

HETEROGENEITY OF NEUROPSYCHOLOGICAL PROFILES
IN OLDER ADULTS WITH VASCULAR DISEASE:
A LATENT CLASS ANALYSIS APPROACH

A Dissertation
Submitted to
the Temple University Graduate Board

In Partial Fulfillment
of the Requirements for the Degree
DOCTOR OF PHILOSOPHY

by
Gregory A. Seidel
December 2014

Examining Committee Members:

Dr. Tania Giovannetti, Advisory Chair, Department of Psychology
Dr. Deborah Drabick, Examining Chair, Department of Psychology
Dr. Peter Marshall, Department of Psychology
Dr. Lauren Alloy, Department of Psychology
Dr. Jason Chein, Department of Psychology
Dr. Thomas Floyd, Stony Brook University Hospital

ABSTRACT

Despite the common co-occurrence of the two main pathological processes in aging, vascular disease and Alzheimer's disease (AD), they are often examined in isolation. Increasing evidence of a mutually enhancing relation between these processes is supported by common risk factors including hypertension and diabetes. Therefore, both processes must be considered in characterizing the cognitive performance of older adults, particularly given high rates of vascular disease. The heterogeneity of cognitive deficits has not been systematically examined in older adults with vascular disease. In a large sample of older adults ($N = 359$, $M_{\text{age}} = 74.7$) with increased vascular risk associated with cardiac disease, classes of participants were identified using latent class analysis (LCA) based on their performance across neuropsychological measures of executive functions and episodic memory. The cognitively-defined classes were compared on neuroimaging variables including white matter lesion (WML) and hippocampal volumes in 203 participants and on vascular risk quantified by Framingham score in 187 participants. LCA on the cognitive variables supported a three-class model, with Class 3 (intact; $n = 178$) showing relatively intact cognitive test scores compared to the other classes and Classes 1 (mildly impaired; $n = 136$) and 2 (dysexecutive; $n = 42$) demonstrating uniformly low scores, with Class 2 showing the lowest and most impaired scores on two executive measures (Trails B and Mental Control). Follow-up analyses found that differences between classes on WML and hippocampal volumes did not reach statistical significance, although a trend was observed in WML volumes ($p = .12$) with greater levels of this pathology in Class 2 (dysexecutive). Significant differences between the classes on vascular risk were revealed, with Class 2 showing significantly higher

Framingham scores ($p = .02$). These findings suggest meaningful heterogeneity in the cognitive presentation of older adults with increased vascular risk, with deficits in executive functions associated with potentially modifiable vascular risk factors/cerebrovascular disease.

TABLE OF CONTENTS

	Page
ABSTRACT	ii
LIST OF TABLES	v
LIST OF FIGURES	vi
CHAPTER	
1. INTRODUCTION	1
2. METHODS.....	11
3. RESULTS	23
4. DISCUSSION.....	37
5. EXTENSIVE LITERATURE REVIEW	48
REFERENCES.....	127

LIST OF TABLES

Table	Page
1. List of Cognitive Tests, Test Descriptions, and Variables by Cognitive Domain.....	15
2. Demographic Characteristics of Participants in the Study.....	24
3. Summary Statistics for Cognitive, Neuroimaging, and Vascular Risk Variables.....	25
4. Intercorrelations between the Cognitive Variables.....	26
5. Correlations between the Cognitive Variables, Demographic Variables, and Imaging Variables.....	27
6. Fit Indices for Latent Class Analysis Models with 1-4 Classes.....	29
7. Neuropsychological Test Scores Across the Three-Class Model	31
8. Comparisons of Covariates between Latent Classes.....	33
9. Comparisons of Vascular Risk and Neuroimaging Variables Across Classes....	35
10. Summary of Neuropsychological Patterns Observed between Dementia Associated with Small Vessel Disease and Alzheimer's Disease.....	109

LIST OF FIGURES

Figure	Page
1. Location and Organization of the Hippocampal Formation.....	52
2. Cerebral Arterial Small Vessels.....	91

CHAPTER 1

INTRODUCTION

Background

Much has been learned regarding the two most frequent neuropathological processes related to cognitive aging and neurodegenerative disease – cerebrovascular disease and pathologies associated with Alzheimer’s Disease (AD). Research on cognition has suggested different domains of cognitive performance to be differentially associated with these various underlying brain pathologies (Libon, Price, Davis Garrett & Giovannetti, 2004). These pathologies are also associated with unique neuroimaging indicators, with AD pathology associated with decreased hippocampal volumes (Braak & Braak, 1991) and cerebrovascular disease associated with white matter hyperintensities (Hachinski, 1987). Vascular risk factors such as hypertension and diabetes have been associated with both of these pathological processes (Pantoni, 2010; van Norden et al., 2010). However, in the context of these diverse perspectives on pathology, the heterogeneity of cognitive profiles among older adults has not been carefully characterized. This study aimed to identify subgroups of older adults with relatively homogeneous cognitive profiles within a large sample with high vascular risk. Differences among these subgroups on neuroimaging variables reflecting integrity of hippocampus and cerebral white matter and on vascular risk factors were examined. The need for understanding the heterogeneity of cognitive deficits in older adults with vascular disease is increasingly urgent given the prevalence of vascular disease in our aging population, greater appreciation of the interaction between vascular disease and AD

pathology, and potential contributions to the diagnosis and treatment of age-related disorders.

Vascular Disease: Associated Cognitive Impairments and Neuroimaging Markers

Older adults with prominent vascular disease and dementia present with a cognitive profile characterized by differential impairment on tests of executive control as compared to other domains of cognitive functioning. The cognitive profile of older adults with this sort of deficit is different from the profile of individuals with AD, another disease of later life affecting cognition. Work by several authors (Bernard et al., 1992; Libon et al., 1996a, 1998; LaFosse et al., 1997; Tierney et al., 2001) has shown patients with evidence of chronic vascular disease demonstrate relative sparing of episodic memory performance relative to patients with AD, although mild difficulty on tests of episodic memory, particularly on free recall trials, may be largely explained by executive functioning deficits (Davis et al., 2002). The executive control deficits associated with chronic vascular disease have been attributed to the disruption of frontal lobe-basal ganglia-thalamic pathways (Alexander, DeLong, & Strick, 1986; Sultzer et al., 1995). Ischemic damage to subcortical-cortical white matter projections and the basal ganglia may disrupt the modulation operations of the prefrontal cortex, including the ability to effectively maintain or shift mental set to meet the needs that may be required over time or when task demands are changed or become complex (Libon et al., 2004).

Atherosclerosis, the most common vascular disease (Fung & Poppas, 2009), is the underlying cause of many cardiovascular events and complications and may affect vessels throughout the body (Miller, Haynes, & Moser, 2009). Atherosclerosis is

associated with a complex series of molecular events leading to cellular accumulation (plaque) that narrows or occludes the lumen, as well as functional changes within the vessel layers that disrupt the natural functioning of the vessel. Although much attention was paid throughout most of the 20th century to the effects of vascular disease on large vessel anatomy manifested by acute stroke, chronic ischemic effects of atherosclerosis and other pathological processes are also found in the small vessels and may be at least equal contributors to cognitive change in later life. Arteriosclerotic small vessel disease is mainly characterized by loss of smooth muscle cells, deposits of fibro-hyaline material, narrowing of the vessel lumen, and thickening of the vessel wall (Pantoni, 2010). Small vessel disease leads to chronic hypoperfusion and degeneration of white matter (Pantoni, 2010). These white matter changes, which manifest as hyperintensities on T2-weighted MRI, have been termed “subcortical hyperintensities,” “white matter lesions,” and “unidentified bright objects” (Roman, 1987). Hachinski, Potter, and Merskey (1987) used the term leukoaraiosis (literally meaning “rarefied white matter”) as a descriptive term for these signal changes. White matter lesions (WML) are found in more than 95% of older adults over the age of 65 (Longstreth et al., 1996), and recent studies have shown that these lesions are directly associated with disruption of the structure of subcortical white matter (Auriel et al., 2014). Some authors have proposed a threshold of small vessel lesion burden at which cognitive changes become symptomatic and impact daily function (Libon et al., 2008; Price, Jefferson, Merino, Heilman, & Libon, 2005; Price et al., 2012; Roman et al., 1993).

AD-pathology: Associated Cognitive Impairments and Neuroimaging Markers

Alzheimer's disease, another common disease associated with dementia in late life, is characterized by a progressive anterograde amnesia with deficits in episodic memory at the level of encoding. The hippocampus, and the entorhinal cortex in particular, is typically the first area where the disease's hallmark pathology is seen in the accumulation of amyloid plaques and neurofibrillary tangles (Braak & Braak, 1991; Raz, 2005). Although Alois Alzheimer's classic paper describing a dementia with postmortem findings of plaques and tangles in the brain appeared in 1906, it was until many decades later that the plaques were described as amyloid and its sequence of either 40 (A β 1–40) or 42 (A β 1–42) amino acids was defined (Glennner & Wong, 1984). Executive control deficits in AD, while also present, are quantitatively and qualitatively different from individuals with dementia associated with cerebrovascular disease. AD patients show less severe executive deficits and the executive deficits in AD appear to be restricted to the response selection of lexical/ semantic information. On list learning tasks, such as the California Verbal Learning Test (CVLT; Delis et al., 1987; Libon, Mattson, & Glosser et al., 1996b), people with AD display poor retention, rapid forgetting, little to no benefit from cued recall or recognition test conditions, and the production of many intrusion errors. In contrast, people with vascular dementia show significantly higher scores on all measures of delayed free and cued recall episodic memory and significant improvement on recognition trials. These findings are similar to prior research showing that people with AD are more impaired on measures of episodic memory relative to people with Parkinson's Disease (PD) or Huntington's disease (HD), two other conditions characterized by subcortical neuropathology and executive dysfunction (Delis et al., 1991; Kramer et al., 1988; Massman et al., 1990).

Historically, AD has been the highest profile disease associated with hippocampal pathology. Not unlike the well-known case of H.M., people with AD show impaired ability to form new memories. In his meta-analysis of 12 longitudinal studies of hippocampal volume in normal aging, Raz found lifetime shrinkage at an average annual rate of approximately 1.23% (2005). Yearly shrinkage is slower in younger subjects ($\leq 1\%$) and faster in those age 70 or older (1.60% - 1.85%), but these rates are still much slower than in AD (3% - 4%) or in those with an early-onset familial form of the disease (up to 8%) (Raz, 2005). HC volumes predict concurrent AD and so are useful to distinguish people with AD from controls. Specifically, in AD, studies have suggested the entorhinal cortex (EC) is most prominently affected, with CA1 and the subiculum also involved, and relative preservation of DG and CA3 (Small et al., 2011). However, structural imaging studies that have compared the structure of the medial temporal lobes in participants with AD versus participants with vascular dementia have not shown differences in hippocampal volumes (Laakso et al., 1996; Mungas et al., 2001).

Cerebrovascular Disease and AD-pathology Continuum

Understanding of the relation between cognition, neuroimaging markers of pathology, and vascular risk factors in an aging cohort with vascular risk has likely been constrained by a tendency to dichotomize vascular disease and AD, and to separate vascular pathology from AD-related hippocampal changes and amyloid buildup. Approaching pathologies related to cognitive aging in this way has been reflective of the diagnostic criteria for AD and vascular dementia through DSM-IV (American Psychiatric Association, 2000), which each excluded the presence of another systemic or brain

disease that can account for deficits in cognition. This interpretation of the criteria created a framework in which each diagnosis was exclusive of the other – the presence of cerebrovascular disease ruling out an AD diagnosis, and the presence of AD ruling out a diagnosis of vascular dementia (American Psychiatric Association, 2000; McKhann et al., 1984; van Norden et al., 2012). However, the portrayal of cerebrovascular disease and AD as pure, separate, and mutually exclusive disease processes ignored a growing literature that acknowledges the co-existence of these pathological processes and points to links between them suggesting possible interdependence. Updated criteria have been improved to better reflect this evolving discussion (American Psychological Association, 2014).

Cerebrovascular and AD pathology are found together in more than 40% of older adults with dementia (van Norden et al., 2012). Patients clinically diagnosed with probable AD show a variety of underlying pathology, including amyloid plaques and tau tangles, as well as vascular pathology, such as white matter lesions and lacunar infarcts (van Norden et al., 2012). Several other issues point to a less than central role for plaques in the neurodegeneration and cognitive decline of AD. Recent efforts to develop pharmaceutical interventions for AD have focused on impacting levels of A β , but have not met with success. AD also shares its most common risk factor, aging, with another disease: cerebrovascular disease. The co-existence of these disease processes in many individuals must be considered.

Several lines of evidence suggest that amyloid aggregation and vascular insufficiency may even be mutually enhancing pathologies. Cerebral amyloid angiopathy,

characterized by deposition of amyloid in walls of small and medium cerebral arteries, is part of a series of findings that have contributed to a progressive blurring of the distinction between dementia of the Alzheimer type and vascular dementia. Indeed, the concept of 'mixed dementia' has been driven by the association between vascular risk factors and increased risk for AD, the identification of concomitant cerebral infarctions in many people with AD, and studies showing white matter lesions to be common in AD (Thoonsen et al., 2010). Whereas a relation between MTL atrophy and AD disease stage is well documented (Braak & Braak, 1991), a relation between vascular risk factors and MTL atrophy has also been observed in both AD and non-demented samples (de Leeuw, Barkhof, & Scheltens, 2004; de Leeuw, Korf, Barkhof, & Scheltens, 2006). There also appears to be overlap in the genes associated with AD and vascular-related pathology. Many current studies of cognitive decline in aging and neurodegenerative disease do not consider the influence of vascular pathology, and studies focused on cerebrovascular disease rarely consider hippocampal neuropathology. Yet, recent epidemiological, neuroimaging, pathological, pharmacotherapeutic, and clinical data suggest an important role of vascular pathology in AD onset and progression (DeCarli, 2004; van Norden et al., 2012). To examine the potential interaction between these pathologies, investigators must shift to a systems approach to understanding cognitive aging and degenerative disease. This approach emphasizes that dysfunction in network systems, such as the vasculature, can have multiplicative effects on other brain pathologies and acknowledges the organization and inter-connectedness of an organism (Kriete, Sokhansanj, Coppock, & West, 2006; Vidal, 2009).

The Current Study

Sample and Rationale. A study aiming to better understand the heterogeneity of cognitive impairment in older adults will consider cognitive performance across domains associated with both vascular disease and AD pathology and consider related neuroimaging markers. Examining these issues in a cohort with increased vascular risk is important because it will allow careful examination of a sample reflective of risk factors of cognitive impairment with high prevalence in the aging population. Therefore, this study examined a sample of older adults with significant vascular disease recruited from cardiology clinics. Currently the baseline cognitive performance of such a sample is poorly characterized. The few authors that have looked at this type of sample consistently found existence of a substantial portion with cognitive impairments (Hogue et al., 2006; Hudetz, Patterson, & Pagel, 2012; Silbert, Scott, Evered, Lewis, & Maruff, 2007). However, these studies have not carefully examined domains of deficits or considered individual profiles across multiple domains of cognition.

Study aims and hypotheses.

Aim 1 – Identify classes of participants exhibiting meaningfully different patterns of performance on neuropsychological measures in a sample of older adults with high vascular risk.

Hypothesis 1 – Identification of multiple classes of participants differing in terms of the dominant cognitive domain of deficit. Specifically, three groups of participants

were expected, exhibiting primary deficits in executive functions, episodic memory, and mixed domains (executive functions and episodic memory).

Aim 2 – Determine whether and to what extent the cognitive classes identified in Aim 1 demonstrate different patterns of neuroimaging data.

Hypothesis 2 – Demonstration of differences between cognitive classes in terms of neuroradiologic indicators of neuropathology. Specifically, the groups were expected to differ such that the predominantly amnesic class would demonstrate smaller hippocampal volumes compared to other classes, the predominantly dysexecutive participants would demonstrate greater volumes of white matter disease, and mixed profile participants would exhibit findings in line with the presence of both pathologies.

Aim 3 – Determine whether and to what extent the cognitive classes identified in Aim 1 demonstrate differences in level of vascular risk.

Hypothesis 3 – Demonstration of differences between cognitive classes in terms of vascular risk as quantified by the Framingham Score (Wolf, 1991). Specifically, the class exhibiting a cognitive profile with predominant executive deficits was expected to exhibit greater vascular risk compared to classes with a mixed profile or with predominant deficits in episodic memory.

Implications. This study considered aspects of cognition and brain pathology that are often examined in isolation, including sophisticated neuropsychological measures of memory and executive functioning, hippocampal and vascular-related pathology, and multiple vascular risk factors. The study also employed a person-centered statistical

technique in its examination of this complex system, an approach that affords consideration of within-person profiles across multiple cognitive measures. The results sought to identify patterns of cognitive performance and examine their association with the brain observable on MRI and with levels of vascular risk. Demonstrating the utility of a specific set of neuropsychological measures to characterize cognitive profiles with predominant deficits in specific domains would enable better prediction of future disease course and facilitate planning for patients and families. The association of cognitive profiles with structural brain measures could strengthen the rationale for neuropsychological assessment when changes in these measures are detected. For example, neuroimaging findings indicative of white matter abnormalities in a patient with memory complaints may strengthen a provider's rationale to request neuropsychological evaluation. The association of vascular risk factors with cognitive profiles is particularly important, as vascular risk factors represent modifiable targets for intervention that can have a substantial impact on future cognition and ultimately on functional independence. Not only are these risk factors modifiable in advanced stages of the lifespan, but they can be targeted early in life to avoid later cognitive change. A study that identifies meaningful cognitive subgroups within a sample of older adults with a broad range of vascular risk and cognitive abilities will inform understanding of the relations between cognition, brain, and vascular risk factors and could have broad impact across disciplines and diseases.

CHAPTER 2

METHODS

Participants

Participants were in the R01-funded study “Stroke and Cognition in Surgical Aortic Stenosis” at The Hospital of the University of Pennsylvania (HUP) and the Presbyterian Medical Center (PMC), both within the University of Pennsylvania Health System. The demographics and clinical characteristics of this sample will be presented in the Results section. The study was approved by the Institutional Review Boards of the University of Pennsylvania and Temple University with the primary aim of determining the incidence of the composite outcome of stroke and cerebral transient ischemic events in older adults after surgery for aortic valve replacement (AVR) for calcific aortic stenosis (AS). A non-surgical control group matched for age and disease was also included in the study. Participants undergoing surgery were recruited from the clinics of and by the participating surgeons. The decision to refer a patient for surgery was made by his/her cardiologist/surgeon in the context of a patient’s regular clinical care based upon severity of AS and other clinical factors. Control subjects were recruited from the cardiovascular clinics of the participating hospitals (HUP/PMC), from echo and catheterization databases of collaborating cardiologists, and from databases of research volunteers at the University of Pennsylvania. The present study considered all participants, including those in the surgical group at baseline (47.1%) and the control group (52.9%), in examining the sample as a single cohort of older adults with increased vascular risk.

Participants were older adults (age ≥ 65) with calcific aortic stenosis and/or coronary artery disease. Aortic valve disease ranged in severity from mild to critical, suggesting a range of vascular risk was present in the sample. In addition, all participants had fluency in English, and completion of a minimum of six grades of education or a work history sufficient to exclude mental retardation. For the present study, Mini-Mental Status Exam (MMSE; Folstein, Folstein, & McHugh, 1975) of ≥ 24 was elected in order to focus the study on a sample without dementia. Participants meeting any of the following criteria were not included: history of aortic valve replacement with root or arch replacement for aortic aneurysm or dissection; any procedure requiring hypothermic arrest; presence of endocarditis; stroke or Transient Ischemic Attack (TIA) within the preceding 6 months; carotid endarterectomy (CEA) / stenting within 6 weeks of surgery; symptomatic or asymptomatic severe occlusive carotid disease requiring concomitant CEA/ stenting and CABG, in accordance with AHA guidelines; any significant neurologic disease, such as Parkinson's disease, Huntington's disease, normal pressure hydrocephalus, brain tumor, progressive supranuclear palsy, seizure disorder, subdural hematoma, multiple sclerosis, or history of significant head trauma followed by persistent neurologic deficits or known structural brain abnormalities; presence of device or condition incompatible with MRI.

Neuropsychological measures

From an original sample of 398 participants, 17 were excluded due to MMSE < 24 , 15 refused or withdrew prior to cognitive testing, and 7 were excluded from the parent study after switching from the control to surgical groups. The remaining

participants ($N=359$) were administered neuropsychological measures of episodic memory and executive functions by trained psychometrists within a full neuropsychological protocol. Most participants (90.5%) had complete data across all cognitive measures with at most 6% of participants missing data on any one cognitive variable. All neuropsychological tests were scored by the psychometrist and a second, independent rater blind to participant group (surgical vs. control); discrepancies were resolved by a third coder who was also blind to group.

Verbal episodic memory was evaluated using the delayed free recall trial of the Hopkins Verbal Learning Test Revised (HVLT-R; Brandt, Benedict, and Lutz, 2001), a twelve-word list learning task administered over three learning trials followed by free recall and recognition trials after a delay. The recognition discriminability index was also used in analyses because it minimizes the retrieval demands inherent to free recall and can distinguish amnesic patients from those with more severe retrieval deficits (Graham et al., 2004; Kramer et al., 1988; Libon et al., 1988; Massman et al., 1990). Visual episodic memory was assessed using the delayed free recall trial of the Rey-Osterrieth Complex Figure Test (RCFT; Meyers & Meyers, 1995; Rey, 1941). Performance on the RCFT was scored for accuracy using standard criteria (Spreen & Strauss, 1998; Taylor, 1959) by two independent raters with resolution of discrepancies by a third rater.

Verbal Fluency (FAS; Spreen & Strauss, 1991), the Trail Making Test (Reitan, 1958, 1971), the Boston Revision of the Mental Control subtest from the Wechsler Memory Scale (WMS; Wechsler, 1945), and the Digit Span subtest from the Wechsler Adult Intelligence Scale Third Edition (WAIS-III) were administered to assess executive

functions. Variables from these measures that were included in analyses were Verbal Fluency total words, Trails B time to completion, Mental Control non-automatized accuracy index, and Digit Span backwards score. The Mental Control Non-Automatized Accuracy index is calculated using the following formula: Mental Control Accuracy Index = $[1 - ((\text{false positives} + \text{misses}) / \text{number of possible correct})] \times 100$. This calculation yielded a percentage score such that patients obtaining a score of 100% correctly identified all targets and made no false positive responses or misses. Tasks in this measure include reciting the months of the year backwards; an alphabet rhyming task requiring patients to identify letters that rhyme with the word 'key'; and an alphabet visualization task requiring patients to provide all block printed letters that contain curved lines. Please see Table 1 for a summary of measures and information of aspects of cognitive abilities indexed by each measure.

Table 1

List of Cognitive Tests, Test Descriptions, and Variables by Cognitive Domain

Domain	Test	Description	Variables in Analyses (possible range)	Aspects of Cognitive Abilities Indexed
Episodic Memory	Hopkins Verbal Learning Test (HVLT)	12-word list administered over 3 learning trials, a delay trial, and a 24-word recognition trial	Delayed free recall total correct (0 - 12) Recognition discriminability index (-12 - +12)	Retain and recall verbal information Recall with increased retrieval support and inclusion of foils
	Rey Complex Figure Test (RCFT)	complex geometric design presented for copy; figure redrawn from memory immediately after the copy (immediate recall) and again after 30 minutes (delayed free recall)	Delayed free recall (0 - 36)	Retain and recall visual information
Executive Functions	Trail Making Test Part B	a line must be drawn alternating between numbers and letters	Total time to complete (0 - 301 sec (max permitted)).	Visuo-motor speed, maintenance of set, switching
	Mental Control-Non-Automated Tasks	3 non-automated tasks must be completed quickly (e.g., recite months backward)	Accuracy Index (0 - 100%)	Sustained mental search, working memory, novel tasks involving verbal and spatial information
	Digit Span Test-Digits Backward	increasing lengths of number sequences are repeated in backwards order	Total correct on digit span backward (0 - 14)	Working memory
	Verbal Fluency (FAS)	as many words as possible beginning with F, A, and S must be generated within 60 seconds in successive trials	Total number of words (0 - no upper limit)	Sustained mental search of verbal information, speeded task

All primary analyses were run using raw scores for each measure. Raw scores indicate the absolute level of test performance, but they do not provide information regarding whether scores are impaired or within normal limits. Therefore, normative-based Z-scores based on published age-based normative data also were used in follow-up analyses. Normative-based Z-scores were used to facilitate the conceptualization of the different classes (HVLTR, Brandt, Benedict, & Lutz, 2001; RCFT, Chiulli, Haaland, LaRue, & Garry, 1995; FAS, Delis, Kaplan, & Kramer, 2001; Trails B, Tombaugh, 2004 using weighted means and weighted standard deviations; Mental Control, D. J. Libon, personal correspondence, August 21, 2012; Digit Span Backward, Wechsler, 1997).

