UNIVERSITY OF CALGARY

Identifying the Neuropsychological Profile of Cerebral Amyloid Angiopathy

by

Nevicia Faith Case

A THESIS
SUBMITTED TO THE FACULTY OF GRADUATE STUDIES
IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE
DEGREE OF MASTER OF SCIENCE

GRADUATE PROGRAM IN MEDICAL SCIENCE

CALGARY, ALBERTA

JULY, 2015

© NEVICIA FAITH CASE 2015
Abstract
Cerebral amyloid angiopathy (CAA) occurs when the protein, beta-amyloid, deposits onto blood vessels in the brain, often resulting in cognitive impairment. This study aims to identify the neuropsychological profile of CAA by comparing CAA participants to the normal population and cognitively-similar patient populations, distinguishing between CAA syndromes, and determining whether white matter hyperintensity volume or APOE ε4 mediate cognitive impairment. Thirty-four CAA, 16 Alzheimer’s disease, 69 mild cognitive impairment, and 27 minor ischemic stroke participants underwent neuropsychological testing. Cross-sectional data revealed lower performance on tests of perceptual speed, episodic memory, and executive functioning in CAA participants when compared to the normal population ($t(33) = -3.76, p = <0.001; t(32) = -2.45, p = 0.02; t(33) = -6.21, p = <0.001$; respectively). Overall, CAA was most cognitively similar to vascular cognitive impairment. Larger sample sizes and longitudinal analyses in future will help to advance understanding of cognitive deficits associated with CAA.
Acknowledgements

Thank you, Dr. Eric Smith, my supervisor, for allowing me the opportunity to contribute to and learn from your research environment. I’m extremely grateful for the excellent supervision and critical feedback you provided me—balanced with kindness and patience throughout my learning process.

Thank you, Dr. Vina Goghari, my committee member, for your invaluable input, support, and advice not only on my thesis, but throughout my Master’s program. Thank you, Dr. Angela Haffenden, my committee member, for your thoughtful feedback on my thesis and for allowing me the opportunity to observe neuropsychological assessments in your clinic. Thank you, Dr. Jayna Holroyd-Leduc, for acting as my external examiner.

Thank you to all my lab members for your essential contributions to my thesis. I’m grateful to Dr. Cheryl McCreary for designing the MRI protocols for FAVR and Brain-IMPACT and also taking time out of her busy schedule to teach me some MRI basics. Special thanks to previous and current research assistants, Aaron Peterson, Angela Zwiers, and Ramnik Sekhon, among others, who were responsible for neuropsychological data collection and entry. I’m particularly thankful to Angela Zwiers for training me on the neuropsychological test preparation, administration, scoring, and reporting. Many thanks to Dr. Saima Batool and Ikreet Cheema for providing WMH volume measurements, Dr. Randall Stafford for affording me a better understanding of MR physics through his teaching series, Anna Charlton for keeping everything in the lab running smoothly, and Ana Alvarez-Veronesi for organizing the blood draw data. I’d also like to thank Dr. Yukun Zhang for statistical consultation, Dr. Jennifer Chan and her research team for analyzing APOE genotype data, and Dr. Shelagh Coutts and her research team for providing data from the CATCH study.
Thank you, my many colleagues and friends in the Hotchkiss Brain Institute who provided encouragement and support throughout my Master’s program.

Thank you, God and my parents, Drs. Neville and Patricia Case, for your endless love and support that have sustained me throughout this journey.

To all—your support, patience, and willingness to collaborate, teach, and offer feedback will always be remembered.

I’d also like to acknowledge the Heart and Stroke Foundation of Alberta, NWT, & Nunavut and the Queen Elizabeth II scholarship and bonus that have helped immensely with funding my studies.
Dedicated to Dr. Eric Smith’s research team and the participants.
Table of Contents

Abstract ............................................................................................................................... ii
Acknowledgements ............................................................................................................ iii
Table of Contents ............................................................................................................... vi
List of Tables ................................................................................................................... viii
List of Figures and Illustrations ......................................................................................... ix
List of Symbols, Abbreviations and Nomenclature ............................................................. x

CHAPTER 1: INTRODUCTION ........................................................................................1
  1.1 Cerebral amyloid angiopathy .....................................................................................1
    1.1.1 Pathogenesis ......................................................................................................2
    1.1.2 Small vessel disease correlates ..........................................................................4
        1.1.2.1 Intracerebral hemorrhages .......................................................................4
        1.1.2.2 White matter hyperintensities ..................................................................4
        1.1.2.3 Other small vessel disease markers of CAA ............................................5
    1.1.3 Cognitive impairment ........................................................................................7
    1.1.4 Risk factors ........................................................................................................9
    1.1.5 Diagnosis .........................................................................................................11
    1.1.6 Clinical presentations ......................................................................................12
  1.2 Alzheimer’s disease .................................................................................................14
    1.2.1 Pathogenesis ....................................................................................................14
    1.2.2 Cognitive impairment ......................................................................................15
  1.3 Mild cognitive impairment ......................................................................................16
    1.3.1 Pathogenesis ....................................................................................................16
    1.3.2 Cognitive impairment ......................................................................................17
  1.4 Minor ischemic stroke .............................................................................................18
    1.4.1 Pathogenesis ....................................................................................................19
    1.4.2 Cognitive impairment ......................................................................................19
  1.5 Research objectives and hypotheses ........................................................................20

CHAPTER 2: METHODS .................................................................................................22
  2.1 Significant contributions ..........................................................................................22
  2.2 Sources of study participants ...................................................................................23
  2.3 Assessment ...............................................................................................................28
    2.3.1 Neuropsychological Assessment .....................................................................28
        2.3.1.1 Mini Mental State Examination (MMSE) .............................................29
        2.3.1.2 Trail Making Test (TMT) .................................................................30
        2.3.1.3 Digit Span (DS) subtest of the WAIS-IV ..............................................30
        2.3.1.4 Boston Naming Test (BNT) ...............................................................31
        2.3.1.5 Controlled Oral Word Association Test (COWAT) .........................32
        2.3.1.6 Digit Symbol-coding subtest (DSST) of the WAIS-IV .......................32
        2.3.1.7 Rey-Osterrieth Complex Figure (ROCFT)/Modified Taylor Complex Figure (MTCF) ........................................................33
        2.3.1.8 California Verbal Learning Test: Second Edition (CVLT-II) ...............34
List of Tables

Table 1. Relation of moderate-to-very severe CAA to five cognitive domains and global cognition .......................................................... 9
Table 2. Boston Criteria for diagnosis of CAA-related ICH .......................................................... 12
Table 3. Parent study inclusion and exclusion criteria. ............................................................... 26
Table 4. MRI parameters. ............................................................................................................. 36
Table 5. Study population characteristics. .................................................................................... 42
Table 6. Z-scores from neuropsychological tests in CAA, AD, MCI, and MIS. .................. 45
Table 7. Z-scores from neuropsychological tests in CAA, AD, MCI, and MIS (post-hoc comparisons). .......................................................... 48
Table 8. Z-scores from neuropsychological tests in different syndrome categories of CAA...... 50
Table A1. Raw scores from neuropsychological tests in CAA, AD, MCI, and MIS. ............... 76
Table A2. Raw scores from neuropsychological tests in different syndrome categories of CAA. .................................................................................................................. 76
List of Figures and Illustrations

Figure 1. APP cleavage and pathophysiology (Biffi & Greenberg, 2011). ........................................ 3
Figure 2. CAA pathogenesis from Aβ formation to deposition (Charidimou et al., 2012). .......... 3
Figure 3. A schematic summary of CAA-related SVD correlates (Charidimou et al., 2012). ....... 6
Figure 4. Relationships between different APOE genotypes and CAA pathology (Charidimou et al., 2012). .......................................................................................................................... 11
Figure 5. Z-scores from neuropsychological tests in CAA, AD, MCI, and MIS (post-hoc comparisons). ........................................................................................................................................ 49
Figure 6. Presenting symptoms of the CAA participants. ................................................................. 50
Figure 7a. Scatterplot of WMH volume correlation with composite episodic memory z-scores in CAA. Figure 7b. Scatterplot of WMH volume correlation with composite executive functioning z-scores in CAA. Figure 7c. Scatterplot of WMH volume correlation with DSST z-scores in CAA. ........................................................................................................................................ 53
Figure 8. T-test of episodic memory z-scores among CAA, AD, and MCI participants with and without an APOE ε4 allele. .................................................................................................................. 54
### List of Symbols, Abbreviations and Nomenclature

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aβ</td>
<td>Beta-amyloid</td>
</tr>
<tr>
<td>AD</td>
<td>Alzheimer’s disease</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
</tr>
<tr>
<td>APOE</td>
<td>Apolipoprotein E</td>
</tr>
<tr>
<td>APP</td>
<td>Amyloid precursor protein</td>
</tr>
<tr>
<td>BNT</td>
<td>Boston Naming Test</td>
</tr>
<tr>
<td>Brain-IMPACT</td>
<td>Brain Imaging and Neuropsychological Assessment of Cognitive Impairment</td>
</tr>
<tr>
<td>CAA</td>
<td>Cerebral amyloid angiopathy</td>
</tr>
<tr>
<td>CADASIL</td>
<td>Cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy</td>
</tr>
<tr>
<td>CATCH</td>
<td>Computed Tomography and MRI in the Triage of Transient Ischemic Attack and Minor Cerebrovascular Events to Identify High Risk Patients—Extended</td>
</tr>
<tr>
<td>CL</td>
<td>Confidence limit</td>
</tr>
<tr>
<td>CMB</td>
<td>Cerebral microbleeds</td>
</tr>
<tr>
<td>COWAT</td>
<td>Controlled Oral Word Association Test</td>
</tr>
<tr>
<td>COWAT—FAS</td>
<td>Controlled Oral Word Association Test—Letter Fluency</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>CVLT—DR</td>
<td>California Verbal Learning Test—Delayed Recall</td>
</tr>
<tr>
<td>CVLT-II</td>
<td>California Verbal Learning Test: Second Edition</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
</tr>
<tr>
<td>DS</td>
<td>Digit Span</td>
</tr>
<tr>
<td>DSST</td>
<td>Digit Symbol-Coding subtest</td>
</tr>
<tr>
<td>FAVR</td>
<td>Functional Assessment of Vascular Reactivity in Small Vessel Disease</td>
</tr>
<tr>
<td>FLAIR</td>
<td>Fluid attenuated inversion recovery</td>
</tr>
<tr>
<td>IADLS</td>
<td>Instrumental Activities of Daily Living Scale</td>
</tr>
<tr>
<td>ICH</td>
<td>Intracerebral hemorrhage</td>
</tr>
<tr>
<td>IQ</td>
<td>Intelligence quotient</td>
</tr>
<tr>
<td>M</td>
<td>Mean</td>
</tr>
<tr>
<td>MCI</td>
<td>Mild cognitive impairment</td>
</tr>
<tr>
<td>MI</td>
<td>Microinfarcts</td>
</tr>
<tr>
<td>MIS</td>
<td>Minor ischemic stroke</td>
</tr>
<tr>
<td>MMSE</td>
<td>Mini Mental State Examination</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>MTCF</td>
<td>Modified Taylor Complex Figure</td>
</tr>
<tr>
<td>NIA</td>
<td>National Institute on Aging</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>NIHSS</td>
<td>National Institutes of Health Stroke Scale</td>
</tr>
<tr>
<td>PCR</td>
<td>Polymerase chain reaction</td>
</tr>
<tr>
<td>RFLP</td>
<td>Restriction fragment length polymorphism</td>
</tr>
<tr>
<td>ROCFT</td>
<td>Rey-Osterrieth Complex Figure</td>
</tr>
<tr>
<td>ROCFT—DR</td>
<td>Rey-Osterrieth Complex Figure—Delayed Recall</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SVD</td>
<td>Small vessel disease</td>
</tr>
<tr>
<td>TFNE</td>
<td>Transient focal neurological episodes</td>
</tr>
<tr>
<td>TIA</td>
<td>Transient ischemic attack</td>
</tr>
<tr>
<td>TMT—A</td>
<td>Trail Making Test—Part A</td>
</tr>
<tr>
<td>TMT—B</td>
<td>Trail Making Test—Part B</td>
</tr>
<tr>
<td>VCI</td>
<td>Vascular cognitive impairment</td>
</tr>
<tr>
<td>WAIS-IV</td>
<td>Wechsler Adult Intelligence Scale: Fourth Edition</td>
</tr>
<tr>
<td>WMH</td>
<td>White matter hyperintensities</td>
</tr>
</tbody>
</table>
CHAPTER 1: INTRODUCTION

Declines in cognitive functioning are normal within the aging population (Jolles, van Boxtel, Ponds, Metsemakers, & Houx, 1998). Persons with abnormally low levels of cognitive functioning in comparison to their age-matched counterparts, however, are described as having cognitive impairment (Yanhong, Chandra, & Venkatesh, 2013). A Canadian population study (Robertson, Rockwood, & Stolee, 1989) found that cognitive impairment affects 2.4-29.3% of people over the age of 65, with the percentage increasing with age. Cognitive impairment is symptomatic of a variety of different pathologies, such as—but not exclusive to—numerous neurological and psychiatric conditions, including cerebral amyloid angiopathy (CAA), Alzheimer’s disease (AD), and ischemic stroke (Charidimou, Gang, & Werring, 2012; McKhann et al., 2011; Serrano, Domingo, Rodriguez-Garcia, Castro, & del Ser, 2007).

The purpose of this thesis is to investigate cognitive impairment in people with CAA in relation to the normal population and the following cognitively-similar patient populations: AD, mild cognitive impairment (MCI), and minor ischemic stroke (MIS). I also aim to determine whether different presentations of CAA differ in their cognitive profile and whether white matter hyperintensity (WMH) volumes—a magnetic resonance imaging (MRI) correlate of small vessel disease (SVD) and apolipoprotein E (APOE) genotype mediate these effects.

1.1 Cerebral amyloid angiopathy

CAA refers to a group of cerebrovascular disorders characterised by beta-amyloid (Aβ) deposition in small- to medium-sized blood vessels of the brain parenchyma and leptomeninges (Biffi & Greenberg, 2011). It occurs in 30% of adults over the age of 60 years (Rensink, de Waal, Kremer, & Verbeek, 2003) and is responsible for 5-20% of spontaneous intracerebral hemorrhages (ICH) (Biffi & Greenberg, 2011). There are two types of CAA: familial and
sporadic. Familial CAA has a rare hereditary basis that involves proteins other than Aβ. Sporadic CAA, the focus of this research, arises in relation to the accumulation of Aβ in the absence of a family history of CAA and consists of the vast majority of CAA cases (Gahr, Nowak, Connemann, & Schonfeldt-Lecuona, 2013).

