the null results can not disprove the predictions of the DED model. It is essential that these predictions be retested using a case-control study design (i.e. the design adopted in Study 5) or regression analysis with treatment response as the outcome variable and executive function as a predictor variable, which would eliminate the influence of differences in the proportion of DED patients recruited to a particular study

Future studies should also aim to examine the potentially confounding effects of age, baseline depression severity and functional impairment. Secondary findings from the current meta-analysis demonstrated that, on average, depressed patients with executive dysfunction are older, and more severely depressed. Other research has shown that people with executive dysfunction experience more functional impairment (Burton, et al., 2006; Cahn-Weiner, et al., 2007; Farias, et al., 2009; Insel, et al., 2006; Okonkwo, et al., 2006; Plehn, et al., 2004; Royall, et al., 2005). Yet, functional impairment was not considered in most of these studies, so could not be examined in the meta-analysis. Any of these factors may explain the observed associations between executive dysfunction and poor antidepressant response. That is, it may be the older age or increased disability in DED patients that causes their poor response to treatment. Multivariate analysis techniques would provide a means for statistically controlling these potentially confounding factors, and should therefore be incorporated into future research designs.

In summary, Study 4 successfully achieved its aim of summarising existing research to determine whether it supports the treatment response predictions of the DED model. The wider overarching aim of the study was to gather evidence that would help to evaluate the validity of the vascular depression model. The results of the meta-analysis did not provide definitive evidence for or against the vascular depression model due to the reliance on retrospective study designs.

8.5 Study 5: Antidepressant Response in Cardiac Patients with Executive Dysfunction

8.5.1 Restatement of the aims and main findings

With the same overarching aim of testing the validity of the vascular depression model, Study 5 examined whether depressed patients who exhibited executive dysfunction (i.e. patients with the DED syndrome) were less likely to respond to antidepressant treatment than other depressed patients. The results showed that all of the patients with the DED syndrome failed to respond to treatment at three months, which was a significantly lower response rate than that seen in the group with normal executive function (40% response rate). People with the DED syndrome maintained a poorer response rate at six months (11% v. 47%), however the difference was not statistically significant at this follow-up point.

8.5.2 Methodological strengths and limitations

A major strength of the study design was that it used a case-control approach and thereby avoided the problems associated with the retrospective designs used in previous studies, including those reviewed in the meta-analysis (ie the potential for an inadequate proportion of DED cases within the study sample to reduce statistical power). Another strength was that it incorporated measures of potentially confounding variables including age,

education, quality of life and functional disability. To maximise the power of the study, the neuropsychological assessment tools that provided the best discrimination between treatment responders and non-responders in the meta-analysis (Chapter 6) were selected to measure executive function (Delis, Kaplan, & Kramer, 2001; Jurica, Leitten, & Mattis, 2001).

A further strength of the study was that it was carried out in a clinical setting with a naturalistic treatment protocol, affording it ecological validity. This provides a degree of confidence that the results produced in the study will translate to real-life clinical settings.

The main weakness of this study was the small sample size. Although there was a strong trend for DED subjects to experience worse treatment outcomes than the other subjects, this trend failed to reach statistical significance at 6 months follow-up. Therefore, it is possible that this trend occurred as a result of statistical chance alone. Power analyses were completed prior to commencement of the study. These were based on the assumption that 310 cardiac patients would be recruited and allocated to the intervention arm of the parent study, and that 40% of these patients would be experiencing depression (based on the prevalence rate reported in a prior study carried out by the same investigators; (Schrader, Cheok, Hordachre, Marker, & Wade, 2005)). This would have resulted in around 124 study participants, rather than the 43 that were ultimately recruited. Due to the small sample size, the results must be viewed as preliminary in nature.

Because the number of cases was limited, it was not possible to complete multiple regression analysis. Participants in this cohort who exhibited the DED syndrome were slightly more depressed than the remaining patients (non-significant). They also had a lower level of education. It is therefore possible that either of these factors may have influenced treatment

response rates. Interestingly, their self-reported quality of life and functional capacity was actually higher (non-significant) than the other participants', so it is unlikely that these factors contributed to the lower treatment response rates in this sample.