Neuroimaging Measures

Magnetic resonance imaging (MRI) was performed at two clinical sites within the University of Pennsylvania Health System: HUP and PMC. MRI brain scans were acquired clinically using 1.5 Tesla Avanto, Espree, and Sonata systems at HUP and a 1.5 Tesla GE system at PMC. The MRI protocols at the two sites were comparable with slight differences due to the settings of the different manufacturers. Multimodal image sets were obtained, including MR modalities of T1-weighted, T2-weighted, proton density-weighted (PD), and fluid attenuation inversion recovery (FLAIR).

Volumes of white matter lesions and hippocampus were identified using a computer-assisted multiparametric segmentation method (Lao et al., 2008) that was specifically developed to process MRI scans of older adults. This technique utilizes the information from multimodal MRI sequences, as each imaging modality offers different contrast effects and sensitivity to ischemic pathology. A support vector machine classifier

trained on expert-defined WMLs was used in the current analysis. Postprocessing analysis further reduces false positives by using anatomic knowledge and measures of distance from the training set. The technique was cross-validated on a population of 35 patients from three different imaging sites with WMLs of varying sizes, shapes, and locations to test the robustness and accuracy of the segmentation method, compared with the manual segmentation results from two experienced neuroradiologists. Volumes of WMLs were calculated in white matter regions including corpus callosum, subcortical white matter regions in frontal, occipital, parietal, and temporal lobes, deep white matter (anterior limbs of internal capsule, posterior limbs of internal capsule including cerebral peduncles, fornix), and white matter in cerebellum. Hippocampal volumes were obtained as a region of interest (ROI) within the WMLS technique described above. Right and left volumes for hippocampus were calculated and summed to produce total hippocampal volume. As volume measures may vary by head size, WML and hippocampal volumes adjusted for intracranial volume were used in analyses.

Imaging analyses were conducted for 203 participants on white matter lesion (WML) and hippocampal volumes obtained from 1.5T MRI. Imaging was acquired within 9 weeks of cognitive testing for 198 of 203 participants in the imaging sample (97.5%), with 90% within 4 weeks of testing. Four participants had imaging between 1 and 2 years after testing, and 1 participant with time difference of 3.5 years. Participants with no imaging data either had their imaging excluded because of poor quality or incorrect scan sequences or never had imaging for reasons including refusal, claustrophobia, or pacemaker implantation or discharge prior to imaging. For participants

in the surgical group of the broader study, pre-surgical baseline imaging was used when available. In the case that baseline neuroimaging data were not obtained, post-operative imaging data was used. When participants whose imaging was acquired post-surgically ($n = 41, 20.2\%$) were compared to the rest of the imaging sample, no significant differences in volumes of white matter lesions ($U = 2972.00, p = .30$) or hippocampus ($t = -0.11, p = .92$) were detected. When participants with acute post-surgical lesions ($n = 22, 10.8\%$) identified on DWI were compared to the rest of the imaging sample, no significant differences in volumes of white matter lesions ($U = 2340.00, p = .18$) or hippocampus ($t = 0.09, p = .93$) were detected. As white matter lesion volumes were not normally distributed, a nonparametric test (Mann-Whitney's U) was used in comparisons.

Vascular Risk Score

The Framingham Risk Score (Wolf, D'Agostino, Belanger, & Kannel, 1991), included as a measure of vascular load, is calculated based on nine variables: sex, age, blood pressure, diabetes, coronary artery disease, atrial fibrillation, smoking, left ventricular hypertrophy (LVH), and antihypertensive medication. For the current study, the nine variables were collected via interview at baseline (i.e., sex, age, medications, diabetes, smoking, and atrial fibrillation) or chart review (i.e., blood pressure, LVH). Blood pressure data were obtained within 16 weeks of the administration of cognitive testing for all participants; for 80% of the sample blood pressure was obtained within 4 weeks of testing. The presence of LVH was gathered via review of cardiologist reports on clinical echocardiograms performed within 48 weeks of testing; 80% of the sample had estimates of LVH that were obtained within 24 weeks of cognitive testing. Based on the

participant inclusion/exclusion criteria for the overall study, all participants were determined to meet criteria for cardiovascular disease.

To calculate the vascular risk score, weighted scores are assigned to each of the nine variables (Wolf et al., 1991) and then summed. The dependent variable used for the current study was the sum of the weighted score (i.e., Framingham Score), which ranges from 1 to 30 with higher scores reflecting a greater vascular load and a higher risk for stroke. Based on data from the Framingham study population (Wolf et al., 1991), the sum of the weighted scores are associated with an actual estimated risk for future stroke. For example, males with Framingham scores of 10, 20, and 30 are associated with 10-year stroke risks of 10%, 37%, and 88%, respectively.

Framingham Stroke Scores were obtained for 187 participants because of unavailability of blood pressure values (n = 281) or echocardiogram for determination of LVH (n = 214) in the medical chart within established timeframes.

Analyses

Latent class analysis (LCA) was performed on the cognitive data to identify and characterize cognitive subgroups based on the seven previously described cognitive items (see Table 1). Statistical analyses were performed with Mplus Version 7 (Muthén & Muthén, 1998-2012). Raw scores were used to maximize the variability in scores as LCA allows for the use of nonstandardized variables (Nylund, Asparouhov, & Muthén, 2007; Nylund, Bellmore, Nishina & Graham, 2007). Unlike other person-centered techniques such as cluster analysis, which identifies the number of classes requested by a researcher,

LCA uses a stepwise procedure and a variety of fit indices to determine the number of classes providing the best fit to the data (Beauchaine, 2003). LCA models are fit to the data in a series of steps, starting with a one-class (independence) model, and increasing the number of classes one at a time until there is no further improvement in model fit (Nylund et al., 2007a, 2007b) based on fit indices including Bayesian Information Criterion (BIC; Schwartz, 1978), Akaike Information Criterion (AIC; Akaike, 1987), and Sample-size Adjusted BIC (ABIC; Sclove, 1987). The model yielding the smallest values on these indices is considered the best fitting model. In addition, the Bootstrap Likelihood-Ratio Test (BLRT) was considered, which compares the model with k classes to the model with $k - 1$ classes, the resulting p -value indicating whether model fit is improved with an additional class (Nylund et al., 2007a). The Vuong-Lo-Mendell-Rubin Likelihood-Ratio Test (VLMRLRT), another likelihood-based technique, was also used in comparing the LCA models. Another important feature of LCA is that it takes into account uncertainty associated with latent class membership, as cases are not absolutely assigned to classes, but rather have a probability of membership for each class (i.e. posterior probabilities). Entropy, a summary score of posterior probabilities, reflects how well participants fit into the classes of a specific model, with values closer to 1 indicating greater classification certainty.

Conceptual model and theory also influence model selection. Specifically, models were examined to determine if the addition of another class was substantively and clinically meaningful and consistent with previous research and existing conceptual models. The size of the smallest class in a model was also considered, with classes

comprised of less than 10% of the total sample suggestive of data over-fitting and poor reproducibility.

There are no “gold standard” guidelines regarding the number of participants and power for a proposed LCA. Monte Carlo simulation studies using a variety of sample sizes suggest that the BIC and BLRT are the most robust indicators of classes (Nylund et al., 2007a). If the study were underpowered to perform these analyses or a one-class model provided the best fit to the data (suggesting that a person-centered approach is not necessary), fit statistics would converge to suggest that the one-class model should be selected.

LCA models were run with and without the inclusion of age as a variable to determine whether this influenced class membership. Following the identification of classes, the influence of age, education, Mini-Mental State Exam score (MMSE), Geriatric Depression Score (GDS; Yesavage et al., 1983), and State-Trait Anxiety Inventory (STAI; Spielberger, Gorsuch, & Lushene, 1970; Spielberger, Reheiser, Ritterband, Sydeman, & Unger, 1995) was considered in auxiliary analyses by holding class membership (i.e., posterior probabilities) constant and examining differences across classes.

In addition, tests of equality of means across the cognitively-defined classes were conducted on imaging data, to determine if the classes differed in WML and hippocampal volumes, and on Framingham Score, to determine if the classes differed in vascular risk. The test of equality of means provides chi-square statistics for omnibus and pairwise

comparisons across the classes. Pairwise comparisons were examined only if omnibus tests were significant.

CHAPTER 3

RESULTS

Demographic Characterization of the Sample and Subsamples

On average, participants were well-educated older adults, with levels of depression and anxiety symptoms in the normal range, performed well on the MMSE, and were predominantly male (67%) and Caucasian (89%) (see Table 2). Participants with imaging data differed from those without imaging data on all demographic variables (age, education, GDS, STAI, and MMSE). On average, the imaging subsample was younger ($t = 2.22, p = .03, d = .24$), more educated ($t = -3.44, p < .01, d = .36$), had fewer depressive symptoms ($t = 3.33, p < .01, d = .35$), lower levels of anxiety ($t = 2.86, p < .01, d = .32$) and higher scores on the MMSE ($t = -2.44, p = .02, d = .25$) than those without imaging data (Table 2). Although differences were statistically significant, they were small and not considered meaningful (e.g., one-point difference in MMSE score) individually. When considered together, however, these group differences suggest that the imaging subsample may have had somewhat less overall impairment than the total study sample. When MMSE scores were converted to age-based normative z-scores (Crum, Anthony, Basset, & Folstein, 1993), there was no significant difference between the imaging subsample and those without imaging data ($t = -1.60, p = .11, d = .17$). In terms of sex and race, the imaging sample (68% male; 89% Caucasian) was not significantly different from those without these data [65% male; 89% Caucasian; sex: $X^2(1, N = 359) = 0.42, p = .52$; race: $X^2(4, N = 359) = 2.16, p = .71$].

Demographic characteristics did not differ between the subsample of participants for whom Framingham data were available and those without Framingham data ($t < |1.20|$, $p > .05$ for all), with the exception of slightly higher scores on a measure of anxiety (STAI) in those with Framingham data ($t = -2.50$, $p = .01$). Although statistically significant, the difference is not clinically meaningful and the effect size is small ($d = .27$). In terms of sex and race, participants with Framingham data (63% male; 90% Caucasian) were not significantly different from those without these data [70% male; 87% Caucasian; sex: $X^2(1, N = 359) = 2.12$, $p = .15$, race: $X^2(4, N = 359) = 2.77$, $p = .60$].

Table 2

Demographic Characteristics of Participants in the Study

	Total Sample ($N = 359$)		Vascular Risk Subsample ($n = 187$)		Imaging Subsample ($n = 203$)	
	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range
Age	74.70 (6.05)	65-90	75.16 (5.84)	65-88	74.08 (6.07)	65-88
Education	14.54 (3.10)	4-20	14.24 (3.09)	4-20	15.02 (2.89)	6-20
GDS	3.21 (3.77)	0-20	3.44 (3.89)	0-20	2.64 (3.50)	0-16
STAI	31.93 (10.36)	20-73	33.30 (10.20)	20-66	30.60 (9.99)	20-73
MMSE	27.91 (1.50)	24-30	27.78 (1.52)	24-30	28.07 (1.44)	24-30

Note. GDS = Geriatric Depression Score; STAI = State-Trait Anxiety Inventory; MMSE = Mini-Mental Status Examination.

Summary Statistics

Summary statistics for the cognitive measures, neuroimaging variables, and vascular risk scores are presented in Table 3.

Table 3*Summary Statistics for Cognitive, Neuroimaging, and Vascular Risk Variables*

	<i>M</i>	<i>SD</i>	Range
Cognitive Variables (N = 359)			
<i>Episodic Memory</i>			
HVLT Delayed Free Recall	7.15	2.76	0-12
HVLT Discriminability Index	9.32	2.03	0-12
RCFT Delayed Free Recall	13.8	6.28	0-31
<i>Executive Functions</i>			
Verbal fluency (FAS)	36.14	12.59	10-71
Trails B	124.92	65.19	43-301
Mental Control	80.89	16.64	25-100
Digits Backwards	6.48	2.42	0-14
Neuroimaging Variables (n = 203)			
WML	5.56	7.85	0.09-61.45
Hippocampus	7.87	0.90	5.92-10.97
Vascular Risk Variable (n = 187)			
Framingham Score	21.27	4.41	8-33

Note. HVLT = Hopkins Verbal Learning Test; RCFT = Rey-Osterrieth Complex Figure Test; WML = white matter lesions. Framingham Score calculated as described in Wolf et al., 1991. Cognitive variable data are raw scores. Neuroimaging variable data are volumes in cm³ and were adjusted for intracranial volume in analyses.

Intercorrelations

Correlations between cognitive measures, demographic variables, imaging variables, and Framingham were examined (see Tables 4 and 5). All associations were in the expected direction. Although many of the correlations reached significance ($p < .05$), most relations were considered weak (i.e., $r < .30$). Moderate correlations were observed between measures in the same domain, i.e., episodic memory and executive functions.

Relations between the memory measures and two of the executive measures, MC and Trails B, appeared stronger in general ($r = .24$ to $.36$) than relations between the memory measures and the other two executive variables ($r = .09$ to $.28$). Two demographic variables, education and MMSE, showed moderate correlations with several executive measures: education with MC ($r = .40$), Trails B ($r = -.30$), and FAS ($r = .30$); MMSE with MC ($r = .45$), Trails B ($r = -.38$), and DB ($r = .36$). Correlations with WML showed significant relations in the expected direction between WML and a measure of executive function (Trails B) and age; however, these correlations should be interpreted with caution because of skewness of the WML variable. Hippocampal volumes did not correlate significantly with any cognitive variables. The Framingham score correlated significantly with age, Trails B, MMSE, and WML.

Table 4

Intercorrelations between the Cognitive Variables

	HVLT DFR <i>n</i> = 352	HVLT DI <i>n</i> = 349	RCFT DFR <i>n</i> = 342	MC <i>n</i> = 356	Trails B <i>n</i> = 346	FAS <i>n</i> = 344	DB <i>n</i> = 339
HVLT DFR		0.63*	0.41*	.35*	-.36*	.25*	.28*
HVLT DI			.30*	.27*	-.24*	.18*	.21*
RCFT DFR				.27*	-.35*	.09	.13*
MC					-.41*	.43*	.40*
Trails B						-.33*	-.38*
FAS							.39*
DB							

Note. N's range from 330 to 359 for correlations between cognitive tests. HVLT = Hopkins Verbal Learning Test. DFR = Delayed free recall. DI = Discriminability Index. RCFT = Rey-Osterrieth Complex Figure Test. MC = Mental Control. DB = Digits Backwards. * = $p < .05$.

Table 5

Correlations between the Cognitive Variables, Demographic Variables, and Imaging Variables

	Age	Education	GDS	STAI	MMSE	HC	WML	Framingham
	<i>n</i> = 359	<i>n</i> = 358	<i>n</i> = 354	<i>n</i> = 336	<i>n</i> = 359	<i>n</i> = 203	<i>n</i> = 203	<i>n</i> = 187
HVLT DFR	-.24*	.17*	-.10	-.06	.29*	.11	-.04	-.14
HVLT DI	-.20*	.10	.00	-.03	.19*	.09	-.10	-.14
RCFT DFR	-.22*	.19*	-.18*	-.17*	.22*	.11	-.07	.00
MC	-.13*	.40*	-.14*	-.18*	.45*	-.01	-.02	-.02
Trails B	.28*	-.30*	.27*	.21*	-.38*	-.03	.15*	.17*
FAS	-.01	.30*	-.13*	-.20*	.28*	-.02	.04	.05
DB	-.15*	.27*	-.11	-.16*	.36*	-.10	-.10	-.15
Age		-.09	.06	.02	-.25*	-.23*	.21*	.60*
Education			-.23*	-.18*	.37*	-.13	-.08	.04
GDS				.37*	-.15*	-.07	.00	.05
STAI					-.10	.06	-.05	-.15
MMSE						-.02	.01	-.22*
HC							.00	-.02
WML								.21*
Framingham								

Note. N's range from 330 to 359 for correlations between cognitive tests and demographic variables, from 172 to 203 for correlations between cognitive tests and imaging variables, and *n* = 95 for correlations between imaging variables and Framingham score. HVLT = Hopkins Verbal Learning Test. DFR = Delayed free recall. DI = Discriminability Index. RCFT = Rey-Osterrieth Complex Figure Test. MC = Mental Control. DB = Digits Backwards. GDS = Geriatric Depression Scale. STAI = State-Trait Anxiety Index. MMSE = Mini-Mental State Examination. HC = Hippocampal volume. WML = White matter lesion volume. Imaging variables were adjusted for intracranial volume. * = $p < .05$.

Aim 1/Hypothesis 1 – LCA on the cognitive variables

LCA models were conducted with the raw scores of the seven cognitive variables (see Table 1). A one-class model was fit first, followed by models with additional classes. As indicated in Table 6, the lowest BIC, AIC, and ABIC were found for the three-class model; moreover, the BLRT indicated that the three-class model provided an improvement in fit from the two-class model. The four-class model did not replicate even with increased starts, and the additional class was comprised of outliers on the Trails B test. Thus, outliers likely influenced the four-class model solution, suggesting the three-class model is more meaningful. Further support for the three-class model was obtained by a separate LCA with z-scores calculated using age-based normative data for each cognitive measure rather than raw scores. The three-class LCA model for z-scores yielded classes of very similar sizes and excellent fit indices (e.g., BLRT = $<.01$; Entropy = 0.87). Finally, when age was included in the three-class model of raw test scores, it did not influence the distribution of individuals within the classes. Thus, the three-class model was stable and meaningful and used for all subsequent analyses.

Table 6*Fit Indices for Latent Class Analysis Models with 1-4 Classes*

Classes	Free parameters	Log likelihood	AIC	BIC	ABIC	VLMRLRT	BLRT	Entropy
1	14	-8292.4	16612.8	16667.2	16622.7	-	<.01	-
2	22	-8091.4	16226.7	16312.2	16242.4	<.01	<.01	0.83
3	30	-8010.8	16081.7	16198.2	16103.0	.13	<.01	0.78
4	38	-7964.2	16004.5	16152.1	16031.5	.02	<.01	0.86

Note. AIC = Akaike information criterion; BIC = Bayesian information criterion; ABIC = Adjusted BIC; VLMRLRT = Vuong-Lo-Mendell-Rubin Likelihood Ratio Test; BLRT = Bootstrap Likelihood Ratio Test. VLMRLRT and BLRT data are *p*-values.

Conceptual considerations and my theoretical framework were used to characterize the three-class model. Both the raw test scores that were used in the LCA and norm-based z-scores were examined to interpret the classes. Mean raw and norm-based z-scores for the cognitive variables across the three classes are included in Table 7. Class 3 (intact; n=178) was characterized by relatively intact cognitive test scores compared to the other classes and compared to normative data. All norm-based z-scores for Class 3 were well within the average range, with mean scores for Digits Backwards and FAS falling within the high average range. Classes 1 (mildly impaired; n=136) and 2 (dysexecutive; n=45) demonstrated uniformly low scores compared to Class 3. Class 1's mean norm-based z-scores fell within the average to mildly impaired range and were generally approximately a standard deviation lower than Class 3. Class 2 showed the lowest and most impaired scores on two executive measures (Trails B and Mental Control). The average norm-based z-scores on these two executive measures were well over two standard deviations below the mean; all other norm-based scores fell within the average to mildly impaired range and were at least a standard deviation lower than Class 3.

Participants from the surgical and control groups of the parent study were relatively evenly distributed over the classes, with Class 1 composed of equal numbers of control and surgical group participants, Class 2 composed of 47.7% controls and 53.3% "surgicals", and Class 3 composed of 56.7% controls and 43.3% "surgicals". Exact binomial tests indicated that these differences did not reach statistical significance ($p > .05$ for all).

Table 7*Neuropsychological Test Scores Across the Three-Class Model*

	Latent Class 1 Mildly Impaired (<i>n</i> = 136)				Latent Class 2 Dysexecutive (<i>n</i> = 45)				Latent Class 3 Intact (<i>n</i> = 178)			
	Raw Score		Norm-derived z-score		Raw Score		Norm-derived z-score		Raw Score		Norm-derived z-score	
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
HVLT Delayed Free Recall	5.58	2.35	-0.93	0.86	5.16	2.79	-1.04	1.00	8.85	1.87	0.24	0.70
HVLT Discrim. Index	8.26	1.82	-1.22	1.06	8.18	2.79	-1.10	1.29	10.40	1.25	0.03	0.78
RCFT Delayed Free Recall	11.71	5.13	-0.47	0.90	8.51	4.63	-0.91	0.84	16.69	5.97	0.33	1.05
Verbal fluency (FAS)	30.43	9.95	-0.39	1.06	29.23	12.74	-0.45	1.30	42.20	11.48	0.75	1.15
Trails B	124.91	35.58	-0.34	1.11	268.44	33.77	-3.55	2.27	88.85	29.14	0.42	0.95
Mental Control	76.26	15.55	-1.29	1.37	63.40	21.26	-2.43	1.88	88.92	10.15	-0.17	0.90
Digits Backwards	5.53	1.85	-0.09	0.90	4.34	1.24	-0.68	0.64	7.69	2.35	0.84	1.03

Note. HVLT = Hopkins Verbal Learning Test; RCFT = Rey-Osterrieth Complex Figure Test. Classes were formed based on raw scores. Norm-derived z-scores were calculated using age-based normative data for each cognitive measure and were examined to facilitate the characterization of the classes.

Comparisons of covariates among classes. The influence of five covariates on the three-class model was analyzed by holding class membership (i.e., posterior probabilities) constant and examining differences in age, education, GDS, STAI, and MMSE. Omnibus analyses revealed that the classes differed significantly on all covariates (see Table 8). Follow-up pairwise comparisons showed that on average, Class 3 (intact) was younger, more educated, and had fewer anxiety symptoms and a higher MMSE score than the other classes. Class 2 (dysexecutive) was older, less educated, and had more symptoms of depression and lower MMSE scores than the other classes. Of note is that although the class differences in depression (GDS) and anxiety (STAI) symptoms were statistically significant, the magnitudes of the differences were quite small and are not considered clinically meaningful. For example, all GDS and STAI class means were well within the normal range (Bergua et al., 2012; Yesavage et al., 1983).

When sex was examined across the classes, it was found that Class 2 (dysexecutive) had a smaller proportion of male participants (47% male) compared to Class 1 (72%) and Class 3 (67%) ($X^2(2, N = 359) = 9.91, p < .01, \phi = .17$). Race was also found to differ across the classes, with Class 2 (dysexecutive) having a smaller proportion of Caucasian participants (69%) compared to Class 1 (88%) and Class 3 (94%) when numbers of Caucasian compared to not Caucasian participants were analyzed ($X^2(2, N = 359) = 22.10, p < .01, \phi = .25$). Further inspection revealed that 28.9% of Class 2 was African American, compared to 9.6% of Class 1 and 4.5% of Class 3.

Table 8*Comparisons of Covariates between Latent Classes*

	Latent Class 1		Latent Class 2		Latent Class 3								
	Mildly Impaired <i>n</i> = 136		Dysexecutive <i>n</i> = 45		Intact <i>n</i> = 178		Omnibus chi-square test			Class Comparisons			
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	χ^2	<i>p</i>	ϕ	Interpretation	ϕ 1&2	ϕ 2&3	ϕ 1&3
Age	75.56	6.09	77.62	5.88	73.30	5.69	19.18	<.01	0.23	3 < 1 < 2	0.17	0.30	0.15
Education	13.99	3.05	12.60	3.03	15.44	2.83	29.91	<.01	0.29	2 < 1 < 3	0.20	0.38	0.20
GDS	3.39	3.84	5.41	4.87	2.52	3.15	11.80	<.01	0.18	1&3 < 2	0.17	0.23	0.10
STAI	33.39	10.66	36.97	10.09	29.67	9.61	13.69	<.01	0.20	3 < 1&2	0.14	0.26	0.14
MMSE	27.46	1.39	26.71	1.78	28.54	1.17	40.16	<.01	0.33	2 < 1 < 3	0.19	0.41	0.30

Note. GDS = Geriatric Depression Score; STAI = State-Trait Anxiety Inventory, State Score; MMSE = Mini-Mental Status Exam.