1.1.1 Pathogenesis

Muller and Zheng (2012) describe the amyloid precursor protein (APP) as a transmembrane protein composed of a long extracellular ectodomain and a short cytoplasmic tail. The ectodomain is released when APP is cleaved by β-secretase at the Aβ amino terminus. Subsequent cleavage by γ-secretase isolates the Aβ peptide into either Aβ_{40} or Aβ_{42} (Figure 1). Oligomerized Aβ has the propensity to aggregate and form rigid deposits of fibrils on the vascular media of cerebral lobes (Biffi & Greenberg, 2011). These depositions are largely composed of Aβ_{40} in CAA and are most often found in the occipital lobe; less commonly in the hippocampus, cerebellum, and basal ganglia; and most infrequently in deep central gray matter, subcortical white matter, and the brainstem (Rensink et al., 2003). Aβ remains soluble until deposition, after which, it becomes insoluble. The structure of soluble and deposited Aβ mainly differ in that soluble Aβ is largely formed of β-sheet structures, which have a higher affinity to deposition (Biffi & Greenberg, 2011). The literature suggest that the buildup of Aβ in both the leptomeninges and parenchyma is most likely due to deficiencies in clearance and/or degradation of the peptide (Deane et al., 2003; Miners et al., 2008; Poduslo, Curran, Sanyal, & Selkoe, 1999). A visual representation of this process is presented in Figure 2.
Figure 1. APP cleavage and pathophysiology (Biffi & Greenberg, 2011).

Figure 2. CAA pathogenesis from Aβ formation to deposition (Charidimou et al., 2012).
1.1.2 Small vessel disease correlates

CAA has been found to have an array of pathophysiological effects, the most well-researched include SVD correlates that can be detected through the use of MRI, such as ICH, cerebral microbleeds (CMB), white matter hyperintensities (WMH), and microinfarcts (MI). A visual summary of the pathophysiology associated with CAA is provided in Figure 3. There is also emerging evidence of significantly more severe white matter perivascular spaces (Charidimou, Jager, et al., 2014; Charidimou, Jaunmuktane, et al., 2014) and significantly lower serum uric acid levels in CAA participants when compared to non-CAA participants (Hu et al., 2014).

1.1.2.1 Intracerebral hemorrhages

Annually, approximately 0.3-0.4% of the normal population over the age of 70 experience symptomatic ICH, with hypertensive arteriosclerosis and CAA accounting for 78-88% of these cases (Yates et al., 2014). The rigidity that occurs as a result of Aβ vascular deposition can threaten the integrity of vessel walls, making them brittle, and creating small cracks, resulting in CMB and ICH (Charidimou et al., 2012). Consistent with the spatial distribution of Aβ vasculopathy in CAA, ICH is most often found in the posterior regions of the brain, particularly in the occipital and temporal lobes. The cerebellum, deep brain structures, and brainstem display ICH less frequently (Charidimou et al., 2012).

1.1.2.2 White matter hyperintensities

According to Charidimou et al. (2012), WMH, or leukoaraiosis, in CAA occurs when there is hypoperfusion of periventricular white matter and malfunction of the blood-brain barrier as a result of Aβ deposition on adjacent vessels. Thanprasertsuk et al. (2014) found posterior WMH distribution to be an independent predictor of CAA in patients without lobar ICH, an
important finding given the only current pathology used for the in vivo diagnosis of sporadic CAA is ICH (E. Smith & Greenberg, 2003).

Furthermore, the prevalence of WMH has been associated with the prevalence of lobar ICH (E. Smith et al., 2004) and has also been found to be more heavily concentrated in the posterior region of the brain (Gilbert & Vinters, 1983), consistent with the high concentration of Aβ peptide deposition in the occipital lobe in CAA. Chen et al. (2006) found that, in addition to baseline WMH, cognitive impairment was the sole predictor of WMH progression at one-year follow-up. Other characteristics, such as age, sex, hypertension, diabetes mellitus, ischemic stroke, smoking, and APOE genotype were not associated with WMH progression.

WMH can be identified as periventricular hyperintensities on MRI using T2-weighted, fluid attenuated inversion recovery (FLAIR), or proton density-weighted sequences (Debette & Markus, 2010). Charidimou et al. (2012) caution that, in addition to CAA, WMH are also associated with numerous non-CAA conditions, such as tissue rarefaction, myelin and axonal loss, and mild gliosis; and pathologies, such as neurodegeneration, inflammation, and hypoxia. As a result, WMH that are coupled with other clinical CAA pathology are inferred to be of presumed vascular origin.

1.1.2.3 Other small vessel disease markers of CAA

In addition to ICH and WMH, other markers of small vessel disease in CAA include microinfarcts, CMB, and superficial siderosis.
1.1.2.3.1 Microinfarcts

According to Dumas et al. (2012), ischemia is likely to occur as a result of vascular hyporeactivity when there is a discrepancy between perfusion and metabolic demand. The reduction and possible loss of vasodilation in CAA as a result of Aβ deposition, destroys the vessel wall, paving the way for cerebral infarctions (Biffi & Greenberg, 2011).

1.1.2.3.2 Cerebral microbleeds

Martinez-Ramirez, Greenberg, and Viswanathan (2014) describe CMB as small hemorrhages that are evidenced by the presence of blood degradation products, such as hemosiderin, in macrophages proximal to the affected vessels. These superparamagnetic hemosiderin deposits appear as hypointensities on T2*-weighted gradient-recalled echo MRI, providing a biomarker of SVD (Greenberg et al., 2009). CMB associated with probable CAA are most often found aggregated in a posterior distribution pattern—particularly in the occipital and
temporal lobes (Rosand et al., 2005),—have an increased prevalence as a function of age, and high prevalence of the APOE ε4 allele (Mesker et al., 2011; Vernooij et al., 2008). Thanprasertsuk et al. (2014) also found lobar CMB to be a predictor of CAA in patients with cognitive impairment.

1.1.2.3.3 Superficial siderosis

Following a similar pathology to CMB, superficial siderosis in CAA occurs when the hemosiderin produced by repeated hemorrhaging deposits on the outer cortical layers of the brain (Charidimou et al., 2012). Research by Takeda et al. (2003) shows that the hemosiderin associated with CAA-related hemorrhaging deposits in sulcal subarachnoid spaces distal from the site of hemorrhaging.

1.1.3 Cognitive impairment

Despite the clinical observance of cognitive impairment in CAA (Charidimou et al., 2012; Gorelick et al., 2011; Greenberg, Gurol, Rosand, & E. Smith, 2004), the literature in this area is limited. An animal study conducted by (Xu et al., 2007) suggests an association between cerebral microvascular amyloid aggregation in the subiculum and localized activation of astrocytes and microglia with impaired performance on a maze test of spatial learning and memory.

The Religious Orders Study is an ongoing epidemiological clinical-pathologic study of aging and dementia in older community-dwelling men and women. Arvanitakis, Leurgans, Wang, et al. (2011) analysed post-mortem CAA pathology data in these participants in relation to their ante-mortem cognitive function. Cognitive function was assessed at baseline and annual follow-up clinical evaluations using a standardised neuropsychological testing battery (described in further detail by Wilson et al. (2002)), which included tests of episodic memory (notably,
Word List—Memory, Recall, and Recognition (Morris et al., 1989), semantic memory (notably, Verbal Fluency (Ekstrom, French, Harman, & Dermen, 1976) and Boston Naming (Kaplan, Goodglass, & Weintraub, 1983)), working memory (notably, Digit Span—Forward and Backward from Wechsler Memory Scale—Revised (Wechsler, 1987)), perceptual speed (notably, Digit Symbol Modalities Test (A. Smith, 1984)), and visuospatial abilities (Wilson et al., 2002). Arvanitakis, Leurgans, Wang, et al. (2011) examined data from the Religious Orders Study with the hypothesis that an association exists between CAA severity and specific cognitive domains. The results revealed that while 78% of participants without dementia had CAA pathology, 94% of participants with dementia also had CAA pathology. Regression analyses demonstrated that moderate-to-very severe CAA was associated with impairments in perceptual speed, $\beta = -0.50$, $SE = 0.20$, $p = 0.012$, and episodic memory, $\beta = -0.46$, $SE = 0.23$, $p = 0.047$, (‘moderate’ was defined as strong, circumferential positivity in some but not all leptomeningeal or cortical blood vessels and ‘very severe’ was defined as widespread, strong, circumferential positivity in leptomeningeal and cortical blood vessels with changes of positivity emanating from vessels into surrounding neuropil). It is from these findings of Arvanitakis, Leurgans, Wang, et al. (2011), outlined in Table 1, that the foundation of the present study objectives and hypotheses are derived.

Although the literature on cognitive impairment in CAA is limited, there is evidence for cognitive impairment in several of the SVD biomarkers of CAA. Werring, Gregoire, and Cipolotti (2010) provided a summary of studies investigating the relationship between microbleeds and cognitive impairment, yielding some studies with evidence of cognitive impairment (Goos et al., 2009; Liem et al., 2009; Seo et al., 2007; Viswanathan et al., 2007; Werring et al., 2004; Yakushiji et al., 2008) and other studies that showed no association
between microbleeds and cognitive impairment (Cordonnier et al., 2006; Hanyu, Tanaka, Shimizu, Takasaki, & Abe, 2003; Pettersen et al., 2008). It is important to note, however, that the microbleeds assessed by these various studies were not limited to the cerebrum.

Table 1. Relation of moderate-to-very severe CAA to five cognitive domains and global cognition

<table>
<thead>
<tr>
<th>Cognitive Score</th>
<th>Estimate (^a) (SE), (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perceptual speed</td>
<td>-0.50 (0.20), 0.012</td>
</tr>
<tr>
<td>Episodic memory</td>
<td>-0.46 (0.23), 0.047</td>
</tr>
<tr>
<td>Semantic memory</td>
<td>-0.21 (0.22), 0.340</td>
</tr>
<tr>
<td>Working memory</td>
<td>0.03 (0.16), 0.865</td>
</tr>
<tr>
<td>Visuospatial abilities</td>
<td>-0.27 (0.17), 0.102</td>
</tr>
<tr>
<td>Global cognition</td>
<td>-0.35 (0.19), 0.066</td>
</tr>
</tbody>
</table>

Model terms include CAA class variable predictors for moderate-to-very severe CAA (shown), mild-to-moderate CAA, and terms adjusting for age-at-death, sex, education, AD pathology, cerebral infarcts, and Lewy bodies.

\(^a\) \(\beta\)-Coefficient.

AD = Alzheimer’s disease; CAA = cerebral amyloid angiopathy; SE = standard error.

(Arvanitakis, Leurgans, Wang, et al., 2011)

1.1.4 Risk factors

Age is the greatest risk factor for the development of sporadic CAA, with the vast majority of patients with CAA-related ICH being at least 60 years of age and only occasional cases in patients in their 5\textsuperscript{th} decade (Charidimou et al., 2012). A Canadian pathological study by Vinters and Gilbert (1983) showed an increase in the incidence of CAA associated with advancement in age. Although only 1 of 21 (4.76\%) 60- to 69-year-old patients had CAA, as many as 4 of 7 (57\%) patients over 90 years of age were shown to have CAA.
While 70% of patients with CAA-related ICH have AD pathology (Jellinger, 2002), more than 90% of AD patients were found to have CAA at autopsy (Charidimou et al., 2012), making AD another risk factor for CAA.

Studies on the role of hypertension in CAA-related ICH have yielded mixed results. While one study found significantly more diagnoses of hypertension among CAA patients with ICH than in CAA patients without ICH (Vonsattel et al., 1991), a review of multiple studies found the prevalence of hypertension among CAA patients to be no different from controls (Vinters, 1987), and yet another study found a significantly lower prevalence of hypertension in CAA-related ICH when compared to non-CAA-related ICH (Gregoire et al., 2011). This mixture of results does not provide sufficient evidence supporting hypertension as a risk factor for CAA.

According to Charidimou et al. (2012), two polymorphisms of the APOE gene, €2 and €4, have been identified in relation to CAA pathology (Figure 4). The presence of the APOE €2 allele is associated with an increased risk of hemorrhage in CAA patients (Nicoll et al., 1997); greater hematoma volume, higher mortality, and poorer functional outcome (Biffi et al., 2011). Similarly, APOE €4 has been found to be associated with increases in the severity of CAA, younger age of CAA-related ICH onset, and the acceleration of CAA-related ICH pathological progression from amyloid β-peptide deposition to vascular rupture (Greenberg et al., 1996; Greenberg, Rebeck, Vonsattel, Gomez-Isla, & Hyman, 1995). While the presence of these two alleles has been shown to contribute to the worsening of CAA and €4 increases the risk of developing AD, €2 has, conversely, been shown to reduce the risk of AD (Verghese, Castellano, & Holtzman, 2011).
Figure 4. Relationships between different APOE genotypes and CAA pathology (Charidimou et al., 2012).

1.1.5 Diagnosis

Diagnosis of probable CAA follows the Boston Criteria for diagnosis of CAA-related ICH (Knudsen, Rosand, Karluk, & Greenberg, 2001; E. E. Smith & Greenberg, 2003; Table 2). According to these criteria, there must be both clinical and MRI (gradient-echo MRI is recommended) or computed tomography (CT) data to support the presence of multiple lobar, cortical, cortico-subcortical, or cerebellar hemorrhages. Other causes of hemorrhage, such as arteriovenous malformation, must be absent. Finally, the patient’s age must be equal to or greater than 55 years due to the rare occurrence of CAA in younger age populations. As ICH is only present in a subset of CAA patients, additional criteria for CMB and superficial siderosis have been recommended for inclusion in the Boston Criteria (Linn et al., 2010; van Rooden et al., 2009).
Table 2. Boston Criteria for diagnosis of CAA-related ICH

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Definite CAA</th>
<th>Probable CAA with supporting pathology</th>
<th>Probable CAA</th>
<th>Possible CAA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full post-mortem examination demonstrating:</td>
<td>Full post-mortem examination demonstrating:</td>
<td>Clinical data and pathologic tissue</td>
<td>Clinical data and MRI or CT demonstrating:</td>
<td>Clinical data and MRI or CT demonstrating:</td>
</tr>
<tr>
<td>Lobar, cortical, or cortico-subcortical hemorrhage</td>
<td>Lobar, cortical, or cortico-subcortical hemorrhage</td>
<td>showing:</td>
<td>Multiple hemorrhages restricted to lobar, cortical, or cortico-subcortical regions (cerebellar hemorrhage allowed)</td>
<td>Single lobar, cortical, or cortico-subcortical hemorrhage</td>
</tr>
<tr>
<td>Severe CAA with vasculopathy</td>
<td>Severe CAA with vasculopathy</td>
<td></td>
<td>Age ≥ 55 y</td>
<td>Age ≥ 55 y</td>
</tr>
<tr>
<td>Absence of other diagnostic lesion</td>
<td>Absence of other diagnostic lesion</td>
<td></td>
<td>Absence of other cause of hemorrhage*</td>
<td>Absence of other cause of hemorrhage*</td>
</tr>
<tr>
<td>Probable CAA with supporting pathology</td>
<td>Probable CAA with supporting pathology</td>
<td>Probable CAA</td>
<td>Possible CAA</td>
<td></td>
</tr>
<tr>
<td>Clinical data and MRI or CT demonstrating:</td>
<td>Clinical data and MRI or CT demonstrating:</td>
<td>Possible CAA</td>
<td>Clinical data and MRI or CT demonstrating:</td>
<td>Possible CAA</td>
</tr>
<tr>
<td>Lobar, cortical, or cortico-subcortical hemorrhage</td>
<td>Lobar, cortical, or cortico-subcortical hemorrhage</td>
<td></td>
<td>Single lobar, cortical, or cortico-subcortical hemorrhage</td>
<td>Single lobar, cortical, or cortico-subcortical hemorrhage</td>
</tr>
<tr>
<td>Some degree of CAA in specimen</td>
<td>Some degree of CAA in specimen</td>
<td></td>
<td>Age ≥ 55 y</td>
<td>Age ≥ 55 y</td>
</tr>
<tr>
<td>Absence of other cause of hemorrhage*</td>
<td>Absence of other cause of hemorrhage*</td>
<td></td>
<td>Absence of other cause of hemorrhage*</td>
<td>Absence of other cause of hemorrhage*</td>
</tr>
</tbody>
</table>

*Other causes of hemorrhage may include antecedent head trauma or ischemic stroke, central nervous system tumor, warfarin excess with International Normalized Ratio greater than 3, vascular malformation, or vasculitis.