A second significant limitation of the study was the fact that information about treatment format and treatment adherence rates was not available for analysis. Thus, it is not known whether the group with executive function was prescribed (and/or adhered to) a similar treatment regimen as the group with normal executive function. In addition, the lack of information on treatment format means that it is unclear whether participants with executive dysfunction failed to respond to psychotherapy, to SSRI medication, or to another form of medication.

8.5.3 Implications and recommendations for future research

Cognitive assessment as a tool in treatment planning

Despite the limited information about treatment format, and the small sample size, the clear delineation in the outcomes of people with and without executive dysfunction indicates that the issue deserves further investigation. The potential importance of these preliminary findings is further supported by the fact that another study that used the same design, and one of the same cognitive tests (the DRS-IP) reported almost identical results. That study used the DRS-IP to define executive function and found that 11 of 12 people with DED failed to respond to treatment (Kalayam & Alexopoulos, 1999). In that study, patients had been treated with one of several classes of antidepressant medications.

The present study needs to be replicated using a larger sample, incorporating a regression analysis to control for potentially confounding variables, and more accurately measuring (and preferably controlling) the treatment format. If the findings are replicated in a larger cohort, this would provide some support for the claim that the aetiology or maintaining factors of depression in DED patients is distinct from that of other depressed patients. It would also provide a reasonable basis for considering alternative treatment options for this group.

Alexopoulos (2001) proposed that people displaying the DED syndrome may respond more favourably to drugs that target dopamine receptor sites because dopamine plays a prominent role in regulating prefrontal-subcortical circuits. Of the available antidepressant medications, Sertraline is unique because it has a relatively large effect on dopamine receptor sites (Richelson, 2001). It may therefore be particularly beneficial to people with the DED syndrome given that these circuits appear to be functioning abnormally. The effectiveness of Sertraline has not been compared to other antidepressants in patients with DED. Interestingly, in well controlled trials, in general populations of depressed patients, Sertraline has been associated with greater improvements in cognitive function than other antidepressant drugs (Bondareff, et al., 2000; Finkel, Richter, & Clary, 2005; Rocca, et al., 2005). Further investigation of the efficacy of Sertraline or other drugs that target the dopamine system for the treatment of depression in patients with DED should be considered if the results of the current study are confirmed.

8.6. Summary

To summarise, with the exception of Study 2, which was marred by methodological problems that were not able to be controlled, the studies presented in this thesis have made significant and original contributions to the related fields of vascular-related cognitive

impairment and vascular depression. Specifically, Study 1 demonstrated for the first time that in a sample of patients with CVD, the MoCA's sensitivity was high but its specificity was poor, suggesting it will have limited value as a screening test for MCI in settings where the overall prevalence of MCI is low. Study 3 demonstrated for the first time that cognitive impairment is an independent predictor of functional capacity in patients with CVD, suggesting that mild cognitive impairment is a clinically meaningful problem that needs to be addressed. Study 4 demonstrated that when all of the available evidence is pooled, previous claims about group differences between antidepressant responders and antidepressant non-responders are not supported. This finding does not necessarily negate the DED hypothesis, but rather demonstrates that the research designs in the relevant studies are not optimal for testing the predictions stemming from the DED hypothesis. The final study provided a model of how the DED hypothesis can be tested more definitively. Results suggested that people with the DED syndrome do appear to experience poor response to treatment as predicted, which provides preliminary support for the validity of the vascular depression model, and a basis for replication of the study on a larger scale.

Until very recently, the impact of cerebral small vessel disease had not been recognised. Information generated by this thesis is consistent with other emerging data, which suggests that cerebral small vessel disease is a pervasive problem and plays a significant role in cognitive and mood disorders that are common in old age. The new information generated in this thesis has the potential to contribute to a better understanding of these problems, and ultimately, to their treatment and prevention.

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