Aim 2/Hypothesis 2 – Class differences on neuroimaging variables

Tests of equality of means were conducted to determine whether classes differed on volumes of white matter lesions and hippocampus after controlling for head size (i.e., intracranial volume). White matter lesion volumes were not normally distributed.

Omnibus analyses showed that differences between the classes on white matter lesion volumes did not reach statistical significance, although a trend was present ($p = .12$; see Table 9). Also, effect sizes showed the differences between Class 2 and Classes 1 and 3 were greater than the difference between Class 1 and Class 3. No significant differences between the classes on hippocampal volumes were found.

Table 9*Comparisons of Vascular Risk and Neuroimaging Variables Across Classes*

	Latent Class 1		Latent Class 2		Latent Class 3		Omnibus chi-square test			Class Comparisons			
	Mildly Impaired <i>n</i> = 136		Dysexecutive <i>n</i> = 45		Intact <i>n</i> = 178		χ^2	<i>p</i>	ϕ	Interpretation	ϕ 1&2	ϕ 2&3	ϕ 1&3
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>							
Neuroimaging Variables													
WML	5.51	6.96	7.79	6.20	5.19	8.55	4.28	0.12	0.15	-	0.19	0.17	0.01
Hippocampus	7.72	1.00	7.47	0.55	8.03	0.87	0.54	0.76	0.05	-	0.00	0.06	0.06
Vascular Risk Variable													
Framingham	21.20	4.72	23.19	3.42	20.75	4.28	7.84	0.02	0.20	3 < 2	0.19	0.25	0.05

Note. WML = white matter lesions. Framingham Score calculated as described in Wolf et al., 1991. Neuroimaging data are volumes in ml and were adjusted for intracranial volume in analyses. Neuroimaging Variable class sizes: 66, 21, 116, respectively. Vascular Risk Variable class sizes: 76, 26, 85, respectively.

Aim 3/Hypothesis 3 – Class differences on vascular risk score

Tests of equality of means across latent classes were conducted to determine whether classes differed in terms of vascular risk score (i.e., Framingham score). Omnibus analyses revealed that the classes differed significantly on the Framingham Score. As shown in Table 9, follow-up pairwise comparisons showed that Class 2 (dysexecutive) had a significantly higher stroke risk score compared to Class 3 (intact). The difference between Class 2 (dysexecutive) and Class 1 (mildly impaired) (Class 2 > Class 1) trended towards significance, with a small effect size. In male participants, mean Framingham scores represented approximate 10-year probabilities of stroke of 43% for Class 3 (intact), 44% for Class 1 (mild), and 55% for Class 2 (dysexecutive) (Wolf et al., 1991). In female participants, mean Framingham scores represented approximate 10-year probabilities of stroke of 37% for Class 3 (intact), 41% for Class 1 (mild), and 57% for Class 2 (dysexecutive) (Wolf et al., 1991).

CHAPTER 4

DISCUSSION

To characterize the cognitive functioning of older adults with vascular disease, this study examined performance across neuropsychological measures of executive functions and episodic memory and considered differences between cognitive classes on volumes of white matter lesions and hippocampus and on levels of vascular risk. I expected to identify multiple classes of participants that differed in terms of the dominant cognitive domain of deficit, with groups of participants exhibiting primary deficits in executive functions, episodic memory, and mixed domains (executive functions and episodic memory). An LCA supported a three-class model; however, the cognitive profiles that characterized these classes were not fully consistent with the study hypothesis. Contrary to predictions, Class 3 showed relatively intact cognitive test scores compared to the other classes and a predicted amnesic class did not emerge. Given the level of vascular risk in this sample, I had not hypothesized such a large proportion of participants showing relatively intact abilities. Classes 1 and 2 demonstrated uniformly lower scores, with Class 2 showing the lowest and most impaired scores on two executive measures. The emergence of a dysexecutive class and a class with multi-domain deficits (i.e., mixed/mildly impaired) were in line with predictions. In a subsample of participants, class differences in WML and hippocampal volumes did not reach statistical significance, although a trend was observed in WML volumes in the expected direction. Analyses supported the prediction that participants exhibiting a cognitive profile with relatively greater executive deficits would exhibit greater vascular risk (i.e., higher Framingham Score) than other classes. These findings reveal the presence of homogeneous cognitive subgroups within a cognitively heterogeneous older adult cardiology sample, extending

our understanding of cognition and vascular disease while also providing a characterization of patients with cardiac disease at baseline.

Aim 1

Although Hypothesis 1 was not fully supported, the results suggest meaningful heterogeneity in the cognitive presentation of older patients with vascular disease. Class differences were characterized by varied levels of overall cognitive impairment and the presence of circumscribed executive dysfunction. The existence of cognitive impairment in this population has been observed by several authors (Hogue et al., 2006; Hudetz et al., 2012; Silbert et al., 2007); however, the heterogeneity of cognitive performance patterns in a presurgical cardiology sample has been underappreciated by the literature.

That classes with relative impairment comprised just over half of the participants speaks to the proportion displaying cognitive dysfunction. Given the level of vascular load in this sample, I expected most participants to show some impairment, so it was somewhat surprising that there was an intact group at all and that a larger proportion of the sample did not fall into the class with more prominent executive dysfunction. My finding of impaired cognition within this population is similar to other authors, who have reported between 25% and 45% of presurgical cardiac samples display cognitive impairment using varying criteria (Hogue et al., 2006; Hudetz et al., 2012; Silbert et al., 2007). Estimates of cognitive impairment in older adult community-based samples vary widely, ranging from 3% to 42% (Moyer et al., 2014).

I am aware of no other studies that have considered individual cognitive profiles across multiple neuropsychological measures in examining this population. An intact

class comprising approximately half of the sample indicates that not everyone with cardiac disease will have cognitive impairment, and prompts the question what are the characteristics of this group that are perhaps protective. As discussed further below, my data suggest that individuals with less impairment have a relatively lower burden of vascular risk factors than those in the more impaired groups. The data also suggest that education may be a factor, lending support to cognitive reserve (Deschaintre, 2009; Meng & D'Arcy, 2012; Zieren et al., 2013).

The existence of individuals with poorer neuropsychological performance in this population has numerous implications for research and clinical care of older cardiac patients. Regarding research, the impaired classes emphasize the importance of considering baseline cognition in studies of similar cohorts, such as when examining cardiac surgical outcomes (Erdogan et al., 2012; Haller, Stone, & Walder, 2012). Executive dysfunction has been associated with vascular dysfunction by other authors (Schoor et al., 2010). Individuals with executive dysfunction related to small vessel disease in particular also have been reported to perform poorly in everyday functioning tasks (Boyle, Paul, Moser, & Cohen, 2004; Giovannetti, Schmidt, Gallo, Sestito, & Libon, 2006; Seidel et al., 2013), which could impact their ability to perform aspects of their own care such as medication management.

Groups that were characterized by impairment had class means approximately one standard deviation below the intact class in terms of age-based norms on all measures, including not just executive measures but also measures of memory. This points to the potential contribution of vascular disease not only to executive function but to memory as well. I did not identify a class with predominant memory deficits, although the profiles of

both impaired classes did have amnesic elements to their profiles. For example, these classes performed relatively worse than the intact class in both free recall and verbal recognition trials. This supports authors who have argued for a role for vascular dysfunction in processes impacting memory (Kuller & Lopez, 2011; van Norden et al., 2012). Certainly the findings point to the potential value of considering performance across multiple neuropsychological measures in studies examining older adults with cardiac disease.

It is important to note that the classes also differed on demographic and clinical factors. Although MMSE scores differed between the three classes, all class means differed by less than two points and do not suggest that the classes were meaningfully different in their overall level of cognitive impairment (e.g., dementia vs. healthy). Differences between classes on age (< 5 years) were not unexpected given the strong relations between cognition, cardiovascular disease, and age. As in many studies, age emerges here as an important, but not all-encompassing, statistic in attempts to investigate complex sets of variables. In addition, the classes differed when age-adjusted normative z-scores were used to interpret the cognitive data. Classes also differed in their racial proportions with African Americans comprising a relatively greater percentage of the dysexecutive class, an interesting result given findings of greater vascular risk and higher rates of dementia in this population (Gamaldo, Allaire, Sims & Whitfield, 2010; Gutierrez & Williams, 2014; Kuller et al., 2005; Nyquist et al., 2014). Importantly, the participants in this study were recruited because of presence of cardiac disease only, not due to having cognitive impairment. In fact, on average participants performed well on a cognitive screening measure.

Aim 2

The association between white matter disease, vascular risk, and cognitive dysfunction is well established (Giovannetti et al., 2001; Lamar et al., 1997; Lamar, Price, Davis, Kaplan, & Libon, 2002; LADIS Study Group, 2011; Libon et al., 1997; Yaffe, 2007). Results of the current study suggested a trend in the data in support of a relation between more prominent executive dysfunction and greater WML volumes, although this did not reach statistical significance. Other authors have found that executive dysfunction is associated with white matter lesion volumes (Lamar et al., 2008; Lamar et al., 2007; Lamar, Swenson, Kaplan, & Libon, 2004; Price, Jefferson, Merino, Heilman, & Libon, 2005; Seidel, Giovannetti, & Libon, 2012). One factor in my non-significant findings may be that levels of white matter disease in this sample were lower than expected. Price and colleagues (2012) found in a dementia sample that abnormal white matter explained a significant amount of variance in a mental control task when it involved more than 3% of the total white matter. In the current sample, 40% of participants had white matter lesions above this threshold. However, the maximum level of WML as a proportion of total white matter in the current sample was 10%, which is less than the minimum level Price found (13%) may be required to explain significant variance in another executive task (clock drawing).

Although both the mildly impaired and dysexecutive classes showed relative deficits in memory compared to the intact class, this study did not find any significant differences in hippocampal volumes between classes. Given the lack of a class with primary amnesic deficits, this finding was less unexpected. Some authors have found an additive effect of medial temporal lobe atrophy and white matter changes on cognition.

For example, van der Flier and colleagues (2005) found in a non-disabled elderly sample that the combined presence of these pathologies was associated with much greater frequency of cognitive deficits than the presence of either independently. Perhaps the increased level of vascular disease in this older sample lowered the threshold of hippocampal pathology required to manifest as memory declines, leading to demonstrated memory declines without a detected change in hippocampal volume. A further explanation is that the amount of variation in hippocampal volume in this non-demented cardiology sample was too small and that the study may have been underpowered to detect such differences. Given growing evidence for the contribution of vascular disease to AD, it is significant that this study revealed no prominently amnesic class and no evidence of medial temporal lobe pathology in an older adult sample with increased vascular risk.

Aim 3

Differences in Framingham score may be viewed as validating my interpretation of the cognitively-defined classes, demonstrating that primary deficits in executive functions were associated with a higher vascular load. Broadly, this study included participants with a relatively high level of vascular risk, with an average Framingham score representing a 10-year stroke risk of over 40%, compared to population means of less than 10% (Wolf et al., 1991). The current findings showed that the class with primary executive dysfunction had Framingham scores representing a 10-year stroke risk (52%) that exceeded that of the intact class by 12 percentage points. Therefore, this study emphasizes the association between cognitive profiles and modifiable risk factors. In addition, it is important to recognize that unlike in Alzheimer's disease in which the

literature often focuses on the presence of amyloid beta, about which we can currently do little and which is likely the result of complex events that remain poorly understood, the association of cognition with vascular disease points to a large and available treatment arsenal. Making health changes targeting vascular risk factors not only reduces stroke risk (Cadilhac, Carter, Thrift, & Dewey, 2012; Lich et al., 2014) but may improve cognition (Bourdel-Marchasson, Lapre, Laksir & Puget, 2010; Ryan et al., 2006). Less is known about when changes in chronic vascular risk factors must be made in order to change one's risk of cognitive decline. There is some evidence that levels of vascular risk factors even in one's twenties impact later cognitive performance and that vascular risk in midlife is particularly detrimental to cognitive outcomes. For example, a recent paper by Yaffe and colleagues (2014) found that cumulative exposure to higher levels of vascular risk factors over a 25-year period beginning in early adulthood was associated with worse performance on multiple neuropsychological measures. In the old-old (over age 80), some authors have shown that vascular risk factors may be protective against cognitive decline (Nilsson et al., 2007).

Education was mentioned above as a possible protective factor against cognitive decline related to vascular disease. An additional concept that may explain the existence of a substantial intact group in this study despite generally high levels of vascular risk is found in ischemic preconditioning. Studies of preconditioning have shown that brief periods of ischemia can trigger responses that are protective and induce temporary resistance to more severe ischemia, in the same or even a distant organ, including the brain, through molecular and genetic mechanisms such as de novo gene expression of proteins involved in endothelial health (Koch et al., 2014; Koch & Bonzalez, 2012).

Some studies have applied this concept to chronic ischemia and found that individuals with peripheral vascular disease had better outcomes after stroke than those without this precondition (Connolly et al., 2013). The concept of pre-conditioning suggests that people with chronic vascular disease might fare better in the long term because they accommodate to the slow chronic buildup of cerebrovascular disease. Individual differences in responses to preconditioning, as with differences in protective response to education, may contribute to the cognitive heterogeneity in this sample.

Conclusions

This study was not without weaknesses. This study included multiple measures of cognition in the two major domains associated with neuropathology and cognitive deficits. Measures of other domains such as attention or processing speed that may be important in a vascular pathology group could also have been considered. These were not included as including too many variables can hinder interpretability of latent cognitive classes. Although interpretation of classes was supported by age-based normative z-scores, levels of performance judged to reflect impairment cannot be made categorically without knowledge of the premorbid functioning for each individual. I also cannot say what represents a decline, as a certain level of performance can represent baseline for one, but decline for another. In addition, the normative data used in this study were drawn from multiple samples, which may lead to misinterpretation of variable levels of performance across measures as reflecting cognitive deficits. Inclusion of participants with prior stroke ($n = 15$) or TIA ($n = 43$) also may be viewed as less than ideal as these acute events may contribute disproportionately to cognitive changes and WML volume. However, in a high-risk vascular sample it is to be expected that some individuals have a

history of acute events, and inclusion of these participants makes the current sample more representative of a typical cardiology sample and improves the generalizability of the findings. In fact, of those with a history of stroke or TIA ($n = 55$), 40% were predominantly in class 1, 16% in class 2, and 44% in class 3. Therefore, the distribution of these individuals across classes was similar to the distribution of participants across the three classes. Framingham score and imaging data were only available for a subsample of the main cognitive sample. Differences between the imaging subsample and participants without imaging indicated that the imaging subsample may have been somewhat healthier, which may have limited the power of this study to detect hypothesized differences in WML volumes between classes when examining this relatively healthier subsample. In addition, in this study of cardiac patients at a presurgical baseline it is unfortunate that although all cognitive testing was administered presurgically, some postsurgical imaging data were used in analyses due to unavailability of presurgical scans, a small percentage of whom (10% of imaging sample) had acute lesions on DWI scans. Volumetric measures of WM lesions used in this study do not capture the non-volumetric abnormalities revealed by fractional anisotropy (FA) measured using DTI. Studies have demonstrated that FA in normal appearing WM is variable and predicted by vascular risk factors (Lee et al., 2009).

This study also had numerous strengths. This study attempted to take an approach that acknowledges the complex natures of cognition (using an LCA on multiple neuropsychological variables) and cardiovascular disease (using a measure of vascular load that incorporates data from multiple risk factors). This is thought to lend itself to broader generalizability compared to studies that look at a smaller number of cognitive

data points, do not consider cognitive variables within individual profiles, or take one measure (e.g., systolic BP) to indicate vascular health. This study also considered a large sample with a range of vascular risk which was supported by inclusion of both surgical and control participants from a larger parent study, and therefore was able to examine relations in the context of a large range of vascular risk. Use of age-based normative data to support interpretation of cognitive classes is thought to allow greater appreciation of the clinical implications of the findings.

Clinical implications and future directions

This study identified cognitive subgroups in a large sample of older adults with vascular disease based on their performance on neuropsychological measures of executive functions and memory and compared these subgroups on levels of vascular risk and volumes of white matter lesions and hippocampus. The findings suggest that assessing cognition in this population using approaches that consider individual profiles may have great value in understanding the influence of multiple complex factors on cognitive functioning. This study also addressed a gap in the literature on cognition in patients with cardiac disease that has focused on the effects of surgery and has implications for the clinical care of such patients and for studies of this population. Future studies are needed to better understand why some individuals in this cohort remain intact, and if protective factors beyond cognitive reserve are contributing. The lack of significant differences in imaging indicators of neuropathology may speak to the greater sensitivity of neuropsychological measures, which detect changes in performance in advance of substantial changes in the macrostructure of underlying substrates. The identification of a subgroup with both greater executive deficits and higher levels of

vascular risk points to the importance of strengthening the connection between vascular health and cognition, particularly given recent evidence of impact of cumulative exposure, and encourages greater focus on treating these modifiable factors and communicating their relation to cognition to the public at large.

CHAPTER 5

EXTENSIVE LITERATURE REVIEW

The hippocampus and vascular disease have been the focus of two literatures on cognitive aging and neurodegenerative disease. These literatures have examined the role of medial temporal lobe structures and vasculature in the changes in cognition observed in older adults. An understanding of the anatomy, pathology, and cognitive processes associated with these literatures leads to an appreciation of how much has been learned in these areas. However, the existence of these perspectives in relative isolation ignores a growing literature pointing to links and possible interdependence. This review will acknowledge the complexity of relations at a biological level and suggest a new perspective on cognition and disease.

One literature of cognitive aging and neurodegenerative disease focuses on the hippocampus. I will begin this review with a description of the anatomy and physiology of the hippocampus before proceeding with a discussion of its role in cognition and, finally, a review of hippocampal pathologies associated with aging and neurodegenerative disease.

1. Anatomy and physiology of the hippocampus

The hippocampus (HC) is located within the medial temporal lobe, and is the core structure of the hippocampal formation, extending along the medial posterior to anterior base of the temporal lobes, which consists of the hippocampus proper and surrounding regions including perirhinal and entorhinal cortices and parahippocampal gyrus (See Figure 1). The anterior HC lies below the posterior portion of the entorhinal cortex and the perirhinal cortex, whereas the main body of the HC lies beneath the parahippocampal gyrus (Squire & Wixted, 2011). In contrast to neocortical areas, which adapted for

different functions in different species over hundreds of millions of years, the anatomy, neural pathways, and functional role of the HC and nearby regions (parahippocampal gyrus) were mainly conserved across species (Manns & Eichenbaum, 2006).

Once viewed as a singular structure, the HC is now understood as a complex system of multiple subregions, which are distinguished by their molecular organization and functional connectivity, and targeted differentially by disease or age-related processes affecting different aspects of cognition (Small, Schobel, Buxton, Witter, & Barnes, 2011). In preparation for a broadening discussion of the role of the HC in cognition, this structure can be appreciated as the location of an important circuit of subregions with high connectivity to subcortical and neocortical brain regions, and set within the greater milieu of an individual's central nervous system and body.

The restricted area through which most input to the HC flows contrasts with HC outflow, which fans out to a range of subcortical and cortical sites. When considering the topological input-output relations related to internal functional and molecular organization, the HC is best viewed in long-axis (rostral-caudal). Cortical and subcortical information flows into the hippocampus through monosynaptic input to superficial layers of entorhinal cortex (EC) from regions including perirhinal cortex, parahippocampal cortex, auditory and olfactory cortices, and amygdala, and is organized in an anterior-medial to posterior-lateral gradient in EC, a gradient which is largely preserved as information passes to the HC. As an example of input organization along the long-axis gradient of the HC formation, input from amygdala connects to anterior-medial areas of EC, which then provides input to anterior HC, whereas input from visual cortex connects,

via perirhinal and parahippocampal cortices, to posterior-lateral areas of EC, which then provides input to posterior HC (Small et al., 2011).

Input arriving at the HC flows through a mainly unidirectional circuit of subregions that are best viewed on the transverse axis, including dentate gyrus (DG), CA3, CA1, and subiculum (see Figure 1). Lorente de Nó, a student of Ramon y Cajal who first used the Cornu Ammonis (CA) nomenclature, also described the CA2 subfield but this is not commonly covered in current literature (Lorente de Nó, 1934; Small et al., 2011). The axons of neurons in EC layer II project via the perforant pathway to the DG, which then connects via the mossy fibers to CA3. The axons of CA3 neurons project via the Schaffer collaterals to both the ipsilateral and contralateral CA1. CA3 auto-association fibers are also present, which interconnect CA3 neurons throughout the long axis of the HC. Finally, CA1 connects to the subiculum. Although the primary HC input arrives along the perforant path from EC to DG, the EC does send direct input connections to all 4 of the other subfields, with EC layer II also connecting to CA3, and EC layer III to CA1 and subiculum (Small et al., 2011). There are also weak connections from perirhinal and parahippocampal cortices to the CA1-subiculum border (Squire & Wixted, 2011).

The primary outflow from HC proceeds from the subiculum back to deep layers of EC and then, via parahippocampal gyrus, to a range of cortical and subcortical areas. A small proportion of outflow comes from CA1 to EC. Anatomical tracing studies have determined that there are also direct hippocampal efferents arising in CA1 and subiculum, which connect monosynaptically to cortical and subcortical areas including the medial prefrontal cortex, orbitofrontal cortex, and amygdala (from anterior CA1/subiculum),

posterior cingulate (from posterior CA1/subiculum), as well as the anterior cingulate and nucleus accumbens. The HC-neocortical network with outflow via deep EC and parahippocampal gyrus, as opposed to direct HC efferents, has received the most attention for its role in consolidation of long-term memories (Small et al., 2011).

The long-axis gradient associated with hippocampal input is largely preserved in the pattern of HC output to EC. Functional organization along the long axis of the HC formation is supported by data from gene expression profiling, fMRI studies, and electrophysiological studies that show differences along the long axis in mechanisms of plasticity and place field activity. Broadly, studies have indicated it is the more posterior portions of HC that are involved in memory and cognitive processing, whereas more anterior aspects are more involved in other complex behaviors such as stress, emotion, sensory-motor integration, and goal-directed activity (Fanselow & Dong, 2011; Moser & Moser, 1998).