CAA—cerebral amyloid angiopathy; CT—computed tomography; ICH—intracerebral hemorrhage; MRI—magnetic resonance imaging.

(Knudsen et al., 2001; E. Smith & Greenberg, 2003)

1.1.6 Clinical presentations

Maia, Mackenzie, and Feldman (2007) and Charidimou et al. (2012) agree that the main clinical presentations of CAA are: 1) stroke, such as symptomatic ICH, ischemic infarctions, and subarachnoid hemorrhage, 2) cognitive impairment (CI) and dementia, and 3) transient focal neurological episodes (TFNE), such as transient ischemic attacks. Charidimou et al. (2012) include an additional presentation which they have referred to as rapidly progressive cognitive and neurological decline.
The most characteristic presentation of CAA, symptomatic ICH, is characterised by an acute stroke syndrome with focal neurological deficits that vary depending on the size and location of the hemorrhaging, but may include headaches, nausea, emesis, seizures, and changes in consciousness (Qureshi, Mendelow, & Hanley, 2009). Although these symptoms may be mild following an initial ICH, there is a high risk of recurrent ICH (Passero, Burgalassi, D'Andrea, & Battistini, 1995). Having a history of minor head trauma, thrombolysis, and use of oral anticoagulants are major risk factors for ICH occurrence (Charidimou et al., 2012). Cerebral ischemic infarctions, another form of stroke, may be due to endothelial-induced vessel stenosis/obstruction induced by reduced vasoreactivity (Greenberg, 2002) or thrombotic events in the lumen of leptomeninges (Kalaria, 2000).

Arvanitakis, Leurgans, Wang, et al. (2011) found impairments in the cognitive domains of perceptual speed and episodic memory in patients with CAA, contributing to evidence of CAA as a risk factor for alterations in cognition. Pfeifer, White, Ross, Petrovitch, and Launer (2002) also examined the relationship between CAA, dementia, and cognitive impairment. Although these authors did not find any association of cognitive impairment with either CAA or AD alone, they did find that AD patients with concomitant CAA demonstrated lower cognitive performance on neuropsychological tests. Data from the Neuropathology Group of the Medical Research Council Cognitive Function and Aging Study (2001) support the prominence of SVD in dementia. The study also found a remarkably high frequency of dementia-indicative neuropathological features in participants not diagnosed with dementia pre-mortem.

Greenberg, Vonsattel, Stakes, Gruber, and Finklestein (1993) state that the mechanisms behind TFNEs seem to involve focal seizures and that TFNEs may have been a risk factor for symptomatic ICH in some patients. The most common types of TFNE include paraesthesias,
partial motor seizure-like episodes, and visual disturbances. The episodes typically last less than 30 minutes (Greenberg et al., 1993).

According to Chung, Anderson, Hutchinson, Synek, and Barber (2011), rapidly progressive cognitive and neurological decline often present in patients with a rare, but profound inflammatory manifestation of CAA: cerebral amyloid angiitis. Cerebral amyloid angiitis is differentiated from CAA in that progressive multifocal leucoencephalopathy, neurosarcoidosis, immune-related conditions, and malignancies are typically present in cerebral amyloid angiitis (Chung et al., 2011). Cerebral amyloid angiitis can also relapse after the inflammation has been treated and clinical status has been correlated with vasogenic edema (Kinnecom et al., 2007). These authors also posit an immunological response relationship between APOE ε4 and vascular Aβ.

1.2 Alzheimer’s disease

Based on a systematic review and meta-analysis of existing literature on the incidence of Alzheimer’s disease conducted by Brookmeyer, Johnson, Ziegler-Graham, and Arrighi (2007), it is estimated that approximately 26.6 million people worldwide had Alzheimer’s disease at the time of publication. This number is expected to quadruple to 106.2 million by 2050. It is estimated that CAA pathology is present in approximately 83% of people with Alzheimer’s disease (Ellis et al., 1996). Its shared Aβ pathology and significant comorbidity with CAA makes cognitive impairment in AD an interesting comparison.

1.2.1 Pathogenesis

Vinters (1987) states that, similar to CAA pathology, AD pathology also involves deposition of Aβ. However, in AD, this deposition involves Aβ42, which forms extracellular plaques in the brain parenchyma, as opposed to Aβ40 in CAA which deposits onto the
vasculature (Biffi & Greenberg, 2011). Terry et al. (1991) assert that AD pathology also involves the development of neurofibrillary tangles as a result of tau hyperphosphorylation.

1.2.2 Cognitive impairment

Both amyloid plaques and neurofibrillary tangles have been associated with neuronal death (Terry et al., 1991). In their study of synaptic loss and cognitive impairment, Terry et al. (1991) found that axon terminal density in the midfrontal part of the neocortex, an area implicated in AD, has a strong positive correlation with global cognition test scores.

AD is the most common cause of dementia (Forstl & Kurz, 1999). Clinically, AD can be subdivided into amnestic and non-amnestic presentations, where amnestic AD dementia, the most common presentation, involves impairments in learning and recalling recently learned information and non-amnestic AD dementia is divided even further into language, visuospatial, and executive dysfunction presentations (McKhann et al., 2011). Although dementia is not necessarily a component of AD, clinical AD severity ranges among probable AD dementia, possible AD dementia, and probable or possible AD dementia with evidence of the AD pathophysiological process (McKhann et al., 2011). In their cross-sectional examination of cognitive impairment in controls, MCI, and mild AD, Carter, Caine, Burns, Herholz, and Lambon Ralph (2012) found that the first and most severely impaired domain among mild AD participants was episodic memory (Face Place Test (Dudas, Clague, Thompson, Graham, & Hodges, 2005); Story Recall task from the Wechsler Memory Scale—III (Wechsler, 1997); CVLT (Delis, Kaplan, & Ober, 1987); ROCFT recall (Meyers & Meyers, 1995)). This is followed by impairments in semantic memory and then attention/executive function and visuospatial function. Furthermore, participants with mild AD demonstrated significantly lower performance than controls on virtually all cognitive domains assessed as well as global
cognition. According to Forstl and Kurz (1999), AD is marked by progressive deficits that begin with information acquisition and memory and advance to affect logical reasoning, planning, organizing, and language. By the time the disease has progressed to the severe stage, cognition has been impaired almost globally. These cognitive impairments also manifest themselves functionally, affecting the patient’s ability to perform daily activities, such as housekeeping and banking.

1.3 Mild cognitive impairment

MCI refers to cognition that declines over time and is impaired beyond the normal range of a particular age and education group with functioning that is generally independent requiring only minimal assistance (Albert et al., 2011; American Psychiatric Association, 2013). The rate of cognitive decline seen in MCI is also much faster than the normal, age-related rate of cognitive decline (Bennett et al., 2002). Studies have found that having MCI increases the risk of developing AD by more than 3 times (Bennett et al., 2002) and increases the risk of dementia by 4 times (de Bruijn et al., 2014). Cognitive impairment in MCI, often involving Aβ42 pathology, provides a crucial comparator with cognitive impairment in CAA.

1.3.1 Pathogenesis

Although transition to AD is most common, MCI is a heterogeneous syndrome that may involve a number of different disease pathologies. Aβ plaques (particularly in amnestic MCI), neurofibrillary tangles, neuronal loss in the entorhinal cortex, synaptodegeneration of the hippocampus, changes in the acetylcholinergic system, as well as endosomal hyperactivation, are all characteristics that have been associated with MCI (Mufson et al., 2012). However, given the wide spectrum of underlying neuropathologies and lack of substantial evidence to determine
specific biomarkers of MCI (Mufson et al., 2012), it is most often clinically diagnosed using measures of cognitive impairment and daily functioning.

1.3.2 Cognitive impairment

Clinical criteria for this syndrome include subjective reports of changes in cognition from the clinician or the patient’s loved ones, lower performance on neuropsychological assessments of at least one cognitive domain, no or only mild functional impairments as a result of impaired cognition, and no dementia. Impairments in episodic memory (amnestic MCI) are most common and often present in patients who progress to AD dementia (Albert et al., 2011), whereas, impairments in other cognitive domains (non-amnestic MCI) are less common (Johnson et al., 2010) and prognosis more often than not involves other dementias, including vascular dementia (R. Roberts & Knopman, 2013). Similar to presentations of AD, a subset of MCI participants display impairments in multiple cognitive domains (Johnson et al., 2010). These multiple-domain MCI form a large proportion of the whole—52% according to Alladi, Arnold, Mitchell, and Nestor (2006)—and are distinguished in the literature from ‘pure’ or single-domain MCI. An additional presentation of MCI that is characterized by participant- and informant-supported complaints of cognitive impairment, but no objective evidence of such impairment, is referred to as subjective MCI (Saunders & Summers, 2010). These authors also purport that subjective MCI participants demonstrate age-adjusted performance below the 10th percentile on at least one test of attention or working memory. A guideline for neuropsychology test performance that is indicative of MCI in patients are scores between 1 and 1.5 standard deviations (SD) below the mean of their age- and education-matched peers (Albert et al., 2011).

Zhou and Jia (2009) assert that both verbal memory (World Health Organization—University of California-Los Angeles Auditory Verbal Learning Test; Maj et al., 1994) and
visual memory (modified ROCFT; Osterrieth, 1944) are greatly impaired in MCI. Executive function is also affected to a lesser extent (performance on the Stroop test—part C and Semantic Category Verbal Fluency test—animal (Lezak, 1995) was significantly impaired; performance on the WAIS—RC Picture Arrangement (Dai, Ryan, Paolo, & Harrington, 1990), similarities California Card Sorting Test (Delis, Kaplan, & Kramer, 2000), and DS—backward (Dai et al., 1990) was not significantly impaired).

Although impairments in memory are a widely-recognized feature of MCI, attention, an important precursor to memory, has also been shown to be impaired in MCI. In their examination of subjective and amnestic presentations of MCI, Saunders and Summers (2010) found that 83% of amnestic MCI participants were impaired in at least one test of either attention or working memory, although they showed no impairment in either of these cognitive domains on the Dementia Rating Scale: Second Edition (Griffiths, Sherman, & Strauss, 2011). Impairments in working memory, although greater in multiple-domain MCI (Facal, Juncos-Rabadan, Pereiro, & Lojo-Seoane, 2014; Klekociuk & Summers, 2014) due to its dependence on executive function, may also be present in single-domain amnestic MCI (Guild et al., 2014). Non-memory cognitive deficits, particularly in executive functioning, language, and visuospatial skills domains, are predominant in non-amnestic MCI (R. Roberts & Knopman, 2013).

1.4 Minor ischemic stroke

Stroke was responsible for over 16% of deaths in the United States in 2011 (Mozaffarian et al., 2015). According to Fang, Coca Perraillon, Ghosh, Cutler, and Rosen (2014), 87% of strokes occurring between 1988 and 2008 were ischemic. Its shared vascular pathology and resultant cognitive impairment makes MIS an important comparison group for the investigation of cognitive impairment in CAA.
1.4.1 Pathogenesis

According to Sacco et al. (2013), an ischemic stroke occurs when an artery in the cerebrum, spine, or retina becomes stenosed or occluded and interrupts perfusion, resulting in localized cell death. The National Institutes of Health Stroke Scale (NIHSS; Brott et al., 1989) is a rating scale of the type and severity of symptoms present after a stroke event. The symptoms include level of consciousness, best gaze, visual, facial palsy, motor arm, motor leg, limb ataxia, sensory, best language, dysarthria, and extinction and inattention. They are each rated based on the severity of each symptom, with 0 indicating the absence of a symptom. MIS—as opposed to moderate, moderate to severe, or severe ischemic stroke—is determined by a total score of 0-3 out of a possible score of 42.

1.4.2 Cognitive impairment

Vascular dementia is the second most prevalent dementia in Western countries after Alzheimer’s disease, accounting for approximately 20% of all diagnoses. It is symptomatic of a heterogeneous range of dementia pathologies that are vascular in origin, including ischemia, hemorrhage, anoxia, and hypoxia (Rizzi, Rosset, & Roriz-Cruz, 2014).

The existing literature support a neuropsychological profile of impairments in executive function and psychomotor function in vascular cognitive impairment (VCI). In their examination of VCI in participants with a history of stroke and transient ischemic attack (TIA), Sachdev et al. (2004) also found impairments in both executive function (Color Form Sorting Text (Weigl, 1941), TMT—B, COWAT—FAS, COWAT—Animals) and psychomotor function (TMT—A, Symbol Digit Modalities Test (A. Smith, 1991)). Hurford, Charidimou, Fox, Cipolotti, and Werring (2013) support this in their study of acute ischemic stroke patients of whom, when assessed < 1 month after an event, 72% experienced impairments in speed and attention and 34%
of patients experienced impairments in frontal executive function. Nominal skills, perceptual skills, visual memory, and verbal memory were each impaired in ≤ 30% of patients.