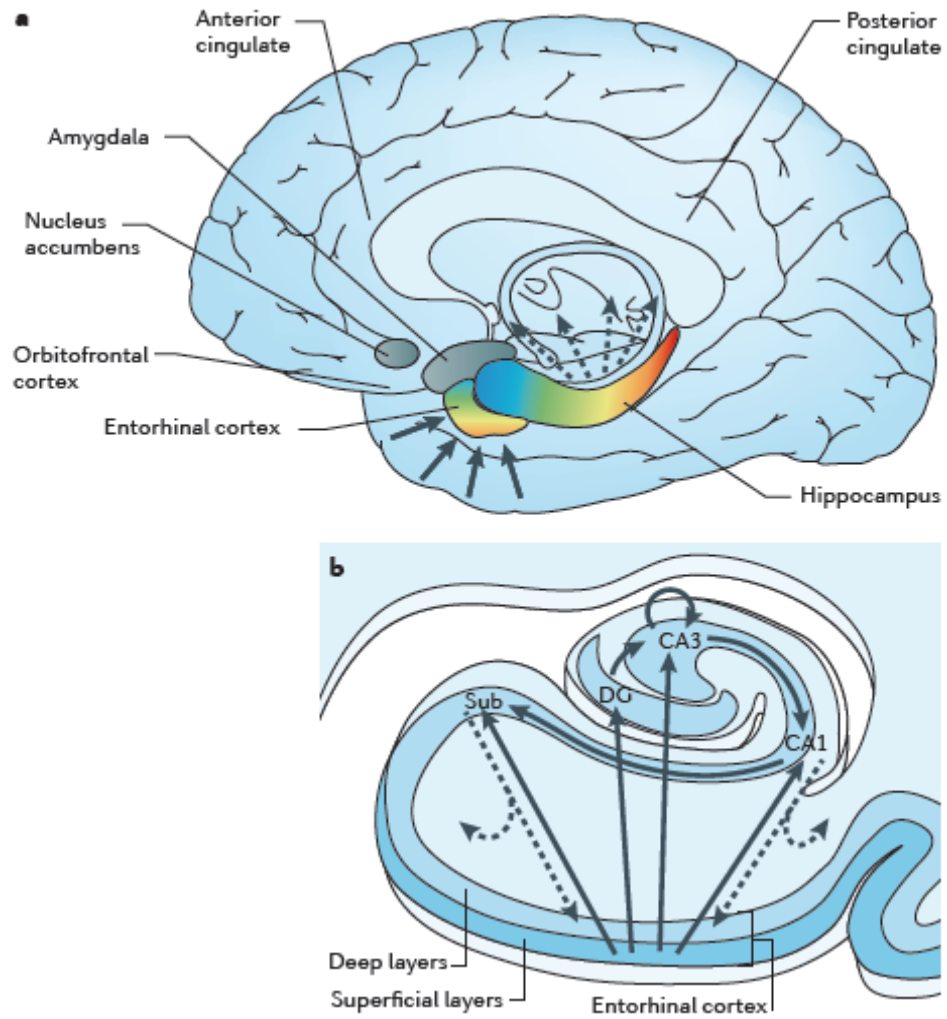


Figure 1: Location (a) and Organization (b) of the Hippocampal Formation

2. Cognitive processes associated with the hippocampus

2.1. H.M. - Establishing that the HC plays a major role in episodic memory

The description of specific cognitive processes associated with the hippocampus is the product of over 50 years of research. Studies in humans and animals with medial temporal lobe (MTL) lesions investigated the role of specific structures in episodic memory, led to the idea of multiple memory systems, and defined the characteristics of hippocampal-dependent memories (Squire, 1992). Research has pointed to the involvement of the hippocampus in all stages of memory, including formation, storage, retrieval, and application to novel situations (Yassa & Stark, 2011).

An association between the hippocampus and memory was not commonly accepted just 50 years ago. The differential association of certain behaviors with specific brain regions was of course advanced before the end of the 19th century, with the classic work of Gall (1825) and Broca (1861). However, this work was not focused on memory, but on sensory, motor, and language processing. By 1950, no brain region was commonly thought to be disproportionately dedicated to memory and this cognitive function was considered to be well integrated with perceptual and intellectual functions (Lashley, 1950).

The publishing of studies on the patient known as H.M. (Scoville & Milner, 1957) led to drastic changes in the conceptualization of memory and drew the focus to the role of structures in the MTL. Henry Molaison, known until his death in 2008 as H.M., underwent bilateral MTL resection in 1953 at the age of 27 to treat intractable epilepsy. Prior to surgery, H.M. was a man of average intelligence who had worked as a motor winder into his mid-20s when his epilepsy made him unable to work. Although his

seizures were effectively treated by this radical surgery, he emerged with a circumscribed and profound anterograde amnesia (Scoville & Milner, 1957; Squire & Zola-Morgan, 2011).

The specificity of his deficit in encoding new information could be linked with the localized nature of his lesion in the MTL. Work with H.M. demonstrated the dependence of episodic memory on the MTL.

One aspect of memory that appeared to be spared in H.M. and other patients with MTL lesions was immediate or short-term memory, now sometimes termed working memory. H.M. had intact ability to hold information in mind and could retain strings of digits by continuous rehearsal. Compared to a preoperative span of 6, postoperatively he could repeat up to 6 digits but could never achieve 7, even after he was given 25 repetitions of the same string. Evidence from comparison of other MTL lesion patients and controls indicated working memory is intact in such amnesia patients (Squire, 1992; Squire & Zola-Morgan, 2011).

The view of memory as a non-unitary construct consisting of multiple memory systems was greatly influenced by amnesic patient work as further exceptions to *global* memory impairment emerged (Squire, 1992). H.M. was particularly important to these ideas when in 1962 he showed day-to-day improvement in a hand-eye coordination skill (mirror writing). His improvement developed despite no recollection of practicing the task. Whereas at first this was considered an isolated exception to his global memory impairment, later it was understood that motor skills are part of a broader category of learning that remains intact in otherwise severely amnesic patients with HC damage. It became clear that the HC is essential for a *specific* kind of memory, referred to as declarative – as was first suggested by Hirsch in the 1970s after rodent lesion work, and

further developed by others including O'Keefe and Nadel (Squire, 1992). The idea of multiple memory systems was in fact present even earlier in writings in traditions including developmental psychology, psychology, philosophy, and artificial intelligence, which included the work of Bergson, 1911 (memory and habit); Bruner, 1969 (memory with and without record); and Ryle, 1949 (knowing how and knowing what) (as cited in Squire, 1992).

Squire used the term *declarative* in the sense that “one can bring to mind or declare the content of this kind of memory” (Squire, 1992, p. 204). The term, derived from human work, is difficult to apply to animal work, but not because of the “verbal” association of the word “to declare”. “Bringing to mind”, as used by Squire, does not imply verbal declaration, as declarative memory includes memory for faces, spatial layouts, and other tasks in which an image is brought to mind. Instead, the difficulty with applying the term to animals is its link to *conscious* memory, referring to information that is accessible to awareness, and affords comparison and contrast (Squire & Wixted, 2011). Squire cautions that, although there are multiple related terms (e.g., declarative, explicit, relational, configural), the focus should not be on terms (1992). The terms are not all exactly equivalent in how they are used, as some are derived from more biological and others more psychological concepts, and some are more related to human work and others to work with rats (Squire, 1992). However, when considered together, a clear sense was emerging of the type of information that is, and is not, dependent on the HC.

Declarative memory stands in contrast to implicit memory, which is expressed only through performance and is independent of the brain structures affected in amnesia. This includes skills (sometimes called procedural memory), habits, priming, and other

tasks where experience changes a person's behavior or facility, but without conscious access to past episodes when the experience was gained (Squire, 1992). For example, amnesic patients were shown to be able to learn eight two-choice concurrent object discriminations after 1000 trials, a task learned by normal subjects in 80 trials, but performed by amnesics purely through habit learning. The learning in amnesics was both outside of awareness and rigid – the task format could not be modified. Amnesic patients, as well as HC-lesioned rabbits and other animals, also show good classical conditioning of the eyeblink despite poor memory for the events of learning (Daum, Channon, & Canavar, 1989; Solomon & Moore, 1975; Weiskrantz & Warrington, 1979). In such tasks, the focus is on behavior change, not recollection, and on changes in specific perceptual or response systems, not about factual information that is true or false (Squire & Wixted, 2011). Squire makes a broad comment on the implications of the unconscious status of nondeclarative memory, observing that such memories add to the mystery of human experience: “Here arise the dispositions, habits, and preferences that are inaccessible to conscious recollection but that nevertheless are shaped by past events, influence our behavior and mental life, and are an important part of who we are.” (Squire & Wixted, 2011, p. 265).

Importantly, implicit memory performance is not dependent on the HC. Skill learning has been associated with the neostriatum, skeletal musculature conditioning with the cerebellum, emotional conditioning with the amygdala, and priming with the systems normally involved in perception (Squire, 1992). Direct or repetition priming, for example, is associated with changes in early-stage perceptual processing systems in posterior

cortex, before conceptual or semantic analysis is carried out, and before involvement of the HC (Cave & Squire, 1992; Graf & Schacter, 1985; Warrington & Weiskrantz, 1974).

H.M.'s cognitive deficits were circumscribed to the formation of new declarative memories. He demonstrated spared general intellectual functioning, perceptual and motor processes, semantic knowledge, and working memory. Therefore, the early descriptions of H.M. established several principles of memory organization: memory is not a unitary process (in light of his preserved motor skill learning); the MTL is not essential for general intellectual functioning, perceptual, or motor functions; and, the MTL is not crucial for working memory (rehearsal and maintenance). The impact of the generally intact status of H.M.'s remote memories of before his surgery will be discussed later in section 4.

The carefully studied case of patient R.B. greatly contributed to firming up findings suggested from earlier work (Zola-Morgan, Squire, & Amaral, 1986). An ischemic event at age 52 after cardiac surgery left this patient with only one cognitive deficit: severely impaired declarative memory. After 5 years of clinical study, postmortem investigation found bilateral CA1 lesions extending along the full rostral-caudal axis, which likely disrupted the unidirectional chain of processing in the HC. The case demonstrated that damage restricted to bilateral HC in humans is sufficient to cause clinically significant episodic memory impairment. These findings were further supported by study of patient G.D., who also had bilateral CA1 lesions and a similar cognitive profile (Squire & Wixted, 2011). R.B.'s lesions were certainly more isolated than those of H.M, who stands separately from other reports of patients with MTL-amnesia in the severe level of his memory deficits. This severity is thought to be due to the damage to

other MTL structures besides HC, a suggestion that was confirmed in work with monkeys (Squire, 1992).

2.2. Replication in Animal Studies

A variety of tasks were found to be sensitive to MTL lesions in monkeys. The most widely used task was delayed nonmatching to sample, in which the monkey must remember a single visual object across a delay ranging from 8 seconds to 10 minutes, and then demonstrate recognition of the object at the end of the delay. Recognition is a 2-choice test, with reward provided for choosing the new object. Also employed was a test of retention of simple object discriminations, in which two easily distinguishable objects are presented and the correct choice is rewarded, with the sequence repeated until correct responses are given consistently (10-20 trials for normal monkeys). Another task used was eight-pair concurrent discrimination learning, in which different pairs of objects are presented successively (8 pairs presented 5 times each during 40 daily trials), until the monkey consistently chooses the rewarded object of each pair, requiring several hundred trials for normal monkeys (Squire, 1992).

On such tasks, monkeys with MTL lesions exhibited impairment similar to H.M. Performance was accurate following a short delay but increasingly inaccurate when the delay period increased (Overman, Ormsby, & Mishkin, 1990). Scores were also shown to be worse when monkeys were trained and tested postoperatively compared to pre-op training and post-op testing (Mishkin, 1978; Zola-Morgan, Squire, & Amaral, 1989), supporting the relevance of the lesioned structures to memory encoding. Consistent with work in humans, monkeys with large HC lesions can still perform motor-skill and

perceptual skill learning, as well as develop associative habits (Mishkin, Malamut, & Bachevalier, 1984; Zola-Morgan & Squire, 1984).

2.3. Animal studies helpful in mapping the role of specific MTL regions in declarative memory

The role of specific structures in performance of MTL-sensitive tasks has been systematically investigated in animal studies. In this work, some animals were studied following lesions of the HC proper, amygdala, and surrounding areas including EC, perirhinal cortex, periamygdalar cortex, and parahippocampal cortex (hereafter H+A+; Squire, 1992). Other animals had lesions that spared the amygdala and were restricted to the HC and areas damaged in reaching this (posterior EC and much of the parahippocampal gyrus; H+). Deficits demonstrated after H+A+ lesion were unmistakably greater than after H+ lesion, indicating that structures important to memory include not only the HC proper, but also adjacent EC, perirhinal cortex, and parahippocampal cortex (Squire & Wixted, 2011). Lesions of the HC, or of related structures such as EC, impair rat performance on tasks including spatial memory tasks, odor-discrimination learning, timing tasks, and discrimination tasks that require learning relationships between stimuli. Impairment in rats associated with restricted HC lesions can be exacerbated by damage to related structures and fiber tracts such as subiculum or alveus, in agreement with findings in monkeys (H++ vs. H+ lesion) and humans (HM vs. RB) indicating that impairment is worse depending on the extent of MTL damage (Squire, 1992).

Cortex adjacent to the HC (entorhinal, perirhinal, parahippocampal cortices) is more than simply a conduit of information and participates with the HC in common

memory functions. Some memory storage can occur by these surrounding structures even if information from neocortex does not reach the HC itself (Squire, 1992). The perirhinal cortex and parahippocampal gyrus provide nearly two thirds of input to the EC, the major afferent projection to DG and the rest of the HC, and are therefore essential for normal information exchange between the neocortex and the HC formation. These adjacent cortical areas are sites of reciprocal connections to widespread unimodal and polymodal cortical association areas and so are vital to the importance in memory functions of the hippocampal formation (Van Hoesen, 1982).

The role of the amygdala in memory was of particular interest to early investigators. Initially, amygdala lesion studies seemed to indicate that the this structure was highly important in memory functions. It became clear, however, that amygdala resection always included underlying cortex, even though this was not a target of study (Squire, 1992). Monkeys with selective stereotaxic amygdala lesion (A lesion) performed normally on four memory tasks (delayed nonmatching to sample, retention of object discriminations, concurrent discrimination, and delayed response), although monkeys with H+ and H+A lesions were impaired on these tasks, demonstrating that the A lesion alone does not impair nor exacerbate memory impairment compared to the H+ lesion. (Zola-Morgan, Squire, & Amaral, 1989b). Further lesion studies, including work in rodents, demonstrated that amygdala damage did not contribute to memory impairment (Sutherland & McDonald, 1990).

Other work in monkeys compared memory performance after surgical H+ lesions to ischemic lesions induced by 15-minute bilateral carotid occlusion with pharmacologically induced hypotension. Ischemic memory impairment, associated with

cell loss primarily in CA1, appeared less severe overall (Zola-Morgan & Squire, 1990). However, performance depended on task, with delayed nonmatching to sample showing about equal impairment following ischemia and surgery, but ischemic lesion monkeys performing better than H+ monkeys on object discrimination and 8-pair concurrent discrimination. Performance of ischemic lesion monkeys was also compared to monkeys with selective lesions of HC proper. In this comparison, performance suggested that even incomplete damage to the HC is sufficient to produce detectable memory impairment in monkeys, just as is the case in humans (e.g., patient R.B.; Zola-Morgan, Squire, & Amaral, 1986).

2.4. Defining the functions of the hippocampus - Association, configuration, flexibility, and space

Having described the sort of information for which the HC is necessary and investigated the contribution of adjacent regions, it remains to be stated what is being done with this information. One important aspect of hippocampal function in memory is in establishing conjunctions. The anatomical and physiological organization of the HC suggests it is highly specialized for forming conjunctions between normally unrelated events. In psychological terms, the HC is for forming links, such as of stimuli with their spatial and temporal context (episodic) or of a fact with a semantic context (conceptual). In the words of Squire, “the system as a whole is likely to be privy to much of the processing that occurs in neocortex” (1992, p. 202), and appears to perform a complex binding function with this information.

In 1949, Hebb described a process in which coincident firing of presynaptic and postsynaptic neurons strengthened the connection between the two cells. Twenty years

later, long-term potentiation (LTP) was identified, a mechanism fitting his prediction, with high-frequency stimulation of rabbit DG resulting in long-lasting enhanced synaptic strength, a process dependent on NMDA receptors (Lister & Barnes, 2009). Dysfunction has been identified in LTP associated with aging and neurodegenerative disease, as will be described later. LTP provides a mechanism of conjunction formation and storage as a rapid-developing and long-lasting form of synaptic plasticity.

However, the formation of connections between stimuli is not always HC-dependent. The HC appears to be essential for making configural as opposed to simple associations (Squire, 1992). A simple association, for example, would be formed in a task in which either light or tone is rewarded, including if both are presented together. Configural learning would be involved if either a light or a tone is rewarded, but NOT a light-tone compound stimulus. HC lesion rats are impaired on configural learning, but can still make simple associations. According to Squire (1992), this idea makes a distinction between a simpler kind of learning that is independent of the hippocampus and similar to the associative learning discussed by Hull (1942) and a more cognitive kind of learning like that discussed by Tolman (1948).”

Another characteristic of HC-dependent memories for connections between stimuli is flexibility. Under this view, the HC is essential for acquiring information about relationships, combinations, and conjunctions among stimuli, in such a way that the resulting lasting representation is flexible and available to multiple response systems. For example, on simultaneous olfactory discrimination problems, fornix-lesioned rats performed about as well as sham-lesioned rats after learning items (although acquisition was impaired), but when the stimuli are recombined (demanding *flexible* use of

previously acquired info), the lesioned rats are close to chance, while the controls are about the same as with the original combinations (Eichenbaum et al., 1989). In another example, monkeys with bilateral fornix lesions or combined lesions of HC, fornix, and mamillary bodies were impaired compared to normal monkeys on a task in which they had to express knowledge in a novel situation. The lesions monkeys had only acquired conditional associations and could not express any knowledge outside of the original context (Saunders & Weiskrantz, 1989).

According to one view, derived particularly from work with rats, the HC is selectively involved in memory for spatial information. Certainly the importance of spatial memory in our understanding of HC function is undeniable. Spatial memory is viewed by some as a common ground between species, a domain in which age-related deficits can be described consistently among humans, non-human primates, and others such as dogs, rats, and mice (Squire, 1992). The relevance of the HC to spatial memory was given particular attention after the identification of place cells, HC neurons that fire in a location-specific manner. The pattern of cell firing is stable on reintroduction to the environment but shows increasing precision, demonstrating that experience modulates place field expression in the HC. Older rodents are impaired as spatial learning tasks such as the Morris water maze, in which they learn the location of a platform hidden below the surface of opaque water but fixed in relation to tank and external cues. Older rodents are also impaired on the Barnes circular platform task, in which they learn which of 18 possible holes leads to a dark escape tunnel to escape a brightly lit platform (Barnes, 1979). The reward hole is indicated by external cues. Impairment in monkeys has been

demonstrated in recognition memory for visual objects, simple-object-discrimination tasks, and concurrent-discrimination learning for objects (Zola-Morgan et al., 1989a).

The hippocampus appears to be just as vital to spatial memory in humans, supported by a range of evidence including that posterior hippocampal expansion is seen in navigationally-dependent individuals (taxi drivers) (Fanselow & Dong, 2011; Maguire et al., 2000; Moser & Moser, 1998) and is important in performance on human analogs of the Morris water maze (Lister & Barnes, 2009). Patients with HC damage, as in AD, may lose their way and cannot learn or remember spatial layouts. Preferential involvement of posterior hippocampus (equivalent to dorsal in rats and rostral in birds) for spatial navigation has been found in rats, birds, monkeys, and humans (Driscoll et al., 2003). Other research suggests the CA1 subregion may be especially important for spatial learning and memory (Small et al., 2011).

Despite the great importance of the HC to spatial memory, it is clear that its functions are not circumscribed to the spatial domain. Although one aspect of declarative memory is that it is representational, providing a way of modeling the external world, it is clear that HC lesions impair nonspatial memory in rats as well: odor discriminations, timing tasks, and configural discriminations involving unique combinations of auditory or visual stimuli (Eichenbaum, Fagan, Mathews, & Cohen, 1988; Meck, Church, & Olton, 1984; Rudy & Sutherland, 1989). Similarly, human patients also show memory impairment using prose passages, tactual impressions, odors, faces, and melodies, and impairment in spatial tasks has been found to be proportional to nonspatial task deficits when compared to healthy individuals (Cave & Squire, 1991; Scoville & Milner, 1957; Squire, 1979).

3. Recall, Recognition, and the Feeling of Familiarity

Another way of investigating the kind of information that depends on the MTL memory system is to consider differences in how previously learned information is recollected. Declarative memory assessment in humans relies primarily on two methods: free recall and recognition. When healthy people provide their responses in either of these methods, it is accompanied by a sense of familiarity about the past. In contrast, the performance of people with amnesia is poor on both types of measure, their responses are accompanied by less of a sense of familiarity, and they provide low confidence ratings in recognition choices (Squire, 1992). However, another point of view is that recognition memory also benefits from perceptual fluency (priming), a nonconscious process in which recently encountered items are processed more quickly and accurately than new items. Subjects can detect the increased fluency of an item, and attribute it to recent occurrence. This view implies that the relation among recall, recognition, and recognition confidence ratings should be different in people with amnesia compared to healthy controls. Specifically, it follows that recognition should be disproportionately spared compared to recall and that recognition should be disproportionately spared compared to confidence ratings, due to a strong role of nonconscious processes in recognition (Squire, 1992). In addition, amnesic patients should be successful on forced-choice paradigms even though they report they are guessing.

In a study looking at recall, forced-choice recognition, and confidence ratings at delays of 15 seconds to 8 weeks, normal subjects outperformed amnesic patients on all three measures, as expected (Haist, Shimamura, & Squire, 1992). Most importantly, however, when performance slopes were matched, all three measures could be seen to be

similarly affected in the two groups. Despite priming and other nonconscious processes being intact in amnesics, recognition performance and confidence ratings were not proportionately different than would be expected from recall scores (Squire, 1992).

Results in studies that do find disproportionate impairment on recall compared to recognition could be attributed to diverse pathologies among subjects. Damage to the frontal lobes, for example, impairs recall more than recognition (Jetter, Poser, Freeman, & Markowitsch, 1986), because retrieval strategies and information organization are essential for recall. People with frontal cortical lesions show deficits in both retrieval (free recall) and poor use of subjective strategy (poor semantic organization of words in recall) (Gershberg & Shimamura, 1995). Overall, the evidence suggests that recall, recognition, and familiarity judgments are similarly dependent on MTL structures (Squire, 1992). Recall involves strategic information retrieval and organization to a greater extent than recognition and familiarity judgments; therefore, lesions of the frontal cortex may differentially impact recall performance.

More recently, a similar debate has been framed as one between recollection and familiarity. Recollection involves remembering specific contextual details about a prior learning episode, and so is a measure similar to recall with a focus on contextual detail (Lister & Barnes, 2009; Nadel & Moscovitch, 1997). Some authors suggested that separate areas of the MTL are involved in recollection and familiarity, with recollection selectively supported by the HC and familiarity by the perirhinal cortex (Brown & Aggleton, 2001; Eichenbaum, 2007). Other authors maintained that both the HC and perirhinal cortex contribute to recollection and familiarity (Wixted & Squire, 2010). Another study found selective HC activation when subjects report a distinct memory for

an episode versus a vague sense of familiarity (Eldridge et al., 2000). As recall performance depends mainly on recollection and recognition mainly on familiarity, studies sought to answer the question by comparing the performance on these measures of patients with HC-specific lesions to subjects with larger MTL lesions. If the functions are selectively supported by different MTL areas, HC-lesion patients should do disproportionately better on recognition. Studies, including groups studies, have shown that the level of impairment is similar (e.g., Kopelman, 2007), indicating the HC is important for both recollection and familiarity.

Another method of comparing recollection to familiarity is the “Remember/Know procedure”, which is based on subjective reports of whether recollection is available when an item is declared old (i.e., was previously presented). If a subject “remembers” an item, they will recollect something about the original encounter with the item such as its context or thoughts they had. In contrast, “knowing” an item means it is familiar but the subject cannot recollect anything about its presentation. Remember/Know judgments are often converted into quantitative data for computational modeling. Although studies are conflicting, generally a proportional difference in performance by HC-lesion subjects is not supported by empirical tests (Lister & Barnes, 2009). Many studies of patients were not first equated for confidence and accuracy, and equate familiarity with weak memory, and recollection with strong memory. However, this is not always the case, as familiarity can be strong, and recollection weak. There are also newer (model-free) methods, which seem to indicate that HC damage impairs familiarity as well as recollection. Overall, most studies find HC lesions impair both recollection and familiarity (Lister & Barnes, 2009).

4. Episodic Memory Storage and Retrieval

Ribot (1881) first observed that in memory “the new perishes before the old”. Indeed, the role of the HC in memory storage and retrieval appears to change over time, though it was not until the 1970s that quantitative studies of this idea began (Sanders & Warrington, 1971). Evidence from individuals with retrograde amnesia suggests a temporary role for the HC in memory storage, in which memory is initially dependent on the HC, but as time passes after learning, a more permanent memory is established in other areas, probably the neocortex (Squire, 1992).