(Sudo et al., 2013) assert that impaired global cognition and fronto-executive function in the presence of periventricular and deep WMH is apparent in probable vascular MCI. Their analyses revealed lower scores in comparison to normal controls on the Cambridge Cognition Examination (Roth et al., 1986), TMT—A, and TMT—B. When controlled for age, the Cambridge Cognition Examination, TMT—A, and TMT—B, also had strong positive correlations with scores on Fazekas scale for white matter lesions (Fazekas, Chawluk, Alavi, Hurtig, & Zimmerman, 1987). Furthermore, Duering et al. (2013) support the theory that a brain network of white matter tracts contribute to impaired processing speed in VCI.

1.5 Research objectives and hypotheses

The objectives of this research are to: 1) identify a neuropsychological profile of CAA that is distinct from the neuropsychological profile of the normal population, 2) determine whether CAA participants are more cognitively similar to AD, MCI, or MIS participants, 3) establish whether the differences in neuropsychological test scores among CAA participants can be attributed to any particular presentation of CAA, and 4) establish whether the differences in neuropsychological test scores between CAA and its comparison groups are mediated by differences in WMH volumes or APOE genotype. Based on the previous literature, my hypotheses are that: 1) CAA participants will perform worse than the normative population on tests of episodic memory, executive functioning, and perceptual speed, 2) CAA participants presenting with ICH will score lower on these tests than CAA participants not presenting with ICH, 3) similar to participants with VCI from MIS, executive functioning will be the most prominent deficit CAA participants (if the null hypothesis is not rejected, then a secondary
hypothesis will be tested that episodic memory will be the most prominent deficit similar to participants with AD and MCI, 4) participants with larger WMH volumes will exhibit more impairment in executive functioning and perceptual speed than participants with smaller WMH volumes, and 5) participants with APOE genotype ε4 will exhibit more impairment in verbal learning and memory and visuospatial construction and memory than participants without APOE ε4. Neuropsychological assessments will assist in identifying which cognitive domains are most prevalently and most severely impaired in CAA patients.
CHAPTER 2: METHODS

2.1 Significant contributions

The data analysed in the present study were derived from three parent studies: the Functional Assessment of Vascular Reactivity in Small Vessel Disease (FAVR) Study, the Brain Imaging and Neuropsychological Assessment of Cognitive Impairment (Brain-IMPACT) Study, and the Computed Tomography and MRI in the Triage of Transient Ischemic Attack and Minor Cerebrovascular Events to Identify High Risk Patients—Extended (CATCH) Study. The successful planning and execution of these studies is attributed to 3 multifaceted teams of research assistants, project managers, graduate students, and postdoctoral fellows under the direction of Drs. Eric Smith, Jennifer Chan, and Shelagh Coutts.

The FAVR and Brain-IMPACT studies were designed by Dr. Eric Smith. MRI protocols were designed by Dr. Cheryl McCreary. WMH volumes were measured by Dr. Saima Batool and Ikreet Cheema. Blood serum was assessed by Dr. Jennifer Chan’s research team to determine participants’ APOE genotypes. Neuropsychological assessments were conducted and scored by research assistants, Aaron Peterson, Angela Zwiers, and Ramnik Sekhon. I had the opportunity to observe some of these assessments and have also become familiar with their preparation and scoring. I also interviewed participants’ informants regarding the Lawton Instrumental Activities of Daily Living Scale (IADLS; Lawton & Brody, 1969), an assessment of participants’ daily functioning. I converted raw neuropsychological test scores into standardized z-scores, culminating in neuropsychological reports reflective of each individual visit. I also created and maintained a database of these raw and z-scores. Under the supervision of Dr. Smith, I designed the objectives, hypotheses, and statistical analyses of the present study.
Dr. Shelagh Coutts designed the CATCH study and provided demographical, neuropsychological, and WMH volume data on the MIS patients assessed in the study.

2.2 Sources of study participants

CAA, AD, and MCI data were obtained from participants enrolled in FAVR study. This study has two phases: FAVR-I and FAVR-II. FAVR-I was approved for participant recruitment from 2010 to 2012. Participants were seen for a baseline assessment and 1-year follow-up assessment. They comprised of 21 CAA patients, 6 cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) patients, and 32 controls. As an amendment of this first phase, FAVR-II expanded to include AD and MCI patients while discontinuing assessment of CADASIL patients. FAVR-II was approved in 2012 indefinitely as a prospective longitudinal cohort study. Thirty-seven FAVR-I patients (13 CAA, 24 controls) were subsequently enrolled in FAVR-II and continued to receive annual assessments. Recruitment for FAVR-II is still ongoing and, as of March 10, 2015, there were 43 CAA, 14 AD, 28 MCI, and 32 control participants enrolled in the study, including those from FAVR-I.

Additional MCI participants were included from Brain-IMPACT study between 2011 and 2013. Brain-IMPACT is a prospective longitudinal cohort study examining neuroimaging markers and their association with neuropsychological test performance in patients with both hypertension and MCI. Participants responded to advertisements in the community regarding memory loss. Participants were assessed at baseline and followed for two annual follow-up assessments. Data from 60 participants were available from this study.

The CATCH study allowed for the collection of data from 27 MIS patients between 2009 and 2012. This prospective, observational study was aimed at the examination of cognition and
use of computer tomography and computer tomography angiography in predicting disability and recurrent stroke at 90 days in MIS and transient ischemic attack patients (Coutts et al., 2012).

All participants from each of the studies received similar assessments that were deemed comparable for analyses of neuropsychological test scores, neuroimaging factors, and demographics. As summarized in Table 3, in accordance with FAVR criteria, participants were included in the CAA group if they had a diagnosis of probable CAA according to the Boston Criteria (Knudsen et al., 2001; E. Smith & Greenberg, 2003). Patients who scored $\leq 23$ on the Mini Mental State Examination (MMSE; M. F. Folstein, Folstein, & McHugh, 1975) were excluded. Participants with a history of stroke were studied at 90 days after onset. Both the MCI and AD groups consisted of participants diagnosed with AD MCI or AD dementia, respectively, according to the National Institute on Aging clinical criteria (Albert et al., 2011; McKhann et al., 2011). Participants in these groups were required to be $\geq 60$-years-old, score $> 20$ on the MMSE, and have no history of stroke. CATCH participants included in the MIS group had a NIHSS score of 0-3 with acute infarct on diffusion weighted MRI imaging, were $\geq 60$ years of age, and had no history of dementia.

Although a total of 43 CAA, 14 AD, 88 MCI, 27 MIS, and 32 control participants were recruited between the three studies, 60 participants were excluded from the present study. The inclusion/exclusion criteria are presented in Table 3. CATCH participants were only included if they were $\geq 55$ years of age. Two MCI participants from FAVR and 17 MCI participants from Brain-IMPACT were retrospectively given diagnoses of subjective cognitive concerns and excluded from the present study based on obtaining scores that were not reflective of cognitive impairment on neuropsychological tests (i.e. not $\leq 1$ SD below normative values). Eight CAA participants were excluded either for scoring $< 23$ on the MMSE, indicating potential difficulty
in the completion of neuropsychological testing, or for the presence of dementia. One CAA participant was excluded due to having asymptomatic familial CAA. Due to the small sample sizes in this study, published normative values based on population studies were used in lieu of the 32 control participants. This resulted in a final sample consisting of 34 CAA, 16 AD, 69 MCI, and 27 MIS participants.

Within this final sample, 1 MIS participant was missing a datum for years of education and 1 CAA participant was missing an ethnicity datum. Data on the MMSE, ethnicity, Lawton IADLS, Geriatric Depression Scale (GDS; Sheikh & Yesavage, 1986) short form, and APOE genotype were not collected in the CATCH study. The NIHSS was not used for participants in either the AD or MCI groups in FAVR or in the Brain-IMPACT study. One AD, 3 MCI, and 2 CAA participants were missing data on WMH volumes due to claustrophobia and 2 AD, 5 MCI, and 5 CAA participants were missing APOE genotype data, for which either blood samples were not drawn or the results were uninterpretable. These missing APOE genotype data will be obtained and analysed after the writing of this thesis. One CAA participant terminated the TMT—B prematurely, another CAA participant terminated the CVLT—DR prematurely, and 1 AD participant refused to attempt the DSST. Testing of the ROCFT—DR did not include two AD participants and 1 CAA participant who refused the task, 1 CAA and 1 MCI participant who did not attempt the task for an unknown reason, and 1 MCI participant who terminated the ROCFT—DR prematurely.
<table>
<thead>
<tr>
<th></th>
<th>CAA</th>
<th>FAVR AD</th>
<th>MCI</th>
<th>Brain-IMPACT MCI</th>
<th>CATCH MIS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recruitment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stroke unit or dementia clinic</td>
<td>Cognitive neuroscience clinic</td>
<td>Cognitive neuroscience clinic; community</td>
<td>Local print advertisements and doctor’s offices</td>
<td>Emergency department or stroke prevention clinic</td>
</tr>
<tr>
<td><strong>Inclusion</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Probable CAA, as per revised Boston Criteria</td>
<td>NIA clinical criteria for AD dementia</td>
<td>NIA clinical criteria for AD MCI</td>
<td>NIA clinical criteria for AD MCI; hypertension</td>
<td></td>
</tr>
<tr>
<td>NIHSS score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical Dementia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rating† score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>—</td>
<td>0.5 or 1.0</td>
<td>—</td>
<td>0.5</td>
<td>&lt; 4</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Patient-reported history of hypertension or use of anti-hypertensive medications</td>
</tr>
<tr>
<td>Time of assessment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt; 90 days after stroke or TFNE onset</td>
<td>—</td>
<td>—</td>
<td>90 days after event</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥ 55</td>
<td>≥ 60</td>
<td>≥ 60</td>
<td>≥ 65</td>
<td>≥ 18</td>
</tr>
<tr>
<td>Housing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Community-dwelling</td>
<td>Community-dwelling</td>
<td>Community-dwelling</td>
<td>Community-dwelling</td>
<td></td>
</tr>
<tr>
<td>Activities of daily living</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No impairment</td>
<td>No impairment</td>
<td>No impairment</td>
<td>No impairment</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acute infarct on diffusion weighted imaging</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Exclusion</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Moderate to severe dementia</td>
<td>Stroke</td>
<td>Stroke</td>
<td>Diabetes mellitus requiring insulin</td>
<td>Dementia</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>-----------------------------</td>
<td>--------</td>
<td>--------</td>
<td>-------------------------------------</td>
<td>----------</td>
</tr>
<tr>
<td>MMSE raw score</td>
<td>≤ 23</td>
<td>≤ 20</td>
<td>≤ 20</td>
<td>Non-English speaker</td>
<td>—</td>
</tr>
<tr>
<td>Language</td>
<td>Non-English speaker</td>
<td>Non-English speaker</td>
<td>Lobar-only microbleeds suggesting asymptomatic unrecognized CAA</td>
<td>Non-English native speaker</td>
<td>Lobar-only microbleeds suggesting asymptomatic unrecognized CAA</td>
</tr>
<tr>
<td>MRI</td>
<td></td>
<td></td>
<td></td>
<td>Same as CAA group</td>
<td>Same as CAA group</td>
</tr>
<tr>
<td>Other conditions</td>
<td>MRI contraindications; secondary cause of cognitive impairment; neurological diseases of the white matter; other neurological or psychiatric diseases; comorbid medical conditions that may interfere with study</td>
<td>Same as CAA group</td>
<td>Same as CAA group</td>
<td>Same as CAA group</td>
<td>MRI contraindications; thrombolysis; pre-morbid Modified Rankin† score of ≥ 2; serious comorbid illness with life expectancy estimated at &lt; 3 months; inability to do obstructive sleep apnea testing</td>
</tr>
</tbody>
</table>

FAVR = Functional Assessment of Vascular Reactivity in Small Vessel Disease Study; Brain-IMPACT = Brain Imaging and Neuropsychological Assessment of Cognitive Impairment Study; CATCH = Computed Tomography and MRI in the Triage of Transient Ischemic Attack and Minor Cerebrovascular Events to Identify High Risk Patients—Extended Study; CAA = cerebral amyloid angiopathy; AD = Alzheimer’s disease; MCI = mild cognitive impairment; MIS = minor ischemic stroke; NIA = National Institute on Aging; NIHSS = National Institutes of Health Stroke Scale; TFNE = transient focal neurological episode.

† (Morris, 1993)
†† (Rankin, 1957)
2.3 Assessment

Each baseline assessment consisted of a clinical evaluation, venous blood draw, the 90-minute neuropsychological test battery proposed by the National Institute for Neurological Diseases and Stroke—Canadian Stroke Network (Hachinski et al., 2006), and a structural MRI scan. Additionally, an informant of each participant was interviewed using either the Lawton IADLS (FAVR) or the modified Lawton IADLS (Brain-IMPACT; Cummings et al., 2002). These scales assess functional ability in several key areas: ability to use a telephone, shopping, food preparation, housekeeping, laundry (only assessed by the Lawton IADLS), transportation, taking medications, and handling finances. In the Lawton IADLS, participants receive a score of 1 on an item if he/she is able to independently complete the task described and a score of 0 if the participant requires assistance to complete the task. The modified Lawton IADLS assigns scores of “independent,” “assistance required,” and “dependent,” accordingly. Annual follow-up assessments (ongoing in both FAVR and Brain-IMPACT) consist of repeat clinical evaluations and neuropsychological testing, as well as a repeat MRI at 1-year follow-up in FAVR.

2.3.1 Neuropsychological Assessment

Each participant in the FAVR, Brain-IMPACT, and CATCH underwent a comprehensive neuropsychological assessment which covered the following 5 cognitive domains: attention, language, executive function, visuospatial construction and memory, and verbal learning and memory.

The following 8 assessments were administered:
1. Mini Mental State Examination (MMSE)
2. Trail Making Test (Parts A and B; TMT)(Reitan, 1986)
4. Boston Naming Test (FAVR used the 15-item Short Form (BNT-15); Brain-IMPACT used the 30-item Half Form (BNT-30)) (Fastenau, Denburg, & Mauer, 1998; Kaplan et al., 1983; Mack, Freed, Williams, & Henderson, 1992)
6. Digit Symbol-Coding subtest (DSST) of the WAIS-IV (Wechsler, 2008)
7. Rey-Osterrieth Complex Figure (copy, immediate, and delayed; ROCFT) (Meyers & Meyers, 1995) / Modified Taylor Complex Figure (copy, immediate, and delayed; MTCF) (Hubley, 1996)

2.3.1.1 Mini Mental State Examination (MMSE)

In their compendium of neuropsychological tests, Strauss, Sherman, and Spreen (2006) describe the MMSE as a brief and easy-to-administer test used for the screening of cognitive impairment and tracking of temporal cognitive changes. The norms (Crum, Anthony, Bassett, & Folstein, 1993) are based on data collected in 1980-1984 from 18,056 participants in five metropolitan areas of the United States: New Haven, CT; Baltimore, MD; St. Louis, MO; Durham, NC; and Los Angeles, CA. Although it is primarily used in geriatric populations, the MMSE has been validated for administration to individuals age 18-85+ years. The individual items assess orientation to time and place, attention and calculation (serial 7s, spell “world” backward), language (naming, repetition, comprehension, reading, writing, copying), and immediate and delayed recall (three words, copy image of overlapping pentagons). However, the MMSE lacks specific items for the assessment of frontal and executive function (M. Folstein, 1998). Advancement in age, a lower intelligence quotient (IQ)/education level, non-White ethnicity, and lower social class are associated with poorer performance on the MMSE. Gender and impending mortality have only small effects (Strauss et al., 2006).
2.3.1.2 Trail Making Test (TMT)

According to Strauss et al. (2006), the Adult Version of the TMT contains two parts: A and B. Both parts assess perceptual tracking of a sequence and speeded performance, with Part B additionally assessing divided attention. The TMT has been validated for use in individuals between the ages of 15 and 89 years. The participant is presented with 25 circles containing numbers (Part A) and 25 circles alternating numbers and letters (Part B) which must be connected by drawing pencil lines. Part B additionally includes a time limit of 300 seconds (5 minutes). Participants who are unable to complete are assigned the maximum time value. Six hundred eighty community-dwelling individuals from across Canada comprised the normative sample (Tombaugh, 2004). Participants were between 18 and 89 years of age and had 5-25 years of education. TMT performance was found to decline with increasing age due to increasingly slower completion times (Tombaugh, 2004). Performance is also lower among individuals who have a lower number of years of education, lower IQ, and are Chinese-English bilinguals (as opposed to English monolinguals). Both participant ethnicity and examiner ethnicity may also impact performance. Gender is of little impact (Strauss et al., 2006).

2.3.1.3 Digit Span (DS) subtest of the WAIS-IV

In the WAIS-IV Canadian manual, Wechsler (2008) describe the DS as a core assessment of working memory. The DS comprises of three task components, however, for the purposes of this study, only the first two tasks are used: DS Forward and DS Backward. During DS Forward task, the test administrator reads a sequence of numbers aloud. The participant must then repeat the numbers in the same sequence. DS Backward follows a similar pattern, except the participant is instructed to repeat the numbers in reverse order. Each task in the DS is composed of 8 items which gradually increase in sequence length and each item consists of two trials. Administration
of the DS is discontinued when the participant provides incorrect responses for both trials in an item. Scoring of the DS is based on the summation of the total number of correct trials in each task. Normative data were collected from 688 participants aged 16-90 years from throughout Canada. The ethnic proportions were reflective of their respective age groups within the Canadian population and over 80% of the participants had obtained a high school diploma or higher (Wechsler, 2008).

2.3.1.4 Boston Naming Test (BNT)

Fastenau et al. (1998) describe the original 60-item BNT (Kaplan et al., 1983) as a measure of confrontational naming that is particularly sensitive to early cognitive impairment in Alzheimer’s disease. Based on this, Mack et al. (1992) developed 4 short forms of the BNT that are each composed of 15 of the 60 original items. In the FAVR study, participants are administered Short Form 4 at baseline assessments, Short Form 2 at one-year follow-up assessments, Short Form 3 at two-year follow-up assessments, and Short Form 4 at third- and fourth-year follow-up assessments. Patients enrolled in Extended CATCH received Short Form 4 at all assessments. Odd-numbered items from the original 60-item form are administered to Brain-IMPACT patients. Administration of the BNT involves presenting the participant with a stimulus which must be named. These stimuli consist of line drawings of different objects that advance in difficulty from high-frequency words (i.e., tree) to low-frequency words (i.e., protractor). Norms (Fastenau et al., 1998) were based on participants aged 40-85 years who were recruited from a large Midwestern city and a metropolitan area on the West coast of the United States. Ninety-five percent were Caucasian and 97% had a Grade 12 education or higher. With language being a key component of this test, it has been recommended that the norms used for monolingual English-speakers not be used as a means of comparison with bilingual English-
speakers, whose scores on the BNT are substantially lower than the scores of monolingual English-speakers (P. M. Roberts, Garcia, Desrochers, & Hernandez, 2002). Fastenau et al. (1998) found an effect for age in each of the short forms used for this study, but none for education or gender.

2.3.1.5 Controlled Oral Word Association Test (COWAT)

Strauss et al. (2006) assert that the COWAT is a test of verbal fluency that assesses an individual’s ability to produce words that fit within a given category. The test has two parts: FAS, an assessment of phonemic fluency and; Animals, an assessment of semantic fluency. During FAS, the participant is instructed to list as many words as possible that begin with the letter ‘F’ within a time span of 1 minute. Words beginning with ‘A’ and ‘S’ are subsequently elicited. The Animals part requires the participant to list as many animals as possible, also within a time span of 1 minute. The norms used for this study (Tombaugh, Kozak, & Rees, 1999) were derived from the data of 1,300 community-dwelling participants Canada-wide. The participants were aged 16-95 and had up to 21 years of education. Lower scores for both parts of the COWAT are associated with old age, lower education (Tombaugh et al., 1999), lower reading level (Johnson-Selfridge, Zalewski, & Aboudarham, 1998), IQ (Diaz-Asper, Schretlen, & Pearlson, 2004), and African American and Hispanic ethnicity. Bilingual English-speakers perform more poorly on semantic fluency than their monolingual English-speaking counterparts (Rosselli et al., 2002). No notable gender differences have been found.

2.3.1.6 Digit Symbol-coding subtest (DSST) of the WAIS-IV

According to the WAIS-IV Canadian manual (Wechsler, 2008), the DSST has been developed as an assessment of processing speed. The participant is provided with a sheet of paper upon which the numbers 1-9 are repeated multiple times in random order so that there are
a total of 135 items; each with a space below it. A key that pairs each number with an abstract symbol is also provided. The participant is instructed to copy each symbol that corresponds with the appropriate number into the space provided. The trials must be done in consecutive order and any trials which deviate are not scored. Nine initial trials, which are not included in the total score, are provided for demonstration and practice purposes. Scoring is done using an answer key template and credit is given for all consecutively drawn symbols that are high in accuracy. Test-retest stability coefficients were used as measures of reliability for the DSST and, in adults aged 55- to 90-years-old, were reasonably high (0.86-0.89). When compared to other processing speed subtests of the WAIS-IV for validity, the DSST had a low correlation with persons aged 16- to 69-years-old on the Cancellation subtest \((r=0.29)\) and a moderate correlation with persons aged 16- to 90-years-old on the Symbol Search subtest \((r=0.58)\). Normative data were the same as collected for the WAIS-IV DS (Wechsler, 2008).

### 2.3.1.7 Rey-Osterrieth Complex Figure (ROCFT)/Modified Taylor Complex Figure (MTCF)

Strauss et al. (2006) describe the ROCFT and the MTCF as comprising of three components wherein the participant is instructed to: 1) draw a copy of a complex figure as an assessment of visuospatial constructional ability, 2) immediately recall and draw the original image as an assessment of visual memory, and 3) recall and draw the original image after a delay of approximately 20 minutes, during which other, non-visual tests are conducted (also an assessment of visual memory). The ROCFT and MTCF also test a multitude of other cognitive areas, such as planning; organizational skills; problem-solving strategies; and perceptual, motor, and episodic memory. The ROCFT is validated for use in ages 6-93 years and is used as the standard version, while the MTCF is used as the alternate version. Total administration time is about 10-15 minutes (excluding the delay). The same criteria are used to score all 3 components.
The norms (Fastenau, Denburg, & Hufford, 1999) were based on a sample of 211 community-dwelling participants from two Midwestern communities and a West coast metropolitan area. The participants, over 95% of which were Caucasian, ranged in age from 30 to 85 years and ranged in education from 12 years to 25 years. As age progresses, there tends to be a decline in scores, which is often due to omission of parts of the images and low retention (less than 40%) of the images, rather than poor quality of the images drawn. There is also an increase in variability on the copy component since drawings become messy. It is unclear whether this is due to visuospatial or motor impairments. Minority status and increases in IQ and education are correlated with modest increases in ROCFT scores.

2.3.1.8 California Verbal Learning Test: Second Edition (CVLT-II)

According to Strauss et al. (2006), the CVLT-II is used as a test of verbal learning and memory, popular for its ability to establish distinct profiles that allow differentiation between different disorders. It consists of immediate and delayed recall of word lists which include both free and cued recall. These are followed by semantic category recall, forced-choice recognition, and yes/no recognition components. Westerberg et al. (2006) differentiate between the two recognition subtests by describing the function of the forced-choice subtest as reflective of familiarity, while the yes-no subtest is sensitive to recollection. Furthermore, their data suggest that AD participants experience more impairment in recollection than in familiarity. In their study of amnestic MCI, McLaughlin et al. (2014) found that participants with amnestic MCI or AD were distinguished from controls and participants with non-amnestic MCI by the former’s attenuated performance on semantic clustering. The ability to use semantic clustering strategies is dependent on the integrity of associations within semantic networks. Although both amnestic MCI and AD participants in this study displayed worse performance on recall tasks, AD
participants were more impaired than amnestic MCI participants, indicating a higher emphasis on information acquisition and consolidation within AD. Administration of the CVLT takes approximately 50 minutes. It is validated for use in individuals age 16 to 89 years. The norms used for the purposes of this study (Paolo, Troster, & Ryan, 1997) were based on data obtained from 212 elderly participants in the United States Midwest. Performance declines with advancement in age, male gender, lower education and IQ. Ethnicity has little effect (Strauss et al., 2006).

2.3.2 MRI Assessment

MRI’s sensitivity to differences in proton density and versatility of contrast manipulation (i.e., T2-weighted FLAIR) make it well suited for the detection of anatomical and vascular changes found in cognitive impairment and dementia due to differences in water content (Ontario, 2014). High water content in the periventricular spaces is not an exclusive indication of vascular dysfunction and has additionally been associated with a number of other pathologies, including blood-brain barrier dysfunction, altered autoregulation of cerebral blood flow, and inflammation (Gouw et al., 2011; Wardlaw et al., 2013; Zhong, Utriainen, Wang, Kang, & Haacke, 2014). However, when considered in combination with demographic and neuropsychological evaluation data, these brain abnormalities can be attributed to WMH of presumed vascular origin (Wardlaw et al., 2013).

The use of MRI is also preferred over other neuroimaging methods due to its non-ionizing radiation and flexibility of using different sequences to assess other qualities of the brain, such as blood perfusion, blood permeability, and functional activation. The safety and feasibility constraints of MRI limit it to use in participants without any contraindications to MRI.
MRI was conducted in the Seaman Family MR Research Centre using 3.0T General Electric whole-body scanners, the parameters for which are outlined in Table 4. T₂-weighted FLAIR sequence images were acquired as recommended by Wardlaw et al. (2013) for detection of WMH volumes. Other MRI sequences assessed brain structure, brain chemical composition, water proton diffusion, and blood flow.

MRI WMH volumes were measured using Quantomo software (Cybertrials, Inc., Calgary, Canada), a custom-designed application. The acquired fluid-attenuated inversion recovery (FLAIR) images underwent preprocessing with a 3D bilateral noise filter and a parametric bias field correction filter. Automated lesion boundaries with the capacity for manual correction were determined by manually-positioned seeds. WMH was defined in accordance with the recommendations provided by a consensus group (Wardlaw et al., 2013). This consensus group also recommends that WMH should be analysed in relationship to brain volume or intracranial volume, to account for differences in head and brain size across persons. However, in this study, this was not possible to do because the FAVR, Brain-IMPACT, and CATCH studies did not include comparable information on either brain volume or intracranial volume. Therefore, in this study, WMH volume was analysed as simple, non-normalized volume, controlling for sex (which is a major determinant of head size) in the fully adjusted models.

<table>
<thead>
<tr>
<th>MRI model</th>
<th>FAVR GE Signa VHi 3.0T scanner (General Electric Healthcare, Waukesha, WI)/GE Discovery MR750 3.0T scanner (General Electric Healthcare, Waukesha, WI)</th>
<th>Brain-IMPACT GE Discovery MR750 3.0T scanner (General Electric Healthcare, Waukesha, WI)</th>
<th>CATCH GE Signa VHi 3.0T scanner (General Electric Healthcare, Waukesha, WI)</th>
</tr>
</thead>
</table>

Table 4. MRI parameters.
<table>
<thead>
<tr>
<th>Sequence</th>
<th>FLAIR</th>
<th>CUBE FLAIR</th>
<th>FLAIR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repetition time</td>
<td>9000ms</td>
<td>5000ms</td>
<td>9000ms</td>
</tr>
<tr>
<td>Echo time</td>
<td>140ms</td>
<td>100ms</td>
<td>146-160ms</td>
</tr>
<tr>
<td>Inversion time</td>
<td>2250ms</td>
<td>1684ms</td>
<td>2250ms</td>
</tr>
<tr>
<td>Acquisition matrix</td>
<td>256 X 256</td>
<td>256 X 256</td>
<td>256 X 192</td>
</tr>
<tr>
<td>Field of view</td>
<td>240mm</td>
<td>240mm</td>
<td>240mm</td>
</tr>
<tr>
<td>Slice thickness</td>
<td>3.0-3.5mm</td>
<td>2mm</td>
<td>3.5mm</td>
</tr>
<tr>
<td>Pixel size</td>
<td>0.9375 X 0.9375</td>
<td>0.4688 X 0.4688 X</td>
<td>0.9375 X 0.9375</td>
</tr>
<tr>
<td>(actual pixel size)</td>
<td></td>
<td>1.0 (reconstructed voxel size)</td>
<td></td>
</tr>
</tbody>
</table>

FAVR = Functional Assessment of Vascular Reactivity in Small Vessel Disease; Brain-IMPACT = Brain Imaging and Neuropsychological Assessment of Cognitive Impairment; CATCH = Computed Tomography and MRI in the Triage of Transient Ischemic Attack and Minor Cerebrovascular Events to Identify High Risk Patients—Extended; MRI = magnetic resonance imaging; FLAIR = fluid-attenuated inversion recovery.

2.3.3 Genotyping

Blood draws were conducted on all participants and buffy coats were processed in the laboratory of Dr. Jennifer Chan to determine APOE genotype, using the restriction fragment length polymorphism (RFLP) method. RFLP was performed by polymerase chain reaction (PCR) amplification of the APOE single nucleotide polymorphism-containing deoxyribonucleic acid (DNA) region followed by HhaI digest of the PCR product to generate allele-discriminating DNA fragments. This protocol was initially described by (Hixson & Vernier, 1990).