Retrograde amnesia can be extensive and temporally graded as measured by performance on recall measures. Temporally graded remote memory impairment is also detectable but less severe when assessed by multiple choice and yes/no recognition measures (Squire, 1992). Similar deficits across etiologically distinct groups have been demonstrated, including in Korsakoff’s syndrome, patients with HC damage, and patients with transient global amnesia (Butters & Cermak, 1986; Corkin, 1984; Squire, Cohen, & Nadel, 1984; Squire, Haist, & Shimamura, 1989). Retrograde amnesia appears to vary in severity and extent as a function of the severity of anterograde amnesia, with brief retrograde amnesia when anterograde is only moderately severe, and more extensive retrograde loss when anterograde amnesia is severe (Squire, 1992). Following R.B.’s damage limited to CA1, no prominent retrograde amnesia could be detected, though he may have shown some for the few years before amnesia onset (Zola-Morgan, Squire, & Amaral, 1986). The severity of H.M.’s retrograde amnesia was less clear, with no formal assessment of this until more than 20 years after amnesia onset. He showed retrograde

amnesia for a period of 3 to 11 years before onset, with other reports of only about 3 years prior to onset (Corkin, 1984; Scoville & Milner, 1957).

Retrograde amnesia is usually assessed with tests for public information such as famous events or faces, as the correct answers are clear. More personal episodic memories (i.e., autobiographical memory) may be assessed by asking participants to recollect personal events in response to fixed cue words or in response to structure questions (e.g., tell me about your first day of college). Frank confabulation can be ruled out by including consistency as a measure or by confirming responses with reliable collaterals. People with amnesia typically show temporally limited retrograde amnesia for autobiographical events. However, they can often show relatively intact personal factual information, which may be acquired through repeated exposure and distilled from contextual information to form personal semantic information (e.g., date of birth, birthplace, social security number). This information may be recalled as terse facts devoid of rich contextual associations (e.g., the place where one obtained her first social security card) (MacKinnon & Squire, 1989).

H.M. produced well-formed autobiographical memories in early reports, and from age 16 and younger according to some papers (Lister & Barnes, 2009). However, this seemed to change as he got older, and some authors have concluded that autobiographical memories remain dependent on MTL for as long as they persist. This is based on updates of H.M. in his 70s (Corkin, 2002) in which he had memories of childhood but they lacked detail and appeared fact-like, and he could not reproduce events specific to time and place. MRIs of H.M. conducted in 2002 and 2003 complicate the situation, showing cortical thinning, subcortical atrophy, large amounts of abnormal WM, and subcortical

infarcts – all thought to have occurred in the prior 10 years (Lister & Barnes, 2009).

These changes may have led to changes in his autobiographical memory, or, perhaps they faded over time as he could not rehearse them or relearn them.

5. Reactivation view of memory

The reactivation view of memory suggests that remembering involves reactivation of the distributed neocortical regions engaged at the time of encoding (Lister & Barnes, 2009). There is considerable evidence using a variety of experimental approaches that regions of brain processing perceptual information are also involved in representing that information during remembering (Buckner & Wheeler, 2001). William James himself referred to this concept as “re-excitation”. The distributed nature of remembering across brain regions may lead to the richness of memory as experienced.

Penfield and Perot (1963) provided early evidence that sensory regions were involved in recall when they stimulated the cortex of awake patients during epilepsy surgery and elicited memories involving the sensory modality associated with the region stimulated. EEG studies also support the reactivation hypothesis, showing word retrieval was associated with left frontal, spatial location retrieval with parietal, and color retrieval with occipital-temporal activation (Buckner & Wheeler, 2001). Single-unit recordings in monkeys using paired-associate retrieval tasks and in humans using imagery and recall also support the view (Buckner & Wheeler, 2001). Evidence from fMRI and PET studies using episodic and associative memory paradigms also indicates that modality-specific or category-specific processes engaged at encoding tend to be re-engaged at retrieval (Danker & Anderson, 2010; Squire & Wixted, 2011). Other work has utilized specific encoding strategies and found that later retrieval also activates areas related to the

relevant encoding strategy (Danker & Anderson, 2010). In addition, fMRI studies show that regions activated in perception of items in specific categories are also activated at recall of those items (Buckner & Wheeler, 2001). One study found that specific regions of the ventral occipital cortex that were activated specific to perception of faces, houses, and chairs were also activated by imagining items from the same category (Ishai, Ungeleider, & Haxby, 2000).

Similar to the previously described account that emphasized the role of the prefrontal cortex in episodic memory retrieval, recollection, and recall, the reactivation view of episodic memory also describes an important role for frontal brain regions. Remembering can be spontaneously triggered, but is most often initiated by a goal-directed attempt. Frontal brain regions may be particularly important in initiating and supporting retrieval. These effects on memory are particularly apparent when patients must remember the specific context or source of an episode, or when minimal cues are provided (Buckner & Wheeler, 2001).

MTL structures have been repeatedly implicated in retrieving facts and events, suggesting the MTL plays a role in neocortical reactivation (Buckner & Wheeler, 2001). Most agree that the HC is necessary for retrieval at least initially (Danker & Anderson, 2010). The role of the HC may be to bind these distributed neocortical sites together, performing a binding function at encoding, and facilitating distributed reactivation at retrieval. Several models of retrieval have proposed that MTL structures rapidly bind neural representations associated with an experience to each other during memory formation, and then for a period of time after, continue to function to reinstate those representations during retrieval (Buckner & Wheeler, 2001). A partial cue processed

through the HC reactivates all of the relevant neocortical sites, and thereby retrieval of the whole memory. Evidence from retrograde amnesia as discussed above indicates that the HC is engaged at retrieval until a memory is fully consolidated, when neocortical regions can reactivate it independently (Squire & Wixted, 2011). As time passes after learning, the role of the HC system decreases until it is no longer necessary for storage maintenance or retrieval. The accompanying changes in organization could involve rehearsal, additional retrieval instances, acquisition of related material, or could be endogenous. At the same time as this reorganization, forgetting may occur due to weakening or loss of existing connections or due to interference from new connections. In addition, distributed networks may cohere in the form of developing cortico-cortical connections or re-representation of information in a more efficient form (Squire, 1992).

It is important not to conceptualize memory as being literally “transferred” from HC to neocortex, but rather that gradual changes in neocortex increase the complexity, distribution, and connectivity among multiple cortical regions (Squire & Wixted, 2011). Declarative memory requires interaction at the time of learning between neocortex and MTL memory system. Neural changes occur at the time of learning at one or more of the brain areas along the hippocampal input pathway, possibly as LTP (Squire, 1992). Neuroplasticity sites bind the areas in neocortex together that originated the convergent input. Neuroplasticity may also occur in adjacent HC areas, such as the EC, and perirhinal and parahippocampal cortices (Squire, 1992).

Certainly, the HC appears to be critical at the time of learning a new declarative memory (Danker & Anderson, 2010). There is a strong correlation between HC activation during encoding and success at retrieval later. In line with this, after transient

amnesic episodes resolve new learning becomes possible again, but events from the episode do not return (Squire, 1992). Therefore, representations encoded during the episode are lost or become disorganized.

It is a point of debate whether retrieval can become HC-independent after years of consolidation. It could be that a sparse representation in HC is able to reinstate an episode in the neocortex. How exactly the HC, other MTL regions, and cortex interact during encoding and retrieval is not really understood and needs further investigation of the functional connectivity using fMRI, intracranial recordings, or other measure capturing the temporal sequence of events. In addition to the PFC, new research also implies the importance of the subiculum in retrieval (Small et al., 2011).

The involvement of the HC in retrieval does not answer the question of where the content of memories resides: perhaps it is in the neocortex and the function of the HC is to permit retrieval through reactivation of the distributed neocortical network (Squire, 1992; Allport, 1981). But given the neural plasticity in the HC in the form of LTP, suited to forming and storing conjunctions, most likely the hippocampus, together with other sites, is where memories are actually stored (Squire, 1992). Also, contrary to a pure retrieval view of HC function, chronic amnesic patients do not recover from retrograde amnesia as time passes, even though normally stored memories become gradually independent of the HC (as discussed later).

6. Pattern separation and completion

Recently, a cognitive operation defined by computational models has gained increasing attention as a possible underlying function of the hippocampus. Discriminating among similar experiences is vital to episodic memory. Pattern separation has been

proposed as an explanation for how this is accomplished, an explanation based on computational models for how similar representations are stored in a distinct, non-overlapping manner (Yassa & Stark, 2011). Pattern separation allows similar stimuli flowing through the HC circuit to be represented with distinct neural codes (Small et al., 2011). Without pattern separation, new information would overwrite similar old information, leading to huge interference. HC-dependent memory clearly requires pattern separation, including recollection, conjunctions, binding-in-context, and complex associations. Some authors have suggested that the hallmark feature of episodic memory is pattern separation (Yassa & Stark, 2011).

This cognitive operation goes hand in hand with another: pattern completion. Pattern completion, in contrast to pattern separation, is how incomplete or degraded representations are filled-in based on previously stored representations. This process allows for accurate generalization when sensory input is noisy or incomplete. Pattern separation and completion are operationally defined as deviations from the linear transformation in which change in input to a circuit equals change in output (Yassa & Stark, 2011). Inspection of electrophysiological recording data shows pattern separation vs. completion, but to evaluate which regions of the HC performed the computation it is necessary to look at upstream regions to tell if transformation of upstream input took place.

Pattern separation and completion can be related to some of types of memory that have been discussed thus far, but these terms do not completely overlap. One such term, recollection, may involve access to memories which must be stored in unique fashion despite many interfering episodes. Recollection requires pattern separation for similar

overlapping memories. However, for the recollection of distinct or unique memories, pattern separation is not required. For example, pattern separation is crucial for when a person remembers where she parked her car today versus yesterday in the same parking lot. Separation is not as essential when locating the car for the first time in a new parking lot. Some authors working with pattern separation have observed that separation could occur without the phenomenological experience of recollection and also without the source details used to infer recollection (Yassa & Stark, 2011). For Yassa, “Recollection is a cognitive construct that might or might not require distinct neural mechanisms.” but pattern separation, however, is “a neural computation referring to a transformation of the representation of information.” (Yassa & Stark, 2011, p. 516). This computational mechanism of a key aspect of memory may have the power to investigate other phenomenological notions such as memory for single items vs. complex associations, objects vs. contexts (source memory), and episodic vs. semantic memory, among others. Demand on HC pattern separation varies in each of these (Yassa & Stark, 2011).

6.1 Pattern separation, pattern completion, and hippocampal subregions

As was described earlier, the HC is composed of subregions, which are distinguished by their molecular organization and functional connectivity. In addition to serving as a conduit, individual subregions have a computational function. Recently, an increasing amount of evidence has been presented that specific cognitive computational operations appear to be differentially linked to specific subregions (Small et al., 2011). Certainly, all subregions are involved in multiple operations, but differential involvement can be identified and examined.

Possible brain mechanisms of pattern separation and completion have been suggested. Computational models of the HC suggest that pattern separation in new learning is associated with the mossy fiber detour synapses that arrive at CA3 from the DG (McNaughton & Morris, 1987). The pattern completion involved in retrieval has been suggested to involve CA3 recurrent collaterals combined with direct input from the EC (Rolls, 1996; Yassa & Stark, 2011). Recurrent collaterals, found in CA3, are axons that circle back to dendrites of cells in same region, forming a recursive feedback loop. Decades ago, David Marr (1971) suggested these recurrent collaterals enable pattern completion for perceptual processes.

A pattern of evidence supports an association between pattern separation deficits and DG dysfunction (Small et al., 2011). The first high-resolution fMRI evidence for pattern separation in the human HC (Bakker, Kirwan, Miller, & Stark, 2008) showed that DG/CA3 activity was consistent with pattern separation. The study used an incidental encoding task, in which pictures were presented either only once or repeated later. Sometimes the second presentation was a similar but not identical picture (a lure). BOLD levels change with repetition, showing some form of adaptation (either suppression or enhancement). If a brain region was treating a lure image as a repetition (pattern completion) then activity should show same adaptation. If treating it as a new stimulus (pattern separation), activity should be like when it was initially presented. In the DG, the brain activity when subjects viewed lures was similar to the pattern of activation when seeing a new stimulus. CA1 and other regions showed activity like pattern completion or a mix of signals. Also it was shown that the input/output ratio was different in different areas, with a smooth linear trend for CA1, but discontinuous response for DG/CA3 – as

suggested by computational models for pattern separation and completion. Pattern separation is encoding a new item, but distinguishing it from an already encoded item. Pattern completion is recognizing an item as already previously encoded (Yassa & Stark, 2011).

Pattern completion is involved in the reactivation of a complete hippocampal-dependent memory when presented with only a fragment of the memory. This operation has been primarily associated with the CA3 subregion of the HC (Small et al., 2011). The CA3 auto-association system, as described by Lorente de No, is uniquely suited to pattern completion, which was computationally suggested by Marr. This is supported by mouse fMRI studies and in vivo recording studies (Gilbert, Kesner, & Lee, 2001; Leutgeb, Leutgeb, Moser, & Moser, 2007). CA3 “associates” the mossy fiber input with direct input from EC to facilitate later recall. The CA3 receives input from 3 sources. First, overlapping/distributed representations arrive from EC to DG via the perforant pathway. DG projects this onto CA3 via mossy fibers – which are powerful and unidirectional, and utilize large synapses (“detonator” synapses – strongly depolarizing) – on proximal apical dendrites of CA3 pyramidal cells. This input can force new pattern separated representations onto CA3 neurons to reduce interference and support new learning. Second, input to CA3 is received intrinsically from its extensive network of recurrent collaterals, which function as an auto-association pattern completion network. Last, CA3 receives direct input from EC (bypassing DG). This comparatively weaker input could function to provide a cue for recall. Supporting these ideas, it has been demonstrated that inactivating mossy fibers/DG input to CA3 interferes with new learning but leaves

retrieval intact. In addition, lesioning direct input to CA3 from EC impairs retrieval but leaves new learning intact (Yassa & Stark, 2011).

Other evidence has been conflicting and suggests multiple roles for CA3, showing pattern separation signals under some circumstances, pattern completion signals under others (Lee, Yoganarasimha, Rao, & Knierim, 2004; Leutgeb, Leutgeb, Traves, Moser, & Moser, 2004). In contrast, the DG is always showing pattern separation signals. Overall, the studies show pattern completion in CA3 with small changes in sensory input and pattern separation in CA3 with larger changes, whereas CA1, in contrast, showed linear transformation indicating neither separation nor completion (Yassa & Stark, 2011).

7. Pathology involving the hippocampus

Changes in hippocampal function and volume are implicated in a broad range of disorders and neurodegenerative processes including AD, cognitive aging, temporal lobe epilepsy (TLE), schizophrenia, depression, PTSD, and transient global amnesia (Small et al., 2011). The current paper will not review all of these in detail and will focus on AD and ageing, but mention contrasting findings in other diseases for emphasis.

Historically, AD has been the highest profile disease associated with hippocampal pathology. The hippocampus, and the EC in particular, is especially important in AD as the first area where the disease's hallmark pathology is seen in the accumulation of amyloid plaques and neurofibrillary tangles (Raz, 2005; Braak & Braak, 1991). Alois Alzheimer's classic paper describing a dementia with postmortem findings of plaques and tangles in the brain appeared in 1906. Many decades later the plaques were described as amyloid and its sequence of either 40 ($A\beta_{1-40}$) or 42 ($A\beta_{1-42}$) amino acids was defined (Glenner & Wong, 1984). Several other substrates and genes involved in $A\beta$ generation

have been associated with its pathological accumulation. Mutations in genes for amyloid precursor protein (APP) and presenilin, a substance involved in APP splicing lead to amyloid buildup. β -secretase and γ -secretase, the sequential action of which cleaves $A\beta$ from APP, are also important in $A\beta$ accumulation. ApoE, involved in clearance of $A\beta$, is associated with increased amyloid burden and cholinergic dysfunction. ApoE is important as a high risk gene for AD, with individuals who are homozygous for the E4 allele of apoE having more than seven times increased risk of developing AD (Corder et al., 1993). These findings have been important observational evidence for the hypothesis that amyloid accumulation is the primary event in AD. The amyloid cascade hypothesis stated that AD is initiated by abnormal cleavage of APP from $A\beta$, leading to chronically increased production and/or decreased clearance of soluble, diffusible $A\beta$, leading to aggregated non-diffusible $A\beta$ as spherical plaques and vascular deposits (Hardey & Higgins, 1992). Animal studies also support a role for $A\beta$ in cognitive decline, showing that neurotoxic $A\beta$ soluble oligomers, which precede formation of amyloid fibrils and are found in brains of humans with AD, impair cognitive function (Cleary et al., 2005; Roher et al., 1996; Walsh et al., 2002). The imbalance between $A\beta$ production and clearance also leads to changes in tau, a microtubule-associated protein that is the major component of neurofibrillary tangles. Initial tau changes are in EC eventually spread to the neocortex (Braak & Braak, 1991).

Recent development of in-vivo measures of amyloid have provided some support for an important role for amyloid in dementia (van Norden et al., 2012). In-vivo detection of $A\beta$ in CSF reliably distinguishes dementia from non-dementia subjects, though results are less promising in distinguishing different dementias (Wahlund & Blennaw, 2003; van

Norden et al., 2012). Some authors observe that CSF measures of A β are not sensitive markers of disease progression (Corder et al., 1993), though others disagree (Blennow, Vanmechelen, & Hampel, 2001). Another method of in-vivo A β measurement is Pittsburgh compound b (PIB) which is used with PET scanning to allow visualization of amyloid in the brain. This method has potential for use in early diagnosis, but there is less evidence for its use for tracking disease progression (van Norden et al., 2012). PIB is also problematic due to its short 20-min half-life. In the past 20 years, the amyloid hypothesis has been the most researched and accepted of the hypotheses for AD, but, as discussed later in the present paper, understanding of the role of A β in AD remains incomplete.

Another process that has pathological effects on the hippocampus is ageing. Normal aging is accompanied by cognitive decline in some domains (episodic (declarative) memory, attention, working memory, spatial learning) and preservation of others (verbal skills, implicit (procedural) learning, and semantic memory) (Driscoll et al., 2003). A great deal is known about the neurobiology of learning and memory, but there is no consensus on the precise nature of neurobiological changes associated with learning and memory in normal and pathological aging (Driscoll et al., 2003). The effects of ageing on the HC may be different from those associated with AD. Some authors view regional brain changes associated with ageing as subtle compared to global brain deterioration. But a growing list of studies have found support for structural and biochemical changes that are specific to the hippocampus related to normal aging, and that these are related to changes in performance on hippocampal-dependent tasks (Geinisman, deToledo-Morrell, Morrell, & Heller, 1995; Driscoll et al., 2003). Age-related structural changes in the HC have been identified with numerous methods,

including neuron count, synapse count, intracellular pathology, and neurofibrillary tangles (Geinisman et al., 1995; Issa, Rowe, Gauthier, & Meaney, 1990; Raz, 1999).

A reduction of hippocampal volume with age has been demonstrated across multiple studies (Driscoll et al., 2003; Jernigan et al., 1991; Golomb et al., 1993). In his meta-analysis of 12 longitudinal studies of hippocampal volume in normal ageing, Raz found lifetime shrinkage at an average annual rate of approximately 1.23% (Raz, 2005). Yearly shrinkage is slower in younger subjects ($\leq 1\%$) and faster in those age 70 or older (1.60 - 1.85%), but these rates are still much slower than in AD (3 - 4%) or in those with genetic AD (up to 8%) (Raz, 2005). HC volumes predict concurrent AD and so are useful to distinguish AD from controls. There are, however, many conflicting studies of hippocampal volume that are not to be ignored (see Driscoll et al., 2003). Possible factors that contribute to conflicting findings include differing definitions of the head of the HC, which is an area that is possibly more vulnerable to AD as well as an area less reliably measured, as it lacks clear anatomical landmarks (Raz, 2005). Samples including individuals with pathological processes other than normal ageing could be another factor behind the variability in the hippocampal volume literature. Studies of ageing and HC function are often confounded by presence of disease, particularly AD and vascular disease, as these occur commonly in older subject and cause HC changes themselves, so studies need to exclude these disease processes (Small et al., 2011). Certainly it is a challenge to separate diseases that are common in older adults, such as AD and cerebrovascular disease, from the process of ageing itself. One approach is to carefully select an older adult sample to reduce heterogeneity by screening for risk factors associated with cognitive decline, such as certain APOE alleles. However, study of pure

ageing may be a poor reflection of what is truly normal ageing, as the presence of cerebrovascular disease or pathology associated with AD are present in a large proportion of the population.

Facilitated by high-resolution imaging techniques, the study of individual hippocampal subregions and their differential vulnerability to pathology has gained increasing prominence. High-resolution fMRI is most useful in functional disorders because there is no cell death to see, but also as this technique can capture the spread of dysfunction over time (Small et al., 2011). It must be kept in mind that image-based volume measurement is always dependent on the specific methodology applied, with procedures varying in technique, sensitivity, and operator subjectivity. In addition, it is impossible to know the etiology of hippocampal volume reductions without postmortem analysis. Some authors have combined imaging methods with biochemical markers such as N-acetylaspartate, which are thought to indicate neuronal death (Driscoll et al., 2003).

It is important to note that metabolic changes can occur acutely and transiently (as in response to transient external stimuli), but can also occur slowly and chronically, affecting a region's basal metabolic state due to factors such as dendritic remodeling, neuronal dysfunction, or therapeutic interventions. fMRI measures using CBV and CBF, because they are quantitative, are better for detecting changes with aging and disease than BOLD. BOLD is sensitive to acute changes in response to a transient stimulus (Small et al., 2011). Interpretation of altered responses is intrinsically ambiguous in disease populations, in ageing, or even in healthy controls on medication. Developers of these methods are working to confront the challenges of imaging HC subregions, including very small target regions measuring only a few millimeters and intersubject variability in

HC subregion anatomy, especially with atrophy. Only CBV can have resolution less than one millimeter, whereas CBF and BOLD offer about one millimeter resolution (Small et al., 2011).

Small and other authors have proposed a pathophysiological framework that proposes to characterize disorders affecting the HC by regional vulnerability and metabolic state. These authors propose that any disorder affecting the HC formation targets specific subregions of the HC circuit differentially, leading to either increase or decrease in neuronal metabolism in that area (Small et al., 2011). This leads to hypotheses on phenotypic manifestation of these disorders and on understanding mechanisms of disease (Wu et al., 2008). Although a lesion or dysfunction in any HC subregion can affect nearby subregions over time, a pattern of more vulnerable and resistant regions emerges across studies of different disorders.

Small et al. (2011) broadly distinguish between disorders of HC cell death (vascular disease, AD, TLE) and disorders of HC dysfunction not prominently characterized by cell loss (ageing). Schizophrenia, depression, and TLE are associated with an abnormal hypermetabolic state in the HC formation. In schizophrenia and depression, HC may act as anatomical driver of gain-of-function (positive) symptoms through connections to the orbitofrontal cortex and nucleus accumbens. Treatment efficacy in depression has been found to be associated with decreased metabolism in the HC formation. TLE has been found in studies so far to alternate between basal hypometabolism and hypermetabolism during seizures, with gain of function symptoms such as psychotic and affective symptoms possibly associated with hypermetabolism in HC outflow areas. Studies using hippocampal 3D shape mapping, an MRI technique,

indicate the anterior HC, specifically anterior CA1 and subiculum, are particularly affected in schizophrenia. This is supported by evidence of basal metabolism changes in the same areas. Additionally, longitudinal studies of individuals found to be in prodromal stages of the disease identified changes in anterior CA1 first, spreading to subiculum and other brain areas over time. Depression also appears to affect anterior areas of the HC. Studies have varied in the specific location of shrinkage, but have included anterior subiculum and anterior CA1, but the CA1 finding could have been influenced by the age and possible vascular dysfunction of the subjects. Longitudinal studies of depression have not been done, but findings in anxious monkeys suggest anterior HC is selectively affected (Oler, 2010).

In AD, studies have suggested the entorhinal cortex (EC) is most prominently affected, with CA1 and the subiculum also involved, and relative preservation of DG and CA3 (Small et al., 2011). Changes in the EC could provide an early warning sign of dementia, with findings showing decreased metabolism in EC predicts cognitive decline three years later (Raz, 2005). EC changes predict MCI to AD conversion and it has been suggested that the EC is the best place to look to distinguish MCI from controls (Raz, 2005).

In contrast to AD, histological studies of vascular disease show the most reliable loss in CA1 (Small et al., 2011). CA1 has been viewed as especially vulnerable to ischemia for decades. Global ischemia produces selective neuronal loss in CA1 and memory impairment in rats and monkeys (Squire, 1992). TLE, a third disorder leading to hippocampal cell loss, shows extensive damage in DG, CA1 and CA3, but as opposed to AD, the subiculum is relatively spared. Cell death is also found in the EC in TLE, but is

greater than in AD and is located in different EC layers (Du et al., 1993; Schwarcz & Witter, 2002).