2.4 Statistical analyses

2.4.1 Descriptions of relevant statistical tests

The one-sample t-test (Student, 1908), assuming a normal distribution, is used to compare the mean of one variable to a constant or hypothesised value (Walker, 1997). The independent t-test (Student, 1908) is differentiated in that it compares the means of two samples while maintaining assumptions that the data are independent, of equal variance, and normally
distributed. The Wilcoxon rank-sum test (Wilcoxon, 1945), the non-parametric counterpart of the independent t-test, compares two groups based on the mean rank of their individual data points (Rosner, 2000). Although more powerful when used to test continuously distributed data, the Wilcoxon rank-sum can also be used to test discrete distributions (McNeil, 1967). The chi-square test (Pearson, 1900) is generally used for the comparison of two discrete variables, although it can be manipulated to accommodate more than two variables. It follows the assumption that the data are normally distributed (Walker, 1997). Fisher’s exact test is used to compare two groups on two discrete variables in which the data are not normally distributed (Rosner, 2000).

The analysis of variance (ANOVA) was developed by Sir Ronald Fisher as a means of determining the ratio of two variance estimates (Lomax & Hahs-Vaughn, 2012). As opposed to the t-test which is limited to the comparison of two samples, the ANOVA is an omnibus test capable of comparison between an independent variable with two or more levels and an interval dependent variable. ANOVA assumes independence, homogeneity of variance, and normality of the data (Lomax & Hahs-Vaughn, 2012). The Kruskal-Wallis test (Kruskal & Wallis, 1952) is useful for instances in which the ANOVA’s assumption of normality is not met or the dependent variable is ordinal. In these situations, the Kruskal-Wallis is a more powerful test than the ANOVA. It compares groups based on ranked order (Lomax & Hahs-Vaughn, 2012).

The Dunnett post-hoc test (Dunnett, 1955) is used for the purpose of conducting pairwise contrasts between a chosen reference group and all remaining groups. This tests assumes equal variances between the reference group and the comparison groups (Lomax & Hahs-Vaughn, 2012). Hsu’s multiple comparisons adjustment is the best test used when the reference group is undetermined (Hsu, 1996).
The Pearson correlation (Pearson, 1895; Stigler, 1989) is useful for determining theassociation between two continuous variables regardless of their dependent and independentvariable assignment. It assumes the data to be normally distributed (Rosner, 2000). TheSpearman rank-sum correlation (Spearman, 1904) is the non-parametric counterpart of thePearson correlation and is best used when at least one of the variables is without a normaldistribution or at least one of the variables is ordinal (Rosner, 2000).

2.4.2 Statistical analyses and power calculations

Since functional impairment was assessed using either the Lawton IADLS or themodified Lawton IADLS, Lawton IADLS scores were converted to modified Lawton IADLSscores for statistical comparison.

Only certain neuropsychological tests were chosen for the primary analysis as opposed toanalysing all of the tests administered. This was done to limit the number of statisticalcomparisons in order to reduce the likelihood of Type I error (that is, false positive findings) due tous multiple hypothesis testing. We used published literature to identify cognitive domainspreviously identified as affected by CAA, VCI, and AD. Based on the previously discussedfindings from the Religious Orders Study (Arvanitakis, Leurgans, Wang, et al., 2011), CAA ismarked by deficits in episodic memory (-0.46 SD) and perceptual speed (-0.50 SD). VCI ismarked by prominent impairment in executive function and AD is marked by prominentimpairment in episodic memory. A composite score of episodic memory derived from thedelayed recall portions of the CVLT-II and ROCFT and a composite score of executivefunctioning obtained from the TMT—B and COWAT—FAS will be used in the analysis of thefirst hypothesis. Data from the CAA, AD, MCI, and MIS patients enrolled in the FAVR, BrainIMPACT, and CATCH studies will be used for analysis. To compare characteristics between
each of these groups and CAA, the chi-square test will be used to compare categorical variables, the two-sample t-test will be used to compare means, and the Wilcoxon rank-sum test will be used to compare non-normal distributions (with display of the median and 25th and 75th percentiles). Due to the larger sample sizes provided by published normative data, neuropsychological test scores will be described in relation to the published normative data rather than data collected from the smaller number of FAVR controls. Due to variations in methods of scoring between tests, raw scores from each of the assessments will be converted into standardized z-scores as recommended by each of the test assessment manuals. For the purposes of this study, a mean z-score of \( \leq -1.00 \) is an indication of cognitive impairment. To test for differences in z-scores between CAA patients and the normative sample, the means of the z-scores for each neuropsychological test under investigation will be compared to zero using one-sample t-tests. In testing the second research hypothesis, differences in z-scores means between CAA and the comparison patient groups will be tested for by conducting an analysis of variance (ANOVA). Dunnett-Hsu’s test will then be used to control for post-hoc comparisons between CAA and each of the comparator groups. The third hypothesis will compare mean z-scores of CAA patients with ICH to non-ICH CAA patients. Multivariable analyses will be used to control for the potential confounding effects of differences in age, education, and gender.

To determine whether WMH volume is associated with neuropsychological test scores, the Spearman correlation coefficient will be used to determine whether they are associated in univariate analysis. Then, multivariable general linear models will be used to determine whether WMH volume is an independent predictor of cognition, controlling for age, sex and education. If WMH volume is associated with group and with the neuropsychological test score and addition of the WMH variable to the model attenuates the association between group and the
neuropsychological test score, then we will conclude that WMH mediates the association between group and neuropsychological test score. To determine whether the relationship between WMH and neuropsychological test score differs by group, we will test an interaction term for group * WMH. If the interaction term is positive then we will separately analyze the relationship between WMH and neuropsychological test score separately in CAA alone, because CAA is the primary group of interest. A similar approach will be used to test whether the presence of one or more APOE ε4 alleles is associated with neuropsychological test scores and whether the APOE ε4 allele mediates the effect of group on neuropsychological test score. Univariate analyses will be carried out by the thesis candidate using SPSS Statistics 21 (IBM, Chicago, IL, USA). Multivariable-adjusted analyses will be carried out by the candidate in collaboration with the supervisor, Dr. Smith, using SAS version 9.3 (SAS Institute, Cary, NC, USA).

Preliminary analyses show that 34 CAA, 16 AD, 69 MCI and 27 MIS patients met eligibility criteria and are available for analysis. Power analyses done using G*Power (Franz Faul, Universitat Kiel, Germany) determined that our sample size of 34 CAA participants will provide 89% power to detect a 0.5 SD difference in perceptual speed, similar to the CAA effect seen in Arvanitakis, Leurgans, Wang, et al. (2011) with alpha=0.05 using the paired t-test. We expect that this power calculation may be conservative, because the previous literature by Arvanitakis, Leurgans, Wang, et al. (2011) studied asymptomatic patients with CAA discovered incidentally on neuropathology, whereas the present study examines symptomatic CAA patients diagnosed during life with CAA-related syndromes.
## Table 5. Study population characteristics.

<table>
<thead>
<tr>
<th></th>
<th>CAA</th>
<th>AD</th>
<th>p</th>
<th>MCI</th>
<th>p</th>
<th>MIS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=34</td>
<td>n=16</td>
<td></td>
<td>n=69</td>
<td></td>
<td>n=27</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>73.0±7.6</td>
<td>69.3±7.0</td>
<td>0.10</td>
<td>73.0±6.7</td>
<td>0.97</td>
<td>66.3±9.0</td>
</tr>
<tr>
<td>MMSE</td>
<td>28.0±1.9</td>
<td><strong>23.1±3.7</strong></td>
<td>&lt;0.001</td>
<td>27.5±2.2</td>
<td>0.28</td>
<td>—</td>
</tr>
<tr>
<td>Female</td>
<td>35.3%</td>
<td>37.5%</td>
<td>0.88</td>
<td>50.7%</td>
<td>0.14</td>
<td>29.6%</td>
</tr>
<tr>
<td>Years of education</td>
<td>13.7±2.7</td>
<td><strong>15.4±3.2</strong></td>
<td>0.05</td>
<td>13.7±3.0</td>
<td>0.97</td>
<td>13.77±2.8</td>
</tr>
<tr>
<td>Education &gt; 12 yrs</td>
<td>58.9%</td>
<td>81.3%</td>
<td>0.12</td>
<td>60.9%</td>
<td>0.84</td>
<td>63.0%</td>
</tr>
<tr>
<td>White Ethnicity</td>
<td>94.1%</td>
<td>93.8%</td>
<td>0.21</td>
<td>89.9%</td>
<td>0.59</td>
<td>—</td>
</tr>
<tr>
<td>Stroke</td>
<td>52.9%</td>
<td><strong>0.0%</strong></td>
<td>&lt;0.001</td>
<td>0.0%</td>
<td>&lt;0.001</td>
<td>100.0%</td>
</tr>
<tr>
<td>Female</td>
<td>14.7%</td>
<td>6.3%</td>
<td>0.46</td>
<td>23.2%</td>
<td>0.28</td>
<td>11.1%</td>
</tr>
<tr>
<td>Coronary artery</td>
<td>73.5%</td>
<td><strong>31.3%</strong></td>
<td>&lt;0.01</td>
<td>73.9%</td>
<td>0.97</td>
<td>70.4%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>47.1%</td>
<td><strong>18.8%</strong></td>
<td>0.05</td>
<td>37.7%</td>
<td>0.34</td>
<td><strong>14.8%</strong></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>11.8%</td>
<td>12.5%</td>
<td>0.94</td>
<td>11.6%</td>
<td>0.98</td>
<td>14.8%</td>
</tr>
<tr>
<td>Current smoker</td>
<td>2.9%</td>
<td>6.3%</td>
<td>0.67</td>
<td>5.8%</td>
<td>0.59</td>
<td>14.8%</td>
</tr>
<tr>
<td>Past smoker</td>
<td>58.8%</td>
<td>62.5%</td>
<td>0.80</td>
<td>44.9%</td>
<td>0.17</td>
<td><strong>18.5%</strong></td>
</tr>
<tr>
<td>NIHSS</td>
<td>67.6%</td>
<td>6.7%</td>
<td>&lt;0.001</td>
<td>79.4%</td>
<td>0.23</td>
<td>—</td>
</tr>
<tr>
<td>Lawton IADLS</td>
<td>0</td>
<td>20.6%</td>
<td>—</td>
<td>18.5%</td>
<td>3.7%</td>
<td>0.0%</td>
</tr>
<tr>
<td>GDS</td>
<td>1</td>
<td>17.6%</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>WMH volume</td>
<td>32.3±30.2</td>
<td><strong>12.5</strong></td>
<td>&lt;0.001</td>
<td>[<strong>6.11,</strong> 37.08]</td>
<td>[<strong>1.76,</strong> 21.23]</td>
<td>[<strong>3.39,</strong> 31.17]</td>
</tr>
<tr>
<td>WMH volume</td>
<td>62.1%</td>
<td>64.3%</td>
<td>0.89</td>
<td>45.3%</td>
<td>0.14</td>
<td>—</td>
</tr>
</tbody>
</table>

CAA = cerebral amyloid angiopathy; AD = Alzheimer’s disease; MCI = mild cognitive impairment; MIS = minor ischemic stroke; MMSE = Mini-mental State Examination; NIHSS = National Institutes of Health Stroke Scale; IADLS = Instrumental Activities of Daily Living Scale; GDS = Geriatric Depression Scale short form; WMH = white matter hyperintensity; APOE = apolipoprotein E.

Normally distributed continuous variables were analysed using a t-test and are displayed as mean±standard deviation. Non-normally distributed continuous variables were analysed using a Wilcoxon rank sum and displayed as median [25th percentile, 75th percentile]. Normally distributed discrete variables were analysed using chi-square and non-normally distributed discrete variables were analysed using Fisher’s exact test. Both are displayed as percentages. p-values represent group differences between CAA and its comparison groups. Results with statistically significant p-values (≤ 0.05) are bolded.
Data from 146 participants (41.8% female) were analysed. There were 34 CAA, 16 AD, 69 MCI, and 27 MIS participants. The demographics for each group are presented in Table 5, with statistical testing for comparisons between CAA (the group of interest) and each of the comparison groups. Participants had mostly similar characteristics across groups except that CAA participants were older than MIS participants. CAA participants also differed from AD participants by being more likely to have hypertension, fewer years of education, and being more functionally independent. Participants in the CAA group also had higher WMH volumes than participants in the control groups.

**Neuropsychological test scores in CAA, AD, MCI and MIS**

Test scores without adjustment are provided in Table A1, while scores expressed as z-scores compared to published age-, education-, and/or sex-adjusted means (from the published testing manuals) are shown in Table 6.

**CAA compared to the normative population**

As shown in Table 6, participants with CAA scored significantly below zero on all tests except the CVLT—DR. A one-sample t-test of the z-scores obtained from the neuropsychological tests of interest revealed that participants in the CAA group (mean \( M = -0.58 \), standard deviation \( SD = 1.17 \)) scored significantly lower than the normative population on the ROCFT—DR, \( t(31) = -2.80, p < 0.01 \). This difference was maintained in the composite score of episodic memory which included both the ROCFT—DR as well as the CVLT—DR and demonstrated poorer episodic memory functioning among CAA participants (\( M = -0.44, SD = 1.03 \)) in comparison to the normative data, \( t(32) = -2.45, p = 0.02 \). CAA participants (\( M = -1.14, SD = 1.07 \)) also performed significantly worse than the normative population on tests of
executive functioning, $t(33) = -6.22, p = <0.001$. Scores for the individual neuropsychological subtests included in this composite score, TMT—B ($M = -1.66, SD = 1.44$) and COWAT—FAS ($M = -0.62, SD = 1.08$), were both significantly lower in CAA participants when compared to the normative data, $t(33) = -6.69, p = <0.001$ and $t(33) = -3.35, p = <0.01$, respectively. There were also significant differences in the DSST ($M = -0.67, SD = 1.03$) and TMT—A ($M = -1.45, SD = 1.44$) between the CAA group and the normative population $t(33) = -3.76, p = <0.001$ and $t(33) = -5.87, p = <0.001$, respectively.
<table>
<thead>
<tr>
<th></th>
<th>CAA (n=34)</th>
<th></th>
<th>AD (n=16)</th>
<th></th>
<th>MCI (n=69)</th>
<th></th>
<th>MIS (n=27)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>z±SD</td>
<td>p</td>
<td>z±SD</td>
<td>p</td>
<td>z±SD</td>
<td>p</td>
<td>z±SD</td>
<td>p</td>
</tr>
<tr>
<td><strong>Memory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVLT—DR</td>
<td>-0.29±1.25</td>
<td>0.20</td>
<td>-1.97±1.18</td>
<td>&lt;0.001</td>
<td>-0.55±1.25</td>
<td>&lt;0.001</td>
<td>-0.37±0.95</td>
<td>0.05</td>
</tr>
<tr>
<td>ROCFT—DR</td>
<td>-0.58±1.17</td>
<td>0.009</td>
<td>-1.98±0.58</td>
<td>&lt;0.001</td>
<td>-0.78±1.19</td>
<td>&lt;0.001</td>
<td>-0.15±1.03</td>
<td>0.47</td>
</tr>
<tr>
<td><strong>Executive function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TMT—B</td>
<td>-1.67±1.45</td>
<td>&lt;0.001</td>
<td>-2.52±1.05</td>
<td>&lt;0.001</td>
<td>-0.71±2.24</td>
<td>0.01</td>
<td>-0.25±1.44</td>
<td>0.38</td>
</tr>
<tr>
<td>COWAT—FAS</td>
<td>-0.62±1.08</td>
<td>&lt;0.002</td>
<td>-0.99±0.75</td>
<td>&lt;0.001</td>
<td>-0.50±0.94</td>
<td>&lt;0.001</td>
<td>-0.28±0.98</td>
<td>0.15</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DSST</td>
<td>-0.67±1.03</td>
<td>&lt;0.001</td>
<td>-1.44±0.80</td>
<td>&lt;0.001</td>
<td>-0.36±1.01</td>
<td>0.004</td>
<td>-0.01±0.97</td>
<td>0.94</td>
</tr>
<tr>
<td>TMT—A</td>
<td>-1.45±1.44</td>
<td>&lt;0.001</td>
<td>-1.74±1.46</td>
<td>&lt;0.001</td>
<td>-0.63±1.34</td>
<td>&lt;0.001</td>
<td>-0.60±1.21</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Composite scores</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Memory</td>
<td>-0.44±1.03</td>
<td>0.02</td>
<td>-1.96±0.76</td>
<td>&lt;0.001</td>
<td>-0.66±1.07</td>
<td>&lt;0.001</td>
<td>-0.26±0.86</td>
<td>0.13</td>
</tr>
<tr>
<td>Executive function</td>
<td>-1.14±1.07</td>
<td>&lt;0.001</td>
<td>-1.75±0.74</td>
<td>&lt;0.001</td>
<td>-0.60±1.28</td>
<td>&lt;0.001</td>
<td>-0.27±0.98</td>
<td>0.17</td>
</tr>
</tbody>
</table>