Ageing is characterized by HC dysfunction without prominent cell loss and can be considered a functional disorder (though it is not a “disease” per se) (Small et al., 2011). Preserved numbers of total neurons are found in ageing across species, including in rats, mice, monkeys, and humans (Lister & Barnes, 2009). Differential effects of ageing have been demonstrated in the DG in humans and animals (Small et al., 2011; Yassa & Stark, 2011). In the HC specifically, cell loss is observed in the subiculum and DG hilus, but not among DG granule cells or in principle cells of the HC proper (Lister & Barnes, 2009). The EC is relatively spared (Small et al., 2011; Raz, 2005). This pattern also has been observed in studies using high-resolution fMRI using BOLD, which show abnormal stimulus-evoked BOLD in normal ageing in combined area of DG and CA3, with normal responses in EC and subiculum (see also Lister & Barnes, 2009). Additionally, a hemodynamic study found age-related decline in the subiculum and DG, and no differences in the EC, except in older participants, those ages 70-88 (Raz, 2005), perhaps due to AD-related processes. Hypermetabolism, especially in anterior CA1 and also in anterior subiculum and orbitofrontal cortex, also has been reported in normal aging (Small et al., 2011).

Whereas the number of neurons appears to be largely preserved in ageing, changes in connectivity appear to accompany ageing (Lister & Barnes, 2009). Reduced numbers of synapses onto the DG have been identified and reduced amplitude of field EPSPs after perforant path stimulation in aged rats (Lister & Barnes, 2009). Suggesting compensation for this change, aged granule cells show stronger depolarizing responses to

stimulation (Lister & Barnes, 2009). In addition, a reduced number of perforant path axon collaterals pass through the DG. Alterations of functional connections in CA1 have also been observed due to possible reductions in postsynaptic density area, leading to functionally silent synapses (Lister & Barnes, 2009). A novel variant of DTI has indicated perforant path alterations and age-related decrease in dendritic integrity in DG or CA3 selectively, but not in EC, CA1, or Sub (Small et al., 2011).

Changes in HC synaptic plasticity also occur in ageing. Changes in LTP, LTD, and depotentiation in aged rats suggest it is more difficult for aged synapses to form new memories, and easier to forget them (Lister & Barnes, 2009). Deficits in LTP induction are seen at Schaffer collateral input to CA1 and perforant path input to DG has a higher depolarization threshold for LTP to occur in aged rats. LTP also decays more rapidly in aged rats and the decay correlates with measures of memory. Increased susceptibility to induction of long-term depression (LTD), a process reducing synaptic strength in naïve synapses, is seen in aged rats. In addition, a greater degree of depotentiation, reversal of LTP in previously strengthened synapses, is seen in aged rats (Lister & Barnes, 2009).

Impairment in tasks assessing pattern separation support fMRI findings pointing to dysfunction in the DG in normal ageing (Small et al., 2011). Given the implicated role of the DG in pattern separation, and the evidence that the DG is differentially targeted by normal ageing, it is not surprising that ageing is associated with pattern separation deficits. Selective changes in DG-CA3 network may lead to the pattern separation deficits that could underlie many of the episodic memory problems in older age (Yassa & Stark, 2011). In contrast, pattern completion is relatively preserved in ageing (Small et al., 2011). Work in a rat model of neurocognitive ageing shows age-associated pattern

separation impairment seen as rigidity in spatial representations while navigating similar environments, in line with a shift from pattern separation to pattern completion in ageing. Also CA3 were abnormally elevated in firing rate, perhaps related to disinhibition after deteriorating inhibitory interneuron modulation and perforant path input from EC, could overall shift the CA3 to favor pattern completion (Yassa & Stark, 2011).

Less investigation has been made of age-related changes along the long axis of DG, but an antero-posterior gradient of age-related vulnerability may exist, with some resilience in the anterior hippocampus to ageing. Meanwhile, large decrease in anterior hippocampus has been reported in AD, so anterior may be more vulnerable to AD. Therefore, looking at anterior hippocampal volume could help distinguish normal aging from those who will develop dementia (Driscoll et al., 2003).

8. Transition

Thus far, this review has provided a description of the anatomy and physiology of the hippocampus, a discussion of its role in cognition, and a review of hippocampal pathologies associated with aging and neurodegenerative disease. The hippocampus has been the focus of one literature on cognitive aging and neurodegenerative disease. In terms of disease entities, a focus on the hippocampus has been most relevant to Alzheimer's disease, which begins with pathological changes in the hippocampus and is characterized by progressive deficits in episodic memory. However, other pathological processes are also associated with hippocampal changes, including vascular disease and aging. Although a hippocampal perspective provides important contributions to understanding cognitive aging and disease impacting older adults, it is not a perspective that can be considered alone or offered as an exclusive representative of perspectives on

cognitive decline in aging. Another important perspective will be considered next, that of cerebrovascular pathology.

An established association between cerebrovascular pathology and cognitive decline points to a vital additional perspective on the complex factors in cognitive aging. The forthcoming sections will provide an overview of vascular anatomy and age-related cerebrovascular disorders and diseases, including stroke and degenerative dementia, as well as describe the cognitive sequelae of these disorders. I will emphasize topics that have been relatively underrepresented in the literature, including pathology of the cerebral small vessels. This discussion will close with a nuanced characterization of the profiles of cognitive impairment associated with insidious small vessel vascular dementia and Alzheimer's disease.

9. Vascular Anatomy

An overview of vascular anatomy is a necessary first step in understanding the behavioral changes associated with age-related cerebrovascular phenomena. The complexity of vascular dysfunction and associated cognitive decline is realized after even brief consideration of the broad range of anatomical substrates and pathological processes involved. The historical focus has been on the large vessels that serve cortical gray matter and the effect of large vessel stroke on higher-level cognitive functions. This has been to the exclusion of other important vascular and vascular-related substrates, including white matter tracts, subcortical gray matter structures, and the small-vessel cerebral vasculature. Extra-cerebral anatomy, most vitally the heart and peripheral vessels, must also be considered.

9.1 Large Vessel Anatomy

In humans, the brain receives up to 20% of cardiac output (Girouard & Iadecola, 2006), which delivers glucose and oxygen and eliminates heat and metabolic by-products. An intricate network of arteries, arterioles, veins, venules, and capillaries serves this purpose. The large arteries of this network – the anterior, middle, and posterior cerebral arteries – and the cortical regions served by each, have been well studied and represent an important component of neuropsychological knowledge and history. The left and right anterior and middle cerebral arteries can be traced back to the internal carotid, with its sister artery, the exterior carotid serving the face, and ultimately to the brachiocephalic artery and aortic arch. The left and right posterior cerebral arteries can be traced back to the basilar artery which runs along the ventral surface of the brain stem, where it is formed by the joining of the vertebral arteries, ultimately originating from the subclavian artery which connects to the aortic arch. Several arterial branches to the brainstem and cerebellum arise from the vertebrobasilar system. The three major cerebral arteries are interconnected in the Circle of Willis at the base of the brain, formed by the anterior and posterior communicating arteries. A fully-formed Circle of Willis is found in only about one-third of the population, but to the extent that it is present, it is thought to provide collateral circulation (Blumenfeld, 2010; Rigs & Rupp, 1963). Watershed regions are present where the coverage zones of the major cerebral arteries meet and, due to this distal location, are especially vulnerable to reduced perfusion.

9.2 Small Vessel Anatomy

The acute nature of large artery stroke is likely responsible for the historical predominance for much of the 20th century of this aspect of the cerebrovasculature in the study of cognition. The epidemiological impact of dysfunction related to the small

vessels, however, is arguably greater than acute stroke and certainly deserving of at least equal attention. Arterial small vessels have two origins: superficially from the subarachnoid circulation and deeper at the base of the brain (Pantoni, 2010). As shown in Figure 2, long penetrating small vessels arising from the leptomeningeal layers extend downward into the brain, perpendicular to its surface, passing through 3-5mm of cortex into the white matter. Smaller distributing vessels branch perpendicularly from these penetrating arteries and perfuse most of the subcortical white matter (Pantoni & Garcia, 1997). A separate set of short, small arteries extend from the subarchnoid layer, but supply only cortex and the 3-4mm strip of cerebral white matter just beneath (U-fibers). In this way, the cortex and white matter U-fibers receive collateral circulation, which could help explain why these regions of white matter are relatively spared from small vessel disease compared to other brain areas (Pantoni & Garcia, 1997).



Figure 2: Cerebral Arterial Small Vessels. Drawing of a coronal section of the right hemisphere showing arterial small vessels originating superficially from the subarachnoid circulation and deeper at the base of the brain. 1: Internal carotid artery; 2: anterior cerebral artery; 3: middle cerebral artery; 4: lenticulostriate small vessels; 5: leptomeningeal branches; 6: cortical penetrating small vessels; 7: long penetrating small vessels; 8: optic chiasm; 9: globus pallidus; 10: septal area; 11: head of the caudate nucleus; 12: frontal horn of the lateral ventricle; 13: corpus callosum; 14: claustrum; 15: insular cortex. (Marinkovic et al., 2001)

Other small vessels arise from arteries at the base of the brain (see Figure 2). The lenticulostriate vessels branch off from the middle cerebral arteries proximal to their source at the internal carotid artery and penetrate upwards to supply large portions of the basal ganglia and internal capsule (Blumenfeld, 2010). Some investigators believe that the lenticulostriate system may, in fact, be veins, implying that the periventricular white matter serves as a distal irrigation field (Pantoni & Garcia, 1997). Pantoni (2010) and de Reuck (1971) appear to side with an arterial lenticulostriate system, which creates a watershed region in the area where the small penetrating arteries arising from subarachnoid circulation and the lenticulostriate arteries projecting from basal areas meet, making this region including the periventricular white matter particularly vulnerable to the effects of small vessel disease.

Other small vessels originating from the anterior cerebral arteries, internal carotid artery, and posterior cerebral arteries also supply deep structures (Blumenfeld, 2010). Although there may be some variability, penetrating branches originate from the anterior cerebral arteries (e.g., recurrent artery of Huebner) to supply portions of the head of the caudate, anterior putamen, globus pallidus, and internal capsule. The anterior choroidal artery arises from the internal carotid artery to supply portions of the globus pallidus, putamen, thalamus (sometimes involving lateral geniculate nucleus), and posterior internal capsule. Small penetrating arteries arising from the proximal posterior cerebral arteries (close to the basilar artery) include the thalamoperforator, thalamogeniculate, and posterior choroidal arteries, which supply a large portion of the thalamus and posterior portions of internal capsule. The posterior cerebral arteries also provide the main blood

supply to the hippocampus, with the anterior and middle hippocampal arteries arising from the trunk of the PCA or its inferior temporal branches and the posterior hippocampal arteries often arising from the splenic artery, a branch of the posterior cerebral artery (Duvernoy, 2006).

10. Vascular Pathologies

A diversity of vascular pathologies may impact the large and/ or small vessels, may be associated with acute or chronic disease processes, and may be ischemic or hemorrhagic in nature. They are uniformly associated with reduced cerebral perfusion show dramatically increasing incidence with age.

10.1 Atherosclerosis and Vessel Disease Processes

Atherosclerosis, the most common vascular disease (Fung & Poppas, 2009), is the underlying cause of many cardiovascular events and complications and may affect vessels throughout the body (Miller, Haynes, & Moser, 2009). The blood vessels are composed of three tissue layers: tunica intima (inner layer which includes the endothelial cells), tunica media (smooth muscle), and tunica adventitia (outer layer of connective tissue). The center cavity of the vessel is called the lumen. Larger vessels (usually those greater than 0.5mm luminal diameter) are served by their own vasculature, known as the vasa vasorum, comprised of small arteries entering the vascular wall either from the abluminal surface (vasa vasorum externa) or from the luminal surface (vasa vasorum interna), arborizing to the outer media (Ritman & Lerman, 2007). Atherosclerosis is associated with a complex series of molecular events leading to cellular accumulation (plaque) that narrows or occludes the lumen, as well as functional changes within the vessel layers that disrupt the natural functioning of the vessel.

Atherosclerotic plaque formation – Multiple elements combine to form an atherosclerotic plaque in a process beginning with injury to the endothelium and lipid accumulation in the tunica intima (Fung & Poppas, 2009). Cytokine release, activation of macrophages, uptake of oxidized lipoproteins and foam cell formation, and activation of platelets and injured endothelial cells leads to release of factors stimulating smooth muscle cells of the tunica media to migrate, proliferate, and produce extracellular matrix and connective tissue that results in plaque formation (Fung & Poppas, 2009). The components of plaques, present in varying proportions, include connective tissue extracellular matrix, forms of cholesterol and phospholipids, cells such as monocyte-derived macrophages, T-lymphocytes, smooth-muscle cells, and thrombotic material containing platelets and fibrin (Fuster, Moreno, Fayad, Corti, & Badimon, 2005). While mainly affecting the intima, changes in the media and adventitia also occur, including growth of vasa vasorum (neovascularization; Fuster et al., 2005). Atherosclerotic plaques narrow the lumen and can lead to chronic hypoperfusion, but also to acute occlusion due to plaque rupture, an event leading to thrombus formation, particularly at high-risk sites (Fung & Poppas, 2009). The thrombus can also travel through the vessel and lodge in a narrow section of lumen. The close linkage between atherosclerotic plaque formation, plaque rupture and erosion, and thrombosis has led to the integrating term atherothrombosis (Fuster et al., 2005). Atherosclerosis can be located in coronary, cerebral, or peripheral arteries and therefore can impact perfusion and create risk for thrombosis in multiple, but selective, locations throughout the body.

Endothelial dysfunction and autoregulatory changes – The luminal narrowing and thrombosis are just one aspect of the impact of atherosclerosis. Healthy vasculature

undergoes continuous structural changes and adaptations that enable the organism to respond to changing requirements for blood supply. Atherosclerosis disrupts these important vessel functions.

Autoregulation of vessel tone is one way the vasculature compensates for the imbalance in oxygen supply/ demand that occurs in an organ suffering ischemia. Autoregulation is mediated by 3 main factors: sympathetic neural control, local metabolites, and endothelial (tunica intima) factors (balance between vaso-relaxing and vaso-constricting factors; Fung & Poppas, 2009). Atherosclerosis may disrupt normal endothelial autoregulation of vascular resistance and lead to inappropriate vasoconstriction and reduced perfusion (Fung & Poppas, 2009).

Other authors have suggested that endothelial dysfunction is not simply a consequence of atherosclerosis, but contributes to the pathogenesis of atherosclerosis and its later complications. Miller, Haynes, and Moser (2009) cite clear evidence that changes in endothelial function *precede* development of atherosclerotic lesions in non-human primates. Given the tight linkage between atherosclerosis and endothelial dysfunction, it is not surprising that every known risk factor for atherosclerosis impairs endothelial function (Miller, Haynes, & Moser, 2009). Also of note, endothelial cells die after approximately 30 years and replacement cells do not function as effectively (Miller, Haynes, & Moser, 2009). The progressive decline in endothelial function as men and women approach the age of 40 or 50 (Miller, Haynes, & Moser, 2009) is a risk factor for the development of atherosclerosis, and likely, dementia. Aging is strongly associated with both endothelial dysfunction and atherosclerosis (Miller, Haynes, & Moser, 2009).

Once the vasculature is appreciated as not simply a passive transport system, but as a dynamic and active participant in our response to constantly changing metabolic demands, the far-reaching and complex impact of atherosclerosis can be more fully realized. In the formation of plaques and development of endothelial autoregulatory dysfunction, atherosclerosis can affect both large and small vessels and can lead to acute and chronic changes in perfusion that can be ischemic and hemorrhagic in nature.

10.2 Stroke

Stroke refers to an acute cerebrovascular event, typically involving the large cerebral arteries. Ischemic stroke, the most common stroke subtype, is the consequence of decreased blood flow to a portion of the brain; hemorrhagic stroke, the second stroke subtype, is the result of bleeding into the brain (Sharma et al., 2005). Ischemic stroke may be caused by a thrombus (stationary blood clot or plaque) or embolus (a thrombus or portion of thrombus that travels through the vasculature). Thrombus in the cerebral arteries is the most common cause of acute stroke. Arterial emboli can take many forms, including air bubbles, bone fragments, atherosclerotic plaque (as described above), and others. Causes of thrombus and embolus are numerous and can include hypercoagulability caused by genetic deficiencies or autoimmune disorders, endothelial cell injury caused by trauma to the vessel wall, infection, or turbulent blood flow due to heart conditions such as atrial fibrillation and heart failure, as well as cardiac surgery (Hatzinikolaou-Kotsakou et al., 2005).

Cardioembolism, in which blood clots arise from a damaged heart, is most commonly caused by atrial fibrillation (AF; Duffis & Fisher, 2009), the most common persistent type of cardiac arrhythmia (Wolf, Mitchell, Baker, Kannel, & D'Agostino,

1998). AF prevalence increases with age, doubling with each decade in adults older than 50 years. Whereas AF was long thought of as inconsequential, recently AF (excluding the form associated with rheumatic heart disease) has been identified as an important cause of death and a powerful independent risk factor for stroke, increasing stroke risk by a factor of 5 (Wolf et al., 1998).

Hemorrhagic stroke occurs when a cerebral blood vessel weakens and bursts open, causing blood to leak into surrounding brain tissue. The flow of blood which follows vessel rupture damages brain cells. Defects in the cerebral vessels present in some individuals make this more likely. Age increases the risk for hemorrhagic stroke (Ariesen, Claus, Rinkel & Algra, 2003), particularly among individuals treated with anticoagulants (Hylek & Singer, 1994).

The ischemic and hemorrhagic stroke events discussed above have predominated in the study of relations between cerebrovascular disease and cognition. This is perhaps understandable, given the salient acute symptoms associated with stroke and that traditionally stroke is defined by clinical symptomatology (e.g. NIH Stroke Scale; Brott et al., 1989) rather than by an underlying disease process (Fisher, 2010). A broadening of the conceptualization of stroke to include information gained from neuroimaging and neuropathology has been proposed, which would lead to an integration of clinical, subclinical, ischemic, and hemorrhagic elements, including subclinical white matter disease and microbleeds (Fisher, 2010) as discussed below. Similar efforts have been made with transient ischemic attack (TIA), which is defined according to recent consensus guidelines as a brief episode of neurological dysfunction resulting from focal cerebral ischemia not associated with permanent cerebral infarction (Easton et al., 2009).

Often thought of as benign events whose effects disappear completely, TIAs are more correctly viewed as next to stroke on a spectrum of serious ischemic brain conditions, with 10-15% of TIA patients going on to have a stroke within 3 months, half of these within 48 hours (Easton et al., 2009).

10.3 White Matter Disease

Ischemic and hemorrhagic effects of atherosclerosis and other pathological processes are also found in the small vessels. Arteriosclerotic small vessel disease is mainly characterized by loss of smooth muscle cells, deposits of fibro-hyaline material, narrowing of the vessel lumen, and thickening of the vessel wall (Pantoni, 2010). Small vessel disease leads to chronic hypoperfusion and degeneration of white matter (Pantoni, 2010). These white matter changes, which manifest as hyperintensities on T2-weighted MRI, have been termed “subcortical hyperintensities,” “white matter lesions,” and “unidentified bright objects” (Roman, 1987). Hachinski, Potter, and Merskey (1987) used the term leukoaraiosis (literally meaning “rarefied white matter”) as a descriptive term for these signal changes. White matter changes are found in more than 95% of older adults over the age of 65 (Longstreth et al., 1996). Some authors have proposed a threshold of small vessel lesion burden at which cognitive changes become symptomatic and impact daily function (Libon et al., 2008; Price, Jefferson, Merino, Heilman, & Libon, 2005; Roman et al., 1993).

Inflammation, which can occur in response to cell damage, is being investigated in relation to white matter disease (Fisher, 2010). Inflammation occurs when tissues are injured by ischemia, bacteria, trauma, toxins, heat, or any other cause. The damaged cells release chemicals including histamine, bradykinin, and prostaglandins, which cause blood

vessels to leak fluid into surrounding tissues, causing swelling and demyelination. In the case of infection, inflammation may serve to isolate the bacteria or a foreign toxin from further contact with body tissues. The fluids that signal inflammatory processes may also have neurotoxic effects. Various inflammatory markers have been identified that may be related to cerebrovascular disease and be useful in future investigation (Cohen, 2009).

When considering radiologic indicators of white matter changes, it is important to note some important limitations. White matter lesions that appear identical on MRI can be histopathologically heterogeneous, with varying degrees of loss of structural integrity (Lee et al., 2009). In addition, early changes in microstructural integrity are not detected by conventional MRI (van Norden et al., 2011). DTI assessment of integrity of the whole white matter is therefore an alternative approach to MRI volume measures when available.

10.4 Derailment of the Blood-Brain Barrier

In addition to atherosclerosis and inflammation, several other pathological processes have been implicated in relation to white matter disease (see Libon, Price, Davis, Garrett, & Giovannetti, 2004 for a review). Research regarding the BBB can be traced to Lewandowsky (1900; cited in Zlokovic, 2008) who commented on the absence of central nervous system pharmacological actions after the intravenous injection of certain bile acids. Lewandowsky (1900) described the BBB as a mechanical membrane whose function was to keep blood from the brain. Goldman (1909, 1913) conducted several experiments and observed that IV injection of certain substances distributed themselves widely throughout the body, but not the brain or spinal cord. Modern research

regarding the BBB begins with the work of Davson (1976) who emphasized mechanical relations between spinal fluid produced in the ventricles and subarachnoid space.

Today the BBB is understood as a very complex endothelial structure that constitutes part of the neurovascular system. The BBB, along with cells that comprise and support the vasculature (e.g., pericytes, astrocytes, and microglia), separate components of the circulating blood from the brain. The BBB can be viewed as a number of different *tight junctions* between adjacent endothelial cells. Each of these tight junctions is associated with unique molecular attributes and transport systems. When functioning properly, these tight junctions/ transport systems allow and disallow molecules into the brain. In the case of damage or dysfunction, the BBB may lead to neuronal disruption by allowing toxins to reach neurons or by preventing the clearance of toxins from the brain.

Investigators have posited a role for BBB damage and dysfunction in cognitive aging and dementia (Zlokovic, 2004, 2008). Aging, independent of diseases of the cerebrovasculature, disrupts the structure and function of the blood-brain barrier (BBB; Mooradian, 1988). Enhanced permeability of the BBB has been suggested as an important mechanism underlying cerebral white matter disease in older adults (Fisher, 2010; Pantoni, 2010). Some authors have proposed that regional differences in BBB structure and permeability (Phares, Kean, Mikheeva, & Hooper, 2006) may account for different dementia syndromes.

10.5 Lacunar Infarction

Research regarding lacunes has a long history reaching back well into the 19th century (see Libon et al., 2004 for a review). Lacunes, defined as hypointense foci on T1-

weighted MRI, are typically seen in areas such as the basal ganglia, internal capsule, thalamus, and pons (Pantoni, 2010). Consensus on size of lacunar infarcts has not been reached. Diameters vary by investigator, ranging from a minimum of 3mm to a generally accepted maximum of 15mm (Pantoni, 2010). Fisher's lacunar hypothesis, though it remains unproven, explains lacunar infarcts as acute, complete occlusion of small vessels (Pantoni, 2010). Authors have proposed that microatheroma, tiny foci of plaque material, are the most common mechanism of an arterial stenosis eventually leading to symptomatic lacunes (Marti-Vilalta, Arboix, & Mohr, 2004). These atherosclerotic plaques have been found in arteries as small as 100µm in diameter (Marti-Vilalta, Arboix, & Mohr, 2004). Small, asymptomatic lacunes are thought to be most associated with lipohyalinosis and fibrinoid necrosis (Marti-Vilalta, Arboix, & Mohr, 2005).

Although white matter disease and lacunar infarction have been viewed as distinct, recent evidence suggests this may be incorrect. Small deep infarcts and cerebral white matter disease may be often indistinguishable by brain imaging, with infarcts incorporated into white matter disease (Fisher, 2010).

10.6 Cerebral Amyloid Angiopathy

The effects of small vessel disease are not exclusively ischemic in nature and increased attention is being paid to hemorrhagic cerebral micro-events. If vessel wall damage reaches the point of rupture, microbleeds, major hematoma, or intracranial hemorrhage can result, with differences in wall thickness thought to determine the size of the rupture (Pantoni, 2010). Cerebral amyloid angiopathy (CAA) is a collective term for a group of diseases with diverse etiology and common pathology (Vasilevko et al., 2010). This pathology is characterized by congophilic deposition of amyloid in the walls of

small and medium sized cerebral blood vessels and sometimes in the microvasculature, mostly in the leptomenigeal space, cortex, and, less often, in the capillaries and veins (Pantoni, 2010). The amyloid can be formed by different peptides such as A β (the same peptide seen in Alzheimer's disease), cystatin C, gelsolin, prion protein, Abri, and ADan. CAA can lead to weakening of vessel walls leading to micro or macro hemorrhage and sometimes show luminal occlusion (Pantoni, 2010). CAA, together with hypertension, is the most common cause of intracerebral hemorrhage in older adults (Vasilevko et al., 2010). While CAA is highly associated with microbleeds, it is also related to ischemic changes such as white matter lesions and lacunes (Pantoni, 2010). There may be common mechanisms for cerebral white matter disease and cerebral microbleeds, at least in the presence of CAA (Fisher, 2010). Cerebral microbleeds can also be related to hypertension and microangiopathy (van Norden et al., 2011).

CAA can be sporadic or associated with rare genetic diseases. CAA appears with high frequency in the general older adult population, including in as much as 50% of individuals in their 90s (Pantoni, 2010). CAA is also a pathological hallmark of Alzheimer's disease (AD), and this has been offered as an explanation for the increased risk of intracerebral hemorrhage in AD and the high prevalence of AD-associated microbleeds (Thoonsen et al., 2010; van Norden, 2011).

10.7 Heart Disease

Although it would appear obvious that the heart and cerebral vasculature are interdependent systems, they are often treated as separate. Atherosclerosis affects any of the organs of the body which are deprived of constant circulation – including the heart. The heart is also the site of some of the mechanisms implemented by the body to

compensate for circulatory dysregulation in distal organs. Coronary artery disease, myocardial infarction, heart failure, and cardiosurgical intervention impact the efficiency of the heart and thereby influence cerebral perfusion, as well as formation of emboli that travel to the brain (see Irani, 2009 & Jefferson, 2010 for reviews).

10.8 Genetic Factors

Finally, genetic small vessel diseases, although not discussed in detail here, are an important consideration, as they could facilitate study in pathological processes that is highly applicable to acquired forms of small vessel diseases that affect older adults (Pantoni, 2010). Cerebral autosomal dominant arteriopathy with subcortical ischemic strokes and leukoencephalopathy (CADASIL) and Fabry's disease are most prominent in a growing list of examples. Symptoms of these conditions impact individuals by midlife, much earlier than the chronic white matter disease seen in older adults. Study of people affected by genetic small vessel disease could provide an opportunity to examine the effects of vascular pathology independently of the multiple other disease processes that are generally present later in life.

11.0 Cerebrovascular Disease and Cognition in Older Adults

The description by Thomas Willis of dementia postapoplexia published in 1672 and Lobstein's dementia arteriosclerotica are often cited as early examples of dementia with vascular etiology. Another example, subcortical arteriosclerotic encephalopathy, was described by Binswanger in 1894. Even Alzheimer, in addition to his well-known descriptions of presenile dementia, described degeneration of smaller blood vessels referred to as "Alzheimer's sclerosis" (van Norden et al., 2011). For much of the 20th century, however, there was a great deal of terminological confusion related to processes

reflecting senile dementia, vascular dementia, and multi-infarct dementia (Roman, 2002; see Libon, Price, Davis, Garrett, & Giovannetti, 2004 for a review). The neuroimaging era again drew focus to the prevalence of vascular changes in the brains of patients with cognitive decline and dementia, leading to a reappraisal of vascular factors (e.g., Hachinski, 1987).

Given the heterogeneity and complexity of CVD-related neuropathology discussed in the above sections, it is hardly surprising that the clinical neuropsychological manifestation of CVD is not represented by a single cognitive profile. Cognitive impairment related to the cerebrovascular pathologies just described may vary according to onset (acute vs. insidious), course (stable vs. progressive), focal vs. global nature of symptoms, and level of severity. In the sections that follow, I review the common presentations and cognitive profiles related to acute stroke, MID, and small vessel disease. In the case of small vessel disease, cognitive deficits are presented in contrast to the cognitive deficits associated with AD-related HC pathology.

11.1 Acute Stroke and Multi-Infarct Dementia

Acute large vessel infarcts (strokes) are characterized by the abrupt onset of symptoms reflecting one of the classic stroke syndromes. Associated cognitive impairment is temporally linked to the infarct and often improves or stabilizes in the following days to months. Infarct location within the vasculature and the cerebral territory affected are commonly associated with specific deficits. Lateralization of motor and sensory deficits is a common feature of the classic syndromes, with motor and sensory deficits observed on the side of the body contralateral to lesion location.

Middle Cerebral Artery Stroke - Large artery infarcts and ischemic events are more common in the middle cerebral artery (MCA) than in the anterior or posterior cerebral arteries (ACA; PCA), partly due to the relatively large area supplied by the MCA. Infarcts can be classified further by the branch of the MCA in which the occlusion occurs: superior division, inferior division, or deep territory. Specific sensorimotor deficits are associated with the MCA division affected, with contralateral face and arm weakness associated with superior division occlusion, contralateral paralysis (arm and leg) with the deep division, and contralateral cortical-type sensory loss (hemianesthesia or homonymous hemianopia) with the inferior division. In individuals with left hemisphere language dominance, left MCA occlusion is classically associated with aphasias, specifically of the nonfluent, or Broca's, type (superior division) and fluent, or Wernicke's, type (inferior division). Right MCA occlusion is classically associated with contralateral hemineglect, particularly when the right MCA inferior division is affected. Proximal MCA occlusion, known as MCA stem infarct, can lead to a combination of these symptoms, and to global aphasia in the case of left hemisphere damage and profound left hemineglect in the case of right hemisphere damage. Infarcts affecting large parts of the MCA territory often result in a gaze preference toward the side of the lesion, particularly in the acute period shortly after onset (Blumenfeld, 2010).

Anterior Cerebral Artery Stroke - ACA infarcts are typically associated with contralateral weakness and sensory loss affecting the leg more than the arm or face. Hemiplegia can occur with larger areas of damage. Manifestations of frontal lobe dysfunction can also be seen, including impaired judgment, flat affect, and apraxia.

Transcortical motor aphasia can be observed in the case of left hemisphere damage or contralateral neglect with right hemisphere damage.

Posterior Cerebral Artery Stroke - PCA infarcts typically lead to a contralateral homonymous hemianopia. Involvement of the small penetrating vessels supplying the thalamus or posterior internal capsule can result in contralateral sensory loss, paralysis, or thalamic aphasia in the case of the language-dominant hemisphere. Alexia without agraphia can result from infarct of the left occipital cortex and the splenium of the corpus callosum. Midbrain dysfunction can also occur, such as third-nerve palsy, ataxia, decorticate posturing, and impaired consciousness. Anterograde amnesia is sometimes observed following PCA stroke, as the PCA supplies large portions of the hippocampus (Benson, Marsden, & Meadows, 1974; Szabo et al., 2009).

Multi-Infarct Dementia - Multiple, serial infarcts may cause a progressive decline in cognition and functioning, with each new infarct associated with decline and subsequent stabilization. Dementia due to multiple strokes is referred to as multi-infarct dementia (MID). Individuals with MID typically present with neuroimaging evidence of focal infarcts and focal findings obtained from the neurological examination. Hachinski's Ischemic Scale, which notes the abrupt onset of symptoms, stepwise progression, vascular risk factors, and other signs, has been the traditional means by which MID has been diagnosed (Hachinski et al., 1975).

11.2 Interim summary

An attempt was made in the preceding sections to describe the complexity of vascular anatomy and related pathologies, and to introduce the heterogeneity of their manifestation in cognitive dysfunction. An emphasis has been placed on several topics

that have been relatively underrepresented in the literature to date, including anatomy of the cerebral small vessels and the pathological impact of small vessel disease. Earlier sections of this review discussed the cognitive processes associated with the hippocampus. Having established sufficient background, the review will now proceed with a nuanced characterization of the cognitive profiles associated with small vessel disease and Alzheimer's disease, the cognitive manifestations of the two major pathologies discussed in this review.

12. Cognitive Profiles Associated with Small Vessel Disease and Alzheimer's Disease

In contrast to the acute onset of stroke and the stepwise progression of MID, an insidious onset with progressive cognitive decline is typical of small vessel disease. Insidious, progressive decline appears to be the most common presentation in patients diagnosed with VaD (Cohen, 2009), suggesting a prominent role of progressive small-vessel damage in dementia patients with a primarily vascular etiology.

It is certainly notable that, like small vessel disease, AD is also characterized by insidious onset with progressive decline. Whereas time course is useful for distinguishing multi-infarct dementia from AD, it cannot be used to differentiate between AD and dementia due to small vessel disease. However, some authors have found that the neuropsychological profiles of small vessel disease and AD can be differentiated. Clinical investigations of patients in an outpatient memory disorder clinic by Libon and colleagues (Seidel, Giovannetti, & Libon, 2012) have shown that MRI scans with significant white matter alterations are rarely associated with an abrupt onset or step-wise decline in cognitive or neurological functioning. Dementia patients with marked white matter pathology on MRI (hereafter small vessel vascular dementia [VaDs]) may be

distinguished from those with AD on neuropsychological measures of executive control, episodic memory, and semantic knowledge and organization. Differences in these cognitive domains are detailed below and summarized in Table 10.

Table 10

Summary of Neuropsychological Patterns Observed between Dementia Associated with Small Vessel Disease and Alzheimer's Disease

	Dementia Associated with Small Vessel Disease (smVaD)	Alzheimer's Disease (AD)
Time Course	gradual, insidious decline	gradual, insidious decline
MRI findings	white matter hyperintensities, prominent in the periventricular and deep region	cortical atrophy with reduced hippocampal volumes
Executive Control	pervasive impairment affecting all response modalities	impairment restricted to lexical/ semantic operations
perseveration	highly perseverative, hyperkinetic/interminable motor perseveration	mildly perseverative, conceptual perseveration
concept formation	fail to establish mental set and the abstract attitude to form concepts	form vague, degraded concepts
working memory/mental search	difficulty maintaining mental set over time, reduced storage and rehearsal, and poor mental manipulation	reduced storage and rehearsal
Episodic Memory	impaired retrieval	impaired encoding and rapid forgetting
cued free recall	some benefit from cues	minimal to no benefit from cues, high rates of high-frequency intrusion errors in response to category cues
delayed recognition	improvement with increased structure of the recognition format, false positives suggest interference effects and source memory failures	little to no benefit from recognition test format, endorse unrelated foils
Semantic Knowledge	mild impairment secondary to executive control deficits	moderate impairment due to semantic degradation
naming	mildly impaired, coordinate errors (acorn - peanut)	moderately impaired, superordinate errors (acorn - nut)
verbal fluency	letter fluency more impaired than category fluency, words on category fluency highly associated	category fluency more impaired than letter fluency, reduced association between consecutive words on category fluency
Everyday Action	high rates of commission errors, interference from distractor objects	high rates of omission errors

12.1 Executive Control

Work by several authors suggests that patients with VaDs can be differentiated from patients with AD on measures of executive control. In particular, careful consideration of patients' perseverations, abstract reasoning, working memory, and mental search abilities elucidates some important differences.

Perseveration - Mental set is the ability to appreciate and understand the nature and parameters of a task and to respond accordingly over time until the task is completed. Lamar et al. (1997) studied deficits in establishing and maintaining mental set by looking at the perseverative behavior produced by patients with AD and VaDs on the Graphical Sequence Test (GST), an assessment procedure inspired by the work of A.R. Luria (1980). The GST requires participants to either draw the shapes or write the names of simple geometric figures, numerals, and other overlearned objects. The overall volume of errors was significantly greater among the VaDs patients, but the types of perseverative errors made by patients with VaDs were also quite distinctive. For example, patients with VaDs frequently persisted in producing responses even when there was no command to do so (i.e., *hyperkinetic/ interminable perseverations*). The perseverative errors made by patients diagnosed with AD were different. For example, when asked to *write* the phrase "three squares and two circles" after drawing a series of simple figures in a prior item, AD patients *drew* three squares and two circles, reflecting perseveration of a prior category (i.e., figures); or when asked to draw a target figure such as a circle, AD patients often produced a different previously drawn figure such as a square or a triangle, reflecting perseveration of a prior item/element (i.e., *semantic/ element perseverations*).

Among patients with VaDs, performance on the GST correlated with performance on tests of motor functions, suggesting impaired regulation of motor behavior contributed to perseverative errors on the test. By contrast performance by patients with AD was correlated with tests of naming and output on a semantic fluency task (animals), suggesting problems in language and the lexical selection of semantically-related information may underlie difficulty in AD patients.

Abstract reasoning - Giovannetti et al. (2001) examined the errors made by a heterogeneous group of dementia patients on a measure of abstract reasoning, the WAIS-R Similarities subtest. She found 0-point responses provided by VaDs patients tended to be ‘out-of-set errors’ reflecting difficulty establishing mental set and the formation of the necessary *abstract attitude* (Goldstein & Scheerer, 1941) as required by the task parameters (e.g., *dog-lion* – “one barks and the other growls”). In contrast, the 0-point responses of AD patients, although vague, tended to be ‘in-set’, indicating an implied superordinate structure (e.g., *dog-lion* – “they’re alive”). Factor analysis indicated that ‘out-of-set errors’ were associated with other measures of executive control impairment while ‘in-set’ errors were related to impairment in language and lexical selection.

Working Memory and Mental Search - The Boston Revision of the Mental Control subtest from the Wechsler Memory Scale (WMS) evaluates working memory and the capacity to establish and maintain a complex mental set through a series of tasks, such as asking patients to state letters that rhyme with the word ‘key’, to identify capital, printed letters with curved lines, and to recite the months of the year backwards. Previous research has shown that patients with VaDs and patients with Parkinson’s disease

dementia perform less accurately on these tasks as compared to patients with AD (Libon et al., 1997). Further analysis of Mental Control performance has revealed that VaDs and AD patients perform differently over time, indicating differential impairment in maintaining mental set (Lamar, Price, Davis, Kaplan, & Libon, 2002). This performance pattern was also observed in letter fluency (Lamar et al., 2002). For example, patients with VaDs generated a larger proportion of words during the initial 15s of the letter fluency task. After the first 15s, however, the output of VaDs patients dropped precipitously below that of the AD patients. The proportion of responses generated by the AD patients within each 15s quadrant was no different than the distribution of output generated by healthy control participants.

Lamar et al. (2007) assessed working memory using a new Backwards Digit Span Test consisting of 3-, 4-, and 5-span trials. Short-term storage and rehearsal was assessed by tallying the total number of digits reported regardless of recall order (ANY-ORDER; e.g., 47981 recalled '18943', score= 4). Mental manipulation in the form of disengagement and temporal re-ordering was assessed by the total number of digits recalled in correct position (SERIAL-ORDER; e.g., 47981 recalled '18943', score= 3). Rather than using clinical diagnosis as the grouping variable, Lamar et al. (2007) used a visual rating scale of white matter hyperintensities on MRI to divide participants into groups with minimal-mild versus moderate-severe white matter disease. No between-group difference for ANY-ORDER recall was found, suggesting groups were equated in terms of short-term storage and rehearsal abilities. By contrast, participants with moderate-severe white matter disease scored lower for SERIAL-ORDER, suggesting

differential impairment for mental manipulation and temporal re-ordering. Step-wise regression analyses showed ANY-ORDER performance variance was explained solely by dementia severity (MMSE). SERIAL-ORDER performance variance was explained by dementia severity (MMSE) and a composite score reflecting executive functioning. In a follow-up study, Lamar et al. (2008) found an association between increased left hemisphere white matter alterations around the posterior ventricular horn and frontal centrum semiovale and reduced SERIAL-ORDER recall.

This body of research suggests that careful examination of perseveration, concept formation, working memory, and mental search performance reveals complex processes that may be differentially impaired in people with AD versus VaDs. The patterns of performance described above are also in line with the view that executive function deficits in dementia are hierarchically arranged in the sense that some deficits are primary and related to more rudimentary motor/ cognitive functions (as in VaDs), whereas other executive deficits may be characterized as secondary to disorders of other domains of cognition, such as language or semantic knowledge (as in AD). These findings are consistent with the theoretical constructs put forth by Luria (1980) and Goldberg (1986) and empirically supported by factor analysis of executive function measures (Lamar, Swenson, Kaplan, & Libon, 2004). The executive deficits associated with VaDs appear to be extensive, pervasive, and context-independent, whereas the executive deficits associated with AD are more restricted and context-dependent (i.e., specific to lexical/ semantic operations). In terms of biological substrates, VaDs ischemic damage to subcortical-cortical white matter projections and the basal ganglia may disrupt the

modulation operations of the prefrontal cortex. Consequently, the prefrontal cortex cannot effectively maintain or shift mental set to meet the needs that may be required over time or when task demands are changed or become complex.

12.2 Episodic Memory

Performance by VaDs and AD patients also show important differences on tests of episodic memory. Past research suggests VaDs patients show relatively preserved performance on tests of episodic memory (Bernard et al., 1992; Libon et al., 1996a, 1998; Tierney et al., 2001; LaFosse et al., 1997). On list learning tasks, such as the California Verbal Learning Test (CVLT; Delis et al., 1987; Libon, Mattson, & Glosser et al., 1996b), AD patients display poor retention, rapid forgetting, little to no benefit from cued recall or recognition test conditions, and the production of many intrusion errors. In contrast, patients with VaDs show significantly higher scores on all measures of delayed free and cued recall episodic memory and significant improvement on recognition trials. These findings are similar to prior research showing that AD patients are more impaired on measures of episodic memory relative to patients with Parkinson's Disease (PD) and Huntington's disease (HD), two other conditions characterized by executive dysfunction (Delis et al., 1991; Kramer et al., 1988; Massman et al., 1990).

Davis et al. (2002) examined the distribution of false positive responses produced by AD and VaDs patients on the delayed recognition task of the CVLT-9. Within-group analyses of the distribution of false positives indicated that patients with VaDs endorsed more interference (list B) foils than semantic or unrelated foils. By contrast, patients with AD endorsed more semantic and unrelated foils. The number of interference (list B) foils

endorsed was positively correlated with perseverative errors on the Graphical Sequence Test (Lamar et al., 1997). These findings suggest that analysis of false positive errors may be necessary to identify the source of failure on delayed recognition testing, which may be influenced by deficits in episodic memory, semantic knowledge, and executive control. The list B foils endorsed by VaDs patients may reflect source memory failures or interference effects from executive function impairment, whereas the semantic and unrelated foils endorsed by AD patients may reflect primary deficits in episodic memory and semantic knowledge.

In a further examination of episodic memory performance, Price et al. (2009) constructed a new 9-word verbal serial list learning test, the Philadelphia (repeatable) Verbal Learning Test (P[r]VLT), a test modeled after the California Verbal Learning Test (CVLT). Price et al. (2009) tested the hypothesis that patients with mild MRI white matter alterations would present with evidence of an amnesic syndrome with primary episodic memory deficits while patients with severe MRI white matter alterations would present with serial list learning deficits consistent with executive function impairment. Finally, patients with moderate MRI white matter alterations were expected to demonstrate a mixed amnesic/dysexecutive profile. Indeed, patients with only mild MRI white matter alterations presented with a flat learning curve on immediate free recall test trials, rapid forgetting with poor recall on delayed free recall/ recognition test trials, and copious cued recall intrusion errors, a profile often associated with AD. By contrast, the severe MRI white matter group demonstrated some learning on immediate free recall test trials, exhibited less forgetting as assessed with delayed recognition versus delayed free recall test trials, and produced far fewer cued recall intrusion errors, a profile often

associated with VaDs. Patients in the moderate MRI white matter group presented with characteristics seen in both the mild and severe MRI white matter groups. Overall, this research suggests that MRI white matter disease can be associated with specific patterns of impairment on measures of episodic memory.

In sum, work by several authors (Bernard et al., 1992; Libon et al., 1996a, 1998; LaFosse et al., 1997; Tierney et al., 2001) shows patients with VaDs demonstrate relative sparing of episodic memory performance relative to patients with AD. Difficulty demonstrated on measures of episodic memory among patients with VaDs may be largely explained by executive functioning deficits (Davis et al., 2002). However, the literature on episodic memory deficits in VaDs is not consistent, as some authors have not observed differences between VaDs and AD on measures of episodic memory (Reed et al., 2007). Some authors have suggested that frank episodic memory impairment may come later in the course of VaDs, while retrieval errors associated with executive dysfunction may appear early in the course (Cohen, 2009).

12.3 Semantic Knowledge and Organization

Deficits in semantic knowledge language in patients with VaDs have not been as extensively studied as those of executive control or memory. While a variety of language-related tasks have been administered, the procedures most commonly reported include tests of naming and verbal fluency. Two general findings emerge from this literature. First, patients with VaDs sometimes produce better scores on tests of naming (Cannata et al., 2002; Kontiola et al., 1990). Second, output on tests of letter fluency produced by patients with VaDs is reduced as compared to AD patients (Carew et al., 1997; Lafosse et al., 1997), a finding often interpreted within the context of greater executive control

deficits associated with VaDs. Careful examination of performance by VaDs and AD patients suggests other differences in their performance on such measures.

Confrontation Naming –The observation that patients with VaDs make fewer semantically-related intrusion errors than patients with AD on tests of episodic memory may suggest that, in general, semantic knowledge is less disrupted in VaDs. Only a few studies have examined this issue. For example, Lukatela et al. (1998) found that patients with VaD made fewer errors on the Boston Naming Test (BNT) as compared to patients with AD. In addition, patients with AD tended to make superordinate errors, (acorn – nut), i.e., errors that tend to place the response within a broader semantic class than the stimulus. Patients with VaDs made more coordinate errors, (acorn – peanut), i.e., errors that tend to place the response within the same semantic class as the stimulus. Lukatela et al. (1998) interpreted their findings as evidence for relative preservation of semantic knowledge in VaDs as compared to AD.

Semantic Fluency - Carew et al. (1997) designed a paradigm to measure semantic organization on a category fluency task. On this task, patients were asked to generate as many different animal names as they could in one minute. All responses were coded into the following six attribute categories: size (big, small), geographic location (foreign, North America), diet (herbivore, carnivore, omnivore), zoological class (insect, mammal, bird, etc), habitat (farm, Africa/jungle, widespread, etc), and biological order/ related groupings (feline, canine, bovine, etc). An Association Index (AI) was calculated by totaling the number of shared attributes and then dividing by the number of total responses. The AI was designed to provide a measure of the semantic organization

between successive responses independent of the number of words produced. Carew et al. (1997) found that the total number of responses made by patients with AD and VaDs did not differ. With respect to the AI, whereas healthy control participants and VaDs patients did not differ, both of these groups obtained higher scores on this measure compared to patients with AD. Carew et al. (1997) interpreted their data as consistent with the idea that semantic knowledge is relatively intact in VaDs as compared to AD.

12.4 Summary of the Cognitive Profile of VaDs and AD

As discussed above, the performance of patients with VaDs on neuropsychological measures reflect a cognitive profile characterized by differential impairment on tests of executive control as compared to other domains of cognitive functioning. Furthermore, the executive control deficits seen in VaDs tend to be ubiquitous, affecting performance on other aspects of cognition including episodic memory and semantic knowledge. Alzheimer's disease, in contrast, is characterized by an anterograde amnesia with deficits in episodic memory at the level of encoding. On list learning tasks, such as the California Verbal Learning Test (CVLT; Delis et al., 1987; Libon, Mattson, & Glosser et al., 1996b), people with AD display poor retention, rapid forgetting, little to no benefit from cued recall or recognition test conditions, and the production of many intrusion errors. Executive control deficits in AD, while also present, are quantitatively and qualitatively different from in vascular patients. AD patients show less severe executive deficits and the executive deficits in AD appear to be restricted to the response selection of lexical/ semantic information. In terms of a hierarchical view of cognition as by Luria (1980), the executive control deficits in VaDs are pervasive and

context non-specific, whereas the executive control deficits in AD are, by contrast, restricted and context specific.