CAA = cerebral amyloid angiopathy; AD = Alzheimer’s disease; MCI = mild cognitive impairment; MIS = minor ischemic stroke; CVLT—DR = California Verbal Learning Test—Delayed Recall; ROCFT—DR = Rey-Osterrieth Complex Figure Test—Delayed Recall; TMT—B = Trail Making Test—Part B; COWAT—FAS = Controlled Oral Word Association Test—Letter Fluency; DSST = Digit Symbol Substitution Test; TMT—A = Trail Making Test—Part A.

One-sample t-tests were conducted to compare the z-scores to zero. Results with statistically significant p-values (≤ 0.05) are bolded.
AD, MCI and MIS compared to the normative population

AD participants performed significantly worse than the normative population on all neuropsychological tests and cognitive domains (Table 6). This included the CVLT—DR ($M = -1.97$, $SD = 1.18$), $t(15) = -6.70$, $p < 0.001$ and ROCFT—DR ($M = -1.98$, $SD = 0.58$), $t(13) = -12.76$, $p < 0.001$, as well as composite episodic memory performance ($M = -1.98$, $SD = 0.76$), $t(15) = -10.36$, $p < 0.001$. Composite executive functioning performance ($M = -1.75$, $SD = 0.74$) was also significantly lower in AD participants, $t(15) = -9.43$, $p < 0.001$. Although performance on both the TMT—B ($M = -2.52$, $SD = 1.05$) and COWAT—FAS ($M = -0.99$, $SD = 0.75$) was poor, $t(15) = -5.29$, $p < 0.001$, TMT—B performance was significantly worse than COWAT—FAS performance, $t(15) = -9.43$, $p < 0.001$. DSST ($M = -1.44$, $SD = 0.80$) and TMT—A ($M = -1.74$, $SD = 1.46$) performance was also lower than the normative population, $t(15) = -6.95$, $p < 0.001$; $t(15) = -4.78$, $p < 0.001$; respectively.

MCI participants also showed significantly poorer performance on all measures of neuropsychological performance in comparison to normative data. CVLT—DR ($M = -0.55$, $SD = 1.25$) and ROCFT—DR performance ($M = -0.78$, $SD = 1.19$) were significantly worse than the normal population, $t(68) = -3.65$, $p < 0.001$; $t(68) = -5.45$, $p < 0.001$; respectively. Composite episodic memory ($M = -0.66$, $SD = 1.07$) was also worse in MCI participants, $t(68) = -5.16$, $p < 0.001$. Z-scores for the TMT—B ($M = -0.71$, $SD = 2.24$) and COWAT—FAS ($M = -0.50$, $SD = 0.94$) were both significantly lower than zero, $t(68) = -2.61$, $p = 0.01$; $t(68) = -4.40$, $p < 0.001$; respectively. Executive function ($M = -0.60$, $SD = 1.28$) was also worse, $t(68) = -3.89$, $p < 0.001$. Deficits in DSST ($M = -0.36$, $SD = 1.01$) and TMT—A ($M = -0.63$, $SD = 1.34$) performance were significant, $t(68) = -2.99$, $p < 0.01$; $t(68) = -3.89$, $p < 0.001$; respectively.
MIS participants displayed poor performance on the least amount of neuropsychological tests. The only neuropsychological test that reflected low performance in these participants is the TMT—A \((M = -0.60, SD = 1.21), t(26) = -2.57, p = <0.02\). Analyses comparing individual test z-scores of MIS participants to individual test z-scores of the normal population on the CVLT—DR, ROCFT—DR, TMT—B, COWAT—FAS, and DSST were non-significant. Composite z-scores of episodic memory and executive functioning were also non-significantly lower than zero.

Comparison of CAA with AD, MCI and MIS

Table 7 shows estimated cognitive domain means with 95% confidence limits (CL) from multivariable models adjusting for age, sex and ≥ 12 years of education. Age, sex and education were included in these models because of residual relationships with one or more cognitive test scores, despite the values already being expressed relative to adjusted normative data. The \(p\)-values in this table represent comparisons between each patient group and CAA, using the Dunnett-Hsu method to control for multiple post-hoc comparisons. Figure 5 displays the estimated means in graphical form, to allow a better appreciation of the relative differences.
Post-hoc comparisons of CAA and the patient control groups

Table 7. Z-scores from neuropsychological tests in CAA, AD, MCI, and MIS (post-hoc comparisons).

<table>
<thead>
<tr>
<th></th>
<th>CAA (n=34)</th>
<th>AD (n=16)</th>
<th>MCI (n=69)</th>
<th>MIS (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>z [95% CL]</td>
<td>z [95% CL]</td>
<td>p</td>
<td>z [95% CL]</td>
</tr>
<tr>
<td>Memory</td>
<td>-0.42 [-0.77, -0.08]</td>
<td>-2.02 [-2.52, -1.52]</td>
<td>&lt;0.001</td>
<td>-0.64 [-0.88, -0.40]</td>
</tr>
<tr>
<td>Executive function</td>
<td>-1.16 [-1.57, -0.83]</td>
<td>-1.87 [-2.13, -1.04]</td>
<td>0.53</td>
<td>-0.73 [-0.96, -0.43]</td>
</tr>
<tr>
<td>DSST</td>
<td>-0.67 [-0.98, -0.33]</td>
<td>-1.44 [-1.91, -0.94]</td>
<td>0.03</td>
<td>-0.36 [-0.67, -0.21]</td>
</tr>
</tbody>
</table>

CAA = cerebral amyloid angiopathy; AD = Alzheimer’s disease; MCI = mild cognitive impairment; MIS = minor ischemic stroke; DSST = Digit Symbol Substitution Test.

General linear models were performed using the Dunnett-Hsu post-hoc test with CAA as the reference group and multivariable adjustment for age, sex, and education.

Results with statistically significant p-values (≤ 0.05) are bolded.

The results of these analyses maintain that CAA participants (\(M = -0.42, CL = -0.77, -0.08\)) display better performance on neuropsychological tests of episodic memory than do AD participants (\(M = -2.02, CL = -2.52, -1.52\)), \(t(3) = 34.36, p < 0.001\).

Performance on executive functioning tests was better among CAA participants (\(M = -1.16, CL = -1.57, -0.83\)) than among MIS participants (\(M = -0.27, CL = -0.49, -0.38\)), \(t(3) = 30.21, p < 0.001\). CAA participants (\(M = -0.67, CL = -0.98, -0.33\)) scored higher on the DSST than AD participants (\(M = -1.44, CL = -1.91, -0.94\)) but lower than MIS participants (\(M = -0.01, CL = -0.22, -0.54\)) \(t(3) = 25.10, p < 0.001\). CAA and MCI participants did not differ on any of the mean composite or individual neuropsychological test z-scores analysed using multivariate analyses.
Figure 5. Z-scores from neuropsychological tests in CAA, AD, MCI, and MIS (post-hoc comparisons).

CAA = cerebral amyloid angiopathy; AD = Alzheimer’s disease; MCI = mild cognitive impairment; MIS = minor ischemic stroke; DSST = Digit Symbol Substitution Test. General linear models were performed using the Dunnett-Hsu post-hoc test with CAA as the reference group and multivariable adjustment for age, sex, and education. Error bars represent 95% confidence intervals.

* $p < 0.05.$

** $p < 0.001.$

Presenting symptoms in CAA

As displayed in Figure 6, 17 (50%) of the CAA participants presented with ICH, while the remainder presented with either headache, cognitive symptoms, TFNE, or had an incidental MRI finding (Figure 6). One of the participants who presented with TFNE and the two participants who presented with headache had MRI evidence of inflammation ($n = 3, 2.1\%$).
One participant presented with both ICH and TFNE and is represented in both of these groups.

A summary of the raw scores divided by the different syndrome categories, as defined by their presenting symptoms, is provided in Table A2. Due to small sample sizes, participants presenting with TFNE, headache, or incidental MRI were grouped into one category for analysis. Univariate analyses revealed no significant differences between syndrome categories in their neuropsychological test performance on the DSST or on composite z-scores of executive function and episodic memory (Table 8).

### Table 8. Z-scores from neuropsychological tests in different syndrome categories of CAA.

<table>
<thead>
<tr>
<th></th>
<th>ICH (n=17)</th>
<th>CI (n=5)</th>
<th>Other* (n=12)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Composite scores</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Memory</td>
<td>-0.45±1.00</td>
<td>-0.87±1.02</td>
<td>-0.24±1.10</td>
<td>0.53</td>
</tr>
<tr>
<td>Executive function</td>
<td>-1.39±1.02</td>
<td>-1.46±0.96</td>
<td>-0.65±1.08</td>
<td>0.15</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DSST</td>
<td>-0.82±1.25</td>
<td>-0.60±0.95</td>
<td>-0.47±0.71</td>
<td>0.67</td>
</tr>
</tbody>
</table>

ICH = intracerebral hemorrhage; CI = cognitive impairment; DSST = Digit Symbol Substitution Test.

General linear models were performed and multivariable adjustments for age, sex, and education were used.
* This category includes CAA participants presenting with transient focal neurological episodes, headache, and incidental MRI.

**WMH volumes**

WMH volumes varied significantly by patient group, with CAA participants having the highest WMH volumes (Table 5). Univariate Spearman correlations revealed that higher WMH volume was associated with lower executive function \( (r = -0.17, p = 0.04) \) and lower DSST \( (r = -0.19, p = 0.02) \), but not episodic memory \( (r = 0.05, p = 0.56) \). Multivariate models adjusting for patient group, age, education, and female sex examined whether WMH volume was associated with executive function or DSST performance. In the model of executive function, the WMH volume term was not significant \( (p = 0.71) \) and in another model including an interaction term, there was no evidence for different relationships between WMH volume and executive function across the four patient groups \( (interaction p = 0.21) \). By contrast, in the multivariable-adjusted model of DSST, the interaction \( p \)-value was positive \( (p = 0.04) \); therefore, only the adjusted relationship between WMH volumes and DSST in CAA participants was analysed. Scatterplots of WMH volumes and cognitive domain scores in CAA participants are shown in Figure 7. In the 32 CAA participants who completed MRI, there was a significant relationship between higher WMH and lower DSST in the fully adjusted model, such that for each 1 cm\(^3\) increase in WMH, the estimated DSST was 0.013 lower \([95\% \text{ CL} -0.002, -0.023]\).
APOE genotypes were assessed for CAA, AD, and MCI participants, but not for MIS participants because genetic analysis was not part of the CATCH study. The prevalence of the APOE ε4 was 62.1% in 29 CAA participants, 64.3% in the 14 AD participants, and 45.3% in 64 MCI participants (Table 5). Although the prevalence of the APOE ε4 allele was higher in CAA than in MCI, this difference was not significant (p = 0.14).

Figure 8 shows the scores for episodic memory, executive function, and DSST in participants with and without the APOE ε4 allele. Univariate testing by ANOVA showed that, contrary to the pre-specified hypothesis, there was no association between the APOE ε4 and memory score (p = 0.12), executive function (p = 0.11), or DSST (p = 0.21). In a fully adjusted
multivariable model, we found no association between the presence of the APOE ε4 allele and episodic memory function (p = 0.12) after controlling for age, sex, education, and patient group, and no evidence that the APOE ε4 effect differed by patient group (interaction p = 0.59). In secondary analyses using multivariable-adjusted models, we also found no evidence for an effect of the APOE ε4 allele on executive function or DSST, including no significant interactions with patient groups (data not shown).

Figure 8. T-test of episodic memory z-scores among CAA, AD, and MCI participants with and without an APOE ε4 allele.

CAA = cerebral amyloid angiopathy; AD = Alzheimer’s disease; MCI = mild cognitive impairment.
General linear models were performed and multivariable adjustments for age, sex, and education were used.
Error bars represent 95% confidence intervals.
CHAPTER 4: DISCUSSION

The overall results of this study suggest a vascular role in the cognitive impairment of people with CAA that is concentrated on executive dysfunction, perceptual speed, and, to a lesser extent, episodic memory. The effect of CAA on cognition is partly mediated by WMH volume and independent of APOE ε4 genotype.

**Primary research findings**

The most prominent findings of this study are that people with CAA perform significantly worse on neuropsychological tests of executive functioning, perceptual speed, and episodic memory, when compared to the normative population. Furthermore, performance on the TMT—A, TMT—B, and composite executive functioning tests met criteria for clinical impairment. This pattern is consistent with the profile of cognitive impairment identified in VCI (Hurford et al., 2013; Sachdev et al., 2004) and also with the previous literature on the cognitive domains associated with CAA pathology based on the Religious Orders study (Arvanitakis, Leurgans, Wang, et al., 2011). However, the present study is the first to comprehensively describe the cognitive profile of CAA in non-demented living persons with CAA-related syndromes such as ICH, cognitive impairment, and TFNE.

The degree of lowered performance in CAA was similar to patients with MCI. Indeed, there were no significant differences between CAA and MCI in tests of episodic memory, executive function, or the DSST. This poorer cognitive performance in CAA as well as the study exclusion of CAA participants with dementia suggest that the results may be reflective of MCI in CAA participants. As expected, participants with mild AD dementia had worse cognitive performance than non-demented CAA participants in episodic memory and on the DSST.
However, executive function was not significantly different between CAA and AD participants, although this may partly reflect the relatively small sample size in the AD participant group.

The mildly attenuated episodic memory in CAA participants contrasts with the severe episodic memory impairment seen in the AD participants. Early impairment in delayed recall is considered a hallmark of AD (McKhann et al., 2011). Therefore, the relatively mildly poorer episodic memory in CAA, compared to the greater degree of executive dysfunction, supports the possibility that the pathology of poorer cognitive performance in CAA may not be simply the consequence of accompanying AD pathology. Other mechanisms, such as VCI, can be invoked to explain the cognitive profile of CAA. Performance in CAA participants was worse than for MIS participants with similar stroke severity, indicating that poorer cognitive performance is a more prominent feature in CAA than in similar severity ischemic stroke caused by atherosclerosis and conventional vascular risk factors.

Secondary research findings

WMH are common findings in patients with stroke. WMH have been associated with cognitive impairment in stroke populations, and are known to be extensive in CAA (E. E. Smith, 2010). Therefore, WMH volumes were analysed to determine whether the cognitive performance in CAA depended on WMH volume. After including WMH volume in our models, we found that higher WMH volumes contribute to worse scores on the DSST. Although this finding is statistically significant, the effect was not large, indicating that factors other than WMH contribute to DSST performance. In fully adjusted models in the entire group, the disease group effect (CAA vs. other) remained highly significant even after adding WMH to the model. This indicates that the association between CAA and cognition is independent of the degree of WMH
volume, suggesting that other unmeasured consequences of CAA must contribute to the cognitive profile of CAA when compared to AD, MCI, and MIS.

Furthermore, we found similar cognitive profiles in CAA patients with and without ICH, and with and without cognitive symptoms as a presenting complaint, although our comparisons are limited by small numbers. Similar to MCI, CAA involves a wide range of pathology which are potentially indicative of cognitive subtypes of CAA that may become apparent with larger sample sizes. It is possible that poor performance on memory tasks may be characteristic of an “amnestic” CAA, whereas, executive dysfunction may be reflective of a “non-amnestic” CAA.

Together, these results suggest that unmeasured aspects of CAA pathology may cause cognitive dysfunction. Arvanitakis, Leurgans, Barnes, Bennett, and Schneider (2011) found that the post-mortem presence of both single and multiple cortical microinfarcts was associated with lower pre-mortem performance in perceptual speed, semantic memory, and, to a lesser degree, episodic memory in AD participants. The presence of microbleeds have been shown to result in lower executive functioning test performance (Werring et al., 2004). Case studies also support a possible role of superficial siderosis in the presence of impaired executive functioning (van Harskamp, Rudge, & Cipolotti, 2005).

In this study, we found a prevalence of the APOE ε4 of 62% in CAA, 45% in MCI, and 64% in AD. Previously published studies show that the prevalence of APOE ε4 in the general Canadian population is approximately 12.5-19% (Singh, Singh, & Mastana, 2006). However, we did not find that cognitive performance was related to the ε4 allele in the participants in this study, although we did not include normal controls. In this study, disease group status and cognition were independent of the APOE ε4 allele.
Implications of findings

Based on the results of this study, my hypotheses were supported in that: 1) CAA participants differ from the normative population in performance on tests of executive functioning, perceptual speed, and episodic memory, 2) CAA participants differ from AD participants without CAA by exhibiting relatively worse performance in executive functioning and perceptual speed compared to the performance in episodic memory, and 3) higher WMH volume was negatively correlated with perceptual speed. My hypotheses were not supported by the following: 1) CAA participants presenting with ICH did not score lower on tests of episodic memory, executive functioning, or perceptual speed than CAA participants not presenting with ICH and 2) the presence of APOE genotype ε4 was not positively correlated with lower performance in verbal learning and memory and visuospatial construction and memory.

The objectives of this research were met by the results of this study in that: 1) the neuropsychological profile of CAA was distinguished from the neuropsychological profile of the normal population, 2) CAA participants were identified as following a cognitive pattern most comparable to the cognitive pattern attributed to VCI, 3) it was established that, based on the limited sample size, differences in neuropsychological test scores among CAA participants cannot be attributed to any particular presentation of CAA, and 4) it was established that the differences in test scores between CAA and its comparison groups are not wholly explained by group differences in WMH volumes or APOE genotype, and must be related to consequences of CAA not measured in this study.

Limitations

The MMSE’s lack of items to assess executive functioning may have limited its ability to detect cognitive impairment in CAA participants. The Montreal Cognitive Assessment
(Nasreddine et al., 2005) is able to detect mild SVD with higher sensitivity in comparison to performance on the MMSE (Pasi et al., 2015); however, the Montreal Cognitive Assessment was not used in the present study.

Both the Lawton IADLS and the modified Lawton IADLS are limited in their discrimination between lowered functioning due to cognitive impairment and lowered functioning due to other causes (i.e., chronic pain, disability). Furthermore, there is no distinction made between chronically lowered functioning and recent functional decline.

WMH volumes were measured in this study without adjusting for expected participant differences in head size, because comparable data on brain or intracranial volumes were not collected across all the studies. Because a given WMH volume may have greater clinical consequences in a smaller brain than a larger brain, this lack of accounting for head size may have made it more difficult to detect associations with WMH volume. However, the variation in WMH volume (Table 5) is much larger than variation in head sizes in the population, and sex, a major determinant of head size (women have smaller heads than men, consistent with their smaller stature) was controlled for in the models; therefore, this is probably not a severe limitation. In future work, brain volume will be analysed consistently across all the studies using the same software to allow a standardized determination of participant brain volume.

Specific Aβ markers were not used in this study. Cerebrospinal fluid concentrations of Aβ_{42} and total tau are well established biomarkers of AD pathology and have been shown to be > 80% accurate in predicting MCI conversion to AD dementia. Other biomarkers include amyloid brain imaging and positron emission tomography (18F-fluorodeoxyglucose and amyloid; Molinuevo et al., 2014). These biomarkers were not assessed in the present study, limiting the diagnostic accuracy of AD. However, while these biomarkers are able to detect AD from
psychiatric and non-dementia disorders with high specificity, they lack specificity for identifying AD among other dementia disorders (Andreasen et al., 2001) and CAA (Renard et al., 2012). Furthermore, amyloid-binding ligands for positron emission tomography studies bind with high affinity to either parenchymal or vascular Aβ, making them useless for discriminating AD from CAA pathology.

The small sample sizes in this study, particularly in the AD group, limit its statistical power and increase the chances of Type II errors. In order to minimize the effects of small sample sizes, the neuropsychological test raw scores were standardized according to published normative data derived from population studies rather than normative data derived from the 32 control participants recruited through the FAVR-I and FAVR-II studies. While using published normative data increases the generalizability of the results of this study to CAA patients internationally, its validity to Calgary-based CAA patients, in particular, may be limited. Small sample sizes also limited the statistical power of the ANOVAs to detect a difference between subgroups of CAA.

The reliance on CAA-related ICH and CMB for clinical diagnosis necessitates excluding persons with CAA pathology who have not had ICH or CMB events. Thus, the results of this study cannot necessarily be generalized to persons with asymptomatic CAA, or CAA without MRI evidence of bleeding. A recent study by Charidimou et al. (2015) distinguishes the pathology of CAA participants without hemorrhage from CAA participants with hemorrhage. CAA without ICH was significantly associated with APOE ε4 and the burden of neurofibrillary tangle pathology, while CAA with ICH was significantly more likely to also have cortical superficial siderosis and APOE ε2.
MCI is a syndrome stemming from a plethora of heterogeneous pathologies. These pathologies include, but are not limited to vascular and amyloidogenic origins. Distinguishing between different subtypes of MCI (i.e., amnestic MCI and non-amnestic MCI) in the statistical analyses may have produced clearer results for the purpose of comparison with CAA.
Areas of future research

Having a larger sample size in future would allow for more power in the statistical analysis of neuropsychological test performance between different presenting symptom subgroups of CAA. It is still hypothesized that participants with ICH perform worse on neuropsychological tests of executive functioning and episodic memory.

Although there were no significant differences in White and non-White ethnicity between groups, the present study had an underrepresentation of non-White ethnicities. As supported by much of the referenced neuropsychological test literature, ethnic differences may affect test scores. Although the results of this study may be reflective of cognitive patterns among persons of White ethnicity, future research in this area may benefit from the inclusion of more participants of non-White ethnicity.

Increased post-stroke cognitive impairment severity is a predictor of increased dependency and mortality (Narasimhalu et al., 2011). Thus, a more robust knowledge of the neuropsychological profile of CAA not only has the potential to improve the clinical identification of patients with CAA who present with cognitive impairment, but also to better inform the management of their cognitive symptoms, and predict illness outcomes. Analysis of longitudinal data is a key component in identifying a more dynamic neuropsychological profile of CAA and uncovering prognostic information about the trajectory of potential recovery or deterioration of cognition in this syndrome (Jurado & Pueyo, 2012). Outcomes from these analyses may determine 1) whether changes in cognition over time differ between CAA participants and the normative population, 2) whether changes in cognition over time in CAA participants are most similar to AD, MCI, or MIS participants, 3) whether changes in cognition
over time differ between different presenting symptom subgroups of CAA, and 4) the risk for conversion of CAA participants to dementia. Results from these data may be clinically useful in the knowledge translation of the profile of cognitive impairment in CAA by helping both patients and their caregivers better understand and cope with present symptoms and their progression over time.

Further research into the mechanisms by which CAA causes cognitive impairment is warranted. A more enhanced understanding of this process may provide the foundation for prevention strategies and the development of pharmacotherapeutic treatments targeting impaired cognition in CAA. Goldstein, Levey, and Steenland (2013) support the role of hypertension in cognitive decline in MCI participants and prophylactic use of antihypertensives has been shown to decrease the incidence of vascular dementia, AD, and mixed dementia (Forette et al., 2002). Furthermore, treatment of the SVD aspects of CAA are emphasized for the potential amelioration of cognitive impairment (Saito & Ihara, 2014).


Charidimou, A., Gang, Q., & Werring, D. J. (2012). Sporadic cerebral amyloid angiopathy revisited: Recent insights into pathophysiology and clinical spectrum. *Journal of


Pearson, K. (1900). On the criterion that a given system of deviations from the probable in the case of a correlated system of variables is such that it can be reasonably supposed to have arisen from random sampling. Philosophical Magazine Series 5, 50(302), 157-175. doi: 10.1080/14786440009463897


Student. (1908). The Probable Error of a Mean. *Biometrika, 6*(1), 1-25. doi: 10.1093/biomet/6.1.1


## APPENDIX

Table A1. Raw scores from neuropsychological tests in CAA, AD, MCI, and MIS.

<table>
<thead>
<tr>
<th></th>
<th>CAA (n=34)</th>
<th>AD (n=16)</th>
<th>MCI (n=69)</th>
<th>MIS (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Memory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVLT—DR</td>
<td>7.58±4.33</td>
<td>2.69±3.30</td>
<td>7.07±3.74</td>
<td>9.70±3.29</td>
</tr>
<tr>
<td>ROCFT—DR</td>
<td>11.50±6.86</td>
<td>4.04±3.40</td>
<td>10.78±6.59</td>
<td>15.17±6.65</td>
</tr>
<tr>
<td><strong>Executive function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TMT—B</td>
<td>162.61±82.42</td>
<td>241.31±85.63</td>
<td>125.84±46.20</td>
<td>91.67±47.28</td>
</tr>
<tr>
<td>COWAT—FAS</td>
<td>31.38±10.91</td>
<td>29.00±9.03</td>
<td>31.99±10.85</td>
<td>36.52±13.11</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DSST</td>
<td>39.68±13.39</td>
<td>31.80±12.81</td>
<td>44.68±14.09</td>
<td>52.22±13.51</td>
</tr>
<tr>
<td>TMT—A</td>
<td>67.79±33.47</td>
<td>75.13±45.31</td>
<td>51.91±23.03</td>
<td>49.81±30.06</td>
</tr>
</tbody>
</table>

CAA = cerebral amyloid angiopathy; AD = Alzheimer’s disease; MCI = mild cognitive impairment; MIS = minor ischemic stroke; CVLT—DR = California Verbal Learning Test—Delayed Recall; ROCFT—DR = Rey-Osterrieth Complex Figure Test—Delayed Recall; TMT—B = Trail Making Test—Part B; COWAT—FAS = Controlled Oral Word Association Test—Letter Fluency; DSST = Digit Symbol Substitution Test; TMT—A = Trail Making Test—Part A.

Table A2. Raw scores from neuropsychological tests in different syndrome categories of CAA.

<table>
<thead>
<tr>
<th></th>
<th>ICH (n=17)</th>
<th>Cognitive impairment (n=5)</th>
<th>Other* (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Memory</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVLT—DR</td>
<td>7.31±3.86</td>
<td>5.40±4.39</td>
<td>8.83±4.82</td>
</tr>
<tr>
<td>ROCFT—DR</td>
<td>11.56±6.43</td>
<td>11.90±6.07</td>
<td>11.23±8.31</td>
</tr>
<tr>
<td><strong>Executive function</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TMT—B</td>
<td>191.75±86.59</td>
<td>156.60±86.72</td>
<td>126.25±64.10</td>
</tr>
<tr>
<td>COWAT—FAS</td>
<td>29.65±11.80</td>
<td>32.00±13.11</td>
<td>33.58±9.06</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DSST</td>
<td>38.00±14.75</td>
<td>42.60±14.36</td>
<td>40.83±11.70</td>
</tr>
<tr>
<td>TMT—A</td>
<td>82.88±34.64</td>
<td>55.60±24.21</td>
<td>51.50±26.32</td>
</tr>
</tbody>
</table>

ICH = intracerebral hemorrhage; CVLT—DR = California Verbal Learning Test—Delayed Recall; ROCFT—DR = Rey-Osterrieth Complex Figure Test—Delayed Recall; TMT—B = Trail Making Test—Part B; COWAT—FAS = Controlled Oral Word Association Test—Letter Fluency; DSST = Digit Symbol Substitution Test; TMT—A = Trail Making Test—Part A.  
* This category includes CAA participants presenting with transient focal neurological episodes, headache, and incidental MRI.