The executive deficits in VaDs may be further characterized as a deficit in regulating behavior over time. As noted by Lamar, Price, Davis, Kaplan, and Libon (2002), as patients with VaDs attempt to work through various tasks, such as tasks of mental control, they tend to accumulate more and more errors. On tests of letter fluency, patients with VaDs tend to produce their output during the initial portion of the test. Again, these behaviors are different as compared to AD patients. The disruption of frontal lobe-basal ganglia-thalamic pathways may be the etiology of both the pervasiveness and poor regulation of executive control deficits in VaDs (Alexander, DeLong, & Strick, 1986; Sultzer et al., 1995).

13. Links between the hippocampal and vascular literatures of ageing and neurodegenerative disease

Organisms are organized natural products in which every part is reciprocally both end and means. -Emmanuel Kant, 1790

The preceding sections presented overviews of two perspectives on cognitive ageing and neurodegenerative disease. In line with the extant literature, the anatomy, pathology and cognitive processes associated with the hippocampus and the cerebrovasculature were each discussed largely in isolation. The dichotomy inherent in organizing the information in this way is reflective of the diagnostic criteria for AD and vascular dementia, which each exclude the presence of another systemic or brain disease that can account for deficits in cognition. This interpretation of the criteria creates a framework in which each diagnosis is exclusive of the other – the presence of

cerebrovascular disease ruling out an AD diagnosis, and the presence of AD ruling out a diagnosis of vascular dementia (American Psychiatric Association, 2000; McKhann et al., 1984; van Norden et al., 2012). It also sets up a framework for between group analyses as opposed to multivariate or person-centered statistical approaches. However, the portrayal of cerebrovascular disease and AD as pure, separate, and mutually exclusive disease processes ignores a growing literature that acknowledges the co-existence of these pathological processes and points to links between them suggesting possible interdependence. Evidence discussed below points to a poor relation between AD-pathology and cognition, emphasizes the co-existence of cerebrovascular and AD pathology in many individuals, and highlights genetic links between the disease processes.

Although observational data supporting the amyloid hypothesis appears strong, there are several issues that point to a less than central role for plaques in the neurodegeneration and cognitive decline of AD. In cognitively intact individuals older than 40, plaques and tangles have been found without accompanying neuronal loss (Morris & Price, 2001). Some studies on transgenic animals also show no relation between amyloid deposits and neurodegeneration (Hsia et al., 1999). Perhaps most importantly, studies examining the relation between AD pathology and cognitive performance paint a cloudy picture of amyloid's role in the disease, with numerous human studies showing a poor relation between amyloid pathology and cognitive function (Bennett et al., 2006; Price & Morris, 1999; Rowe et al., 2010; van Norden et al., 2012). These findings underscore the importance of considering additional neuropathologies, such as vascular disease, in conceptualizing the cognitive functioning of people with AD.

More support for this point comes from reports showing that many cognitively intact, healthy older adults have a large amount of amyloid plaques, some even with the same density as patients with AD, but without clinical signs of AD (White et al., 2005; see van Norden et al., 2012, for a review). By the age of 80-85, many individuals who are not demented have substantial AD pathology. The Medical Research Council Cognitive Function and Ageing Study (MRC CFAS), a large population-based prospective study in the UK and Wales, found that both demented and non-demented older adults showed intermediate AD pathology, despite equivalent degrees of vascular pathology (Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study, 2001). In fact, over a third of patients diagnosed with AD had no plaques and one third of non-demented patients had moderate to severe plaques. Thus, amyloid pathology is not sufficient to explain the cognitive decline associated with AD.

Recent efforts to develop pharmaceutical interventions for AD have focused on impacting levels of amyloid. Pharmacologic strategies to decrease amyloid production include preventing APP transcription, inhibiting enzymes involved in A β generation (APP splicing by β - and γ -secretase), preventing aggregation of insoluble amyloid, and increasing rates of amyloid clearance (van Norden et al., 2012). Human clinical trials of an approach using amyloid immunotherapies have been unsuccessful (Rinne et al., 2010; Salloway et al., 2009). A trial of one such therapy was shut down due to severe adverse events and another, while shown to lower amyloid (A β) levels, found no effect on cognitive function compared to controls (Fox et al., 2005). Lack of positive results could be attributed to factors including patient's advanced disease stage, study design, sample

size, or choice of dosage. The results may also reflect the role of other neuropathological factors in the clinical presentation of AD.

AD shares its most common risk factor, aging, with another pathological process: cerebrovascular disease. MRC CFAS (2001) not only showed a poor relation between AD pathology and cognition, it found 80% of participants had vascular abnormalities in the brain, with more severe findings in demented patients. Even Alzheimer himself wondered about the contribution of vascular pathology to AD pathology (Libon et al., 2004; van Norden et al., 2012). Cerebrovascular and AD pathology are found together in more than 40% of older adults with dementia (Jellinger, 2008). Patients clinically diagnosed with probable AD show a variety of underlying pathology, including amyloid plaques and tau tangles, as well as vascular lesions such as WML and lacunar infarcts (Snowdon et al, 1997; van Norden et al., 2012). Although it is possible that vascular pathology may explain the cognitive presentation of some individuals diagnosed with AD, there is strong evidence to suggest that the co-existence of these disease processes in many individuals must be considered. Vascular lesions were only weakly associated with cognitive function and dementia in those who did not meet pathology criteria for AD (Snowdon et al., 1997).

Cerebrovascular disease may exacerbate or facilitate AD pathology, suggesting a smaller burden of AD pathology may be needed to result in a clinical AD diagnosis when vascular pathology is also present. The Honolulu Aging study of very old men found that AD and vascular burdens contributed independently to AD diagnosis, in line with an additive effect of the two types of lesions (Launer, Petrovitch, Ross, Markesbery, & White, 2008). However, the combination of the two pathologies may interact to lower the

cognitive threshold for clinical dementia, and so have a synergistic effect (Brickman et al., 2008; van der Flier, Barkhof, & Scheltens, 2007). Several lines of evidence suggest that amyloid aggregation and vascular insufficiency may be mutually enhancing pathologies. Some points of interaction have been identified between amyloid aggregation and the hypoxia and ischemia related to vascular insufficiency. Presence of atherosclerosis was also found to be related to increased plaques and tangles in AD (Beach et al., 2007; Honig, Kukull, & Mayeux, 2005). Hypoxia and ischemia increase amyloid production. In addition, vascular insufficiency may reduce amyloid clearance, leading to greater amyloid accumulation and more amyloid plaques.

There also appears to be overlap in the genes associated with AD and vascular-related pathology. The main high-risk gene for AD, the E4 allele of ApoE, which plays a role in lipid metabolism and neuronal repair, is associated with not only cognitive impairment but also vascular pathology (Lahoz et al., 2001). E4 homozygotes show more WML than other genotypes (Kokubo et al., 2000). In fact, E4 was originally thought to be related to cognitive impairment because of its association with the presence of WML (van Norden et al., 2012). Relations between hypertension, subcortical WML, lacunes, and blood plasma amyloid (A β) levels were found in E4 carriers in population studies (de Leeuw et al., 2004; van Dijk et al., 2004), although other studies in dementia and population samples did not find this (Hirono, Yasuda, Tanimukai, Kitagaki, & Mori, 2000). E4 modulates amyloid deposit levels in animals and humans, especially in patients with WML (Greenberg, Rebeck, Vonsattel, Gomez-Isla, & Hyman, 1995; Holtzman et al., 2000; Vidal et al., 2000). E4 was also found to be related to small vessel arteriosclerosis, microinfarcts, plaque density, and CAA in autopsy-verified AD patients (Yip et al., 2005).

The association between an APP gene mutation, which is associated with amyloid plaques, and hereditary cerebral hemorrhage with amyloidosis (Dutch type) demonstrates that amyloid-related mutations can result in amyloid deposition in the vasculature. CAA, characterized by deposition of amyloid in walls of small and medium cerebral arteries, is also a particular point of blurring of the distinction between dementia of the Alzheimer type and vascular dementia (Thoonsen et al., 2010). Vascular amyloid is a vasoconstrictor and impairs regulation of cerebral circulation, and may thereby contribute to ischemia (Kalaria, 2002; Thomas, Thomas, McLendon, Sutton, & Mullan, 1996). Analysis of longitudinal data from the Rotterdam study suggests that blood plasma levels of amyloid were related to future vasomotor reactivity in vascular smooth muscle cells (van Dijk et al., 2007). Cerebral microbleeds, a possible link between the amyloid and vascular hypotheses, may be a marker of CAA and associated with AD. The evidence overall suggests amyloid and vascular insufficiency may together favor formation of amyloid plaques and CAA (van Norden et al., 2012).

Whereas a relation between MTL atrophy and AD disease stage is well documented (Braak & Braak, 1991), a relation between vascular risk factors and MTL atrophy has also been observed in both AD and non-demented samples (de Leeuw, Barkhof, & Scheltens, 2004; de Leeuw, Korf, Barkhof, & Scheltens, 2006). In a non-demented sample, subjects with diabetes have greater MTL atrophy on MRI than those without diabetes (den Heijer et al., 2003). Higher blood pressure was also related to greater MTL atrophy in a population sample (den Heijer et al., 2005). MTL atrophy is related to WML in both population studies and in studies of patients with AD, suggesting WML as a possible intermediary in the relation between MTL atrophy and blood pressure

(de Leeuw, Korf, Barkhof, & Scheltens, 2006). In patients with AD, a linear relation between systolic blood pressure and MTL atrophy was shown. In a prospective study, baseline WML volumes were associated with MTL atrophy progression in 35 patients diagnosed clinically with probable AD. In this study, MTL atrophy and blood pressure were only related in AD patients with WML (Korf, Scheltens, Barkhof, & de Leeuw, 2005). In addition, higher total cholesterol and low-density lipoprotein concentrations are also associated with faster cognitive decline in AD (Helzner, 2009), and treatment of vascular risk factors in AD is associated with slower cognitive decline (van Norden et al., 2012). In addition, CA1 volume decrease is related to hypertension and the effect of aging in CA1 has been linked to white matter hyperintensities (S. Mueller, unpublished observations, as cited in Small et al., 2011). Together these findings offer further support for importance in considering the combined effects of MTL/HC pathology and cerebrovascular disease in dementia.

Many current studies of cognitive decline in ageing and neurodegenerative disease do not consider the influence of vascular pathology. As with studies of many disorders, it is tempting to target “pure” samples. Unfortunately, such studies produce a poor reflection of the true population of older adults, which is most characterized by heterogeneity. A study by Driscoll, for example, that examined relations between aging, learning and memory problems, and hippocampal damage (Driscoll et al., 2003), went to great lengths to exclude subjects with even preclinical AD, but included no discussion of a possible role of vascular changes in hippocampal measures or in cognitive performance. Although individuals with current coronary heart disease, significant peripheral vascular disease, insulin-dependent diabetes, and untreated hypertension were excluded, this is not

sufficient to create a sample of supposed avascular purity. Patients treated for hypertension have vascular risk by definition, and may vary in the length of time since diagnosis or consistency of good blood pressure management. Further, presence of MRI white matter disease was not considered in subject selection. Even small changes in blood pressure from normal can impact cognition (Raz, Rodrigue, Kennedy, & Land, 2009).

14. Conclusion

Individuals with dementia are widely heterogeneous in phenotype and genotype. Individuals with dementia exhibit heterogeneity in exposure to vascular risk factors and cerebral amyloid, which likely co-contribute and interact in the clinical syndrome of AD. Current evidence from epidemiological, neuroimaging, pathological, pharmacotherapeutic, and clinical studies suggests an important role of vascular pathology in AD onset and progression (DeCarli, 2004; van Norden et al., 2012). It appears likely AD is not explained by a model based on one single risk factor and is not a disease entity with a single cause. Neither amyloid nor vascular factors are a necessary risk factor or a sufficient risk factor for AD (DeCarli, 2004). There is accumulating evidence that cerebrovascular damage could act synergistically with amyloid plaques to create neuronal dysfunction. These findings blur the traditional boundaries between HC pathology and cerebral vascular disease and emphasize the importance of taking a systems approach to the networks of aging. This approach should emphasize that dysfunction in network systems, such as the vasculature, can have multiplicative effects on organ functions and should acknowledge the inter-connectedness of neuropathological processes in organisms (Kriete, Sokhansanj, Coppock, & West, 2006; Vidal, 2009).

REFERENCES

- Akaike, H. (1987). Factor analysis and AIC. *Psychometrika*, *52*, 317–332.
- Alexander, G. E., DeLong, M. R., & Strick, P. L. (1986). Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annual Review of Neuroscience*, *9*, 357-381.
- Allport, D. A. (1985). Distributed memory, modular subsystems and dysphagia. In S. K. Newman & R. Epstein (Eds.), *Current Perspectives in Dysphagia* (pp. 32-60). Edinburgh: Churchill Livingstone.
- American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders: DSM-IV-TR* (4th ed.). Washington, DC: American Psychiatric Association.
- American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington, VA: American Psychiatric Publishing.
- Ariesen, M. J., Claus, S. P., Rinkel, G. J. E., & Algra, A. (2003). Risk factors for intracerebral hemorrhage in the general population: A systematic review. *Stroke*, *34*, 2060-2065.
- Auriel, E., Edlow, B. L., Reijmer, Y. D., Fotiadis, P., Ramirez-Martinez, S., Ni, J., . . . Greenberg, S. M. (2014). Microinfarct disruption of white matter structure: A longitudinal diffusion tensor analysis. *Neurology*, *83*(2), 182-188.

- Bakker, A., Kirwan, C. B., Miller, M. & Stark, C. E. (2008). Pattern separation in the human hippocampal CA3 and dentate gyrus. *Science*, *319*, 1640–1642.
- Barnes CA. (1979). Memory deficits associated with senescence: A neurophysiological and behavioral study in the rat. *Journal of comparative and physiological psychology*, *93*(1), 74-104.
- Beach, T. G., Wilson, J. R., Sue, L. I., Newell, A., Poston, M., Cisneros, R., ...Roher, A.E. (2007). Circle of Willis atherosclerosis: Association with Alzheimer's disease, neuritic plaques and neurofibrillary tangles. *Acta Neuropathologica*, *113*, 13–21.
- Beauchaine, T. P. (2003). Taxometrics and developmental psychopathology. *Development and Psychopathology*, *15*, 501–527.
- Bennett, D. A., Schneider, J. A., Arvanitakis, Z., Kelly, J. F., Aggarwal, N. T., Shah, R. C., & Wilson, R. S. (2006). Neuropathology of older persons without cognitive impairment from two community-based studies. *Neurology*, *66*(12), 1837-44.
- Benson, D. F., Marsden, C. D., & Meadows, J. C. (1974). The amnesic syndrome of posterior cerebral artery occlusion. *Acta Neurologica Scandinavica*, *50*(2), 133-145.
- Bergua, V., Meillon, C., Potvin, O., Bouisson, J., Le Goff, M., Rouaud, O., . . . Amieva, H. (2012). The STAI-Y trait scale: Psychometric properties and normative data from a large population-based study of elderly people. *International Psychogeriatrics*, *24*(7), 1163-71.

- Bernard, B. A., Wilson, R. S., Gilley, D. W., Bennett, D. A., & Fox, J. H. (1992). Memory failure in Binswanger's disease and Alzheimer's disease. *The Clinical Neuropsychologist*, *6*, 230-240.
- Blennow, K., Vanmechelen, E., & Hampel, H. (2001). CSF total tau, Abeta42 and phosphorylated tau protein as biomarkers for Alzheimer's disease. *Molecular Neurobiology*, *24*, 87-97.
- Blumenfeld, H. (2010). *Neuroanatomy Through Clinical Cases* (2nd ed.). Sunderland, MA: Sinauer Associates.
- Bourdel-Marchasson, I., Lapre, E., Laksir, H., & Puget, E. (2010). Insulin resistance, diabetes and cognitive function: Consequences for preventative strategies. *Diabetes and Metabolism*, *36*, 173-181.
- Boyle, P. A., Paul, R. H., Moser, D. J., & Cohen, R. A. (2004). Executive impairments predict functional declines in vascular dementia. *Clinical Neuropsychologist*, *18*(1), 75-82.
- Braak, H. & Braak, E., (1991). Neuropathological staging of Alzheimer-related changes, *Acta Neuropathologica*, *82*, 239-259.
- Brandt J., Benedict R., & Lutz, FL. (2001). Hopkins Verbal Learning Test-Revised. Professional manual. Psychological Assessment Resources.
- Brickman, A. M., Honig, L. S., Scarmeas, N., Tatarina, O., Sanders, L., Albert, M. S., ... Stern, Y. (2008). Measuring cerebral atrophy and white matter hyperintensity

- burden to predict the rate of cognitive decline in Alzheimer disease. *Archives of Neurology*, 65, 1202–1208.
- Broca, P. (1861). Remarques Sur le Siège de la Faculté Du Langage Articulé, Suivies D'une Observation D'aphémie (Perte de la Parole). *Bulletin Society Anatomique.*, 6, 330–357.
- Brott, T., Adams, H. P., Jr., Olinger, C. P., Marler, J. R., Barsan, W. G., Biller, J., ...Hertzberg, V. (1989). Measurements of acute cerebral infarction: a clinical examination scale. *Stroke*, 20(7), 864-870.
- Brown, M. W. & Aggleton, J. P. (2001). Recognition memory: What are the roles of the perirhinal cortex and hippocampus? *Nature Reviews Neuroscience*, 2, 51-61.
- Buckner, R. L. & Wheeler, M. E. (2001). The cognitive neuroscience of remembering. *Nature Reviews: Neuroscience*, 2(9), 624-34.
- Cadilhac, D. A., Carter, R., Thrift, A. G., & Dewey, H. M. (2012). Organized blood pressure control programs to prevent stroke in Australia: Would they be cost-effective? *Stroke*, 43(5), 1370-1375. doi: 10.1161/STROKEAHA.111.634949
- Cannata, A. P., Alberoni, M., Franceschi, M., & Mariani, C. (2002). Frontal impairment in subcortical ischemic vascular dementia in comparison to Alzheimer's disease. *Dementia and Geriatric Cognitive Disorders*, 13, 101-111.
- Carew, T. G., Lamar, M., Cloud, B. S., Grossman, M., & Libon, D. J. (1997). Impairment in category fluency in ischaemic vascular dementia. *Neuropsychology*, 11, 400-412.

- Cave, C. B. & Squire, L. R. (1992). Intact and long-lasting repetition priming in amnesia. *Journal of experimental psychology: Learning, memory, and cognition*, 18, 509–520.
- Cave, C. B., & Squire, L. R. (1991). Equivalent impairment of spatial and nonspatial memory following damage to the human hippocampus. *Hippocampus*, 1, 329-340.
- Chiulli, S. J. , Haaland, K. Y., LaRue, A., & Garry, P. J. (1995). Impact of age on drawing the Rey-Osterrieth figure. *The Clinical Neuropsychologist*, 9, 219-224.
- Cleary, J. P., Walsh, D. M., Hofmeister, J. J., Shankar, G. M., Kuskowski, M.A., Selkoe, D. J. & Ashe, K. H. (2005). Natural oligomers of the amyloid-beta protein specifically disrupt cognitive function. *Nature Neuroscience*, 8, 79–84.
- Cohen, R. A. (2009). Neuropsychology of Cardiovascular Disease. In R. A. Cohen & J. Gunstad (Eds.), *Neuropsychology and Cardiovascular Disease* (pp. 3-18), New York: Oxford University Press.
- Connolly, M., Bilgin-Freiert, A., Ellingson, B., Dusick, J. R., Liebeskind, D., Saver, J., & Gonzalez N. R. (2013). Peripheral vascular disease as remote ischemic preconditioning for acute stroke. *Clinical Neurology and Neurosurgery*, 115(10), 2124-2129. doi: 10.1016/j.clineuro.2013.07.038
- Corder, E. H., Saunders, A. M., Strittmatter, W. J., Schmechel, D. E., Gaskell, P. C., Small, G. W, ...Pericak-Vance, M. A. (1993). Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science*, 261, 921–923.

- Corkin, S. (1984). Lasting consequences of bilateral medial temporal lobectomy: Clinical course and experimental findings in H. M. *Seminars in Neurology*, 4, 249-259.
- Corkin, S. (2002). What's new with the amnesic patient H.M.? *Nature Reviews Neuroscience*, 3, 153-160.
- Crum, R. M., Anthony, J. C., Bassett, S. S., & Folstein, M. F. (1993). Population-Based Norms for the Mini-Mental State Examination by Age and Educational Level. *JAMA*, 269(18), 2386-2391.
- Danker, J. F. & Anderson, J. R. (2010). The ghosts of brain states past: Remembering reactivates the brain regions engaged during encoding. *Psychological Bulletin*, 136(1), 87-102.
- Daum, I., Channon, S., & Canavar, A. (1989). Classical conditioning in patients with severe memory problems. *Journal of Neurology and Neurosurgery Psychiatry*, 52, 47-51.
- Davis, K. L, Price, C., Kaplan, E., & Libon, D. J. (2002). Error analysis of the nine-word California Verbal Learning Test (CVLT-9) among older adults with and without dementia. *The Clinical Neuropsychologist*, 16, 81-89.
- Davson, H. (1976). The blood-brain barrier, *Journal of Physiology*, 255, 1–28.
- de Leeuw, F. E., Barkhof, F., & Scheltens, P. (2004). White matter lesions and hippocampal atrophy in Alzheimer's disease, *Neurology*, 62, 310–312.

- de Leeuw, F. E., Korf, E., Barkhof, F., & Scheltens, P. (2006). White matter lesions are associated with progression of medial temporal lobe atrophy in Alzheimer disease, *Stroke* 37, 2248–2252.
- de Leeuw, F. E., Richard, F., de Groot, J. C., van Duijn, C. M., Hofman, A., Van Gijn, J., & Breteler, M. M. (2004). Interaction between hypertension, apoE, and cerebral white matter lesions. *Stroke*, 35, 1057–1060.
- de Reuck, J. (1971). The human periventricular arterial blood supply and anatomy of cerebral infarctions. *European Neurology*, 5, 321-334.
- DeCarli, C. (2004). Vascular factors in dementia: An overview. *Journal of the Neurological Sciences*, 226(1-2), 19-23.
- Delis, D. C., Kaplan, E., & Kramer, J. H. (2001). Delis-Kaplan Executive Function System (D-KEFS). San Antonio, TX: The Psychological Corporation.
- Delis, D. C., Kramer, J. H., Kaplan, E., & Ober, B. A. (1987). *The California Verbal Learning Test*. New York: Psychology Corporation.
- Delis, D. C., Massman, P. J., Butters, N., Salmon, D. P., Cermak, L. S., & Kramer, J. H. (1991). Profiles of demented and amnesic patients on the California Verbal Learning Test: Implications for the assessment for the assessment of memory disorders. *Psychological Assessment: A Journal of Consulting and Clinical Psychology*, 3, 19-26.

- den Heijer, T., Launer, L. J., Prins, N. D., van Dijk, E. J., Vermeer, S. E., Hofman, A., ... Breteler, M. M. (2005). Association between blood pressure, white matter lesions, and atrophy of the medial temporal lobe. *Neurology*, *64*, 263–267.
- den Heijer, T., Vermeer, S. E., van Dijk, E. J., Prins, N. D., Koudstaal, P. J., Hofman, A., & Breteler, M. M. (2003). Type 2 diabetes and atrophy of medial temporal lobe structures on brain MRI. *Diabetologia*, *46*, 1604–1610.
- Deschaintre, Y. (2009). Treatment of vascular risk factors is associated with slower decline in Alzheimer disease. *Neurology*, *73*(9), 674- 80.
- Driscoll, I., Hamilton, D. A., Petropoulos, H., Yeo, R. A., Brooks, W. M., Baumgartner, R. N., Sutherland, R. J. (2003). The aging hippocampus: cognitive, biochemical and structural findings. *Cerebral Cortex*, *13*(12), 1344-1351.
- Du, F., Whetsell, W. O., Jr., Abou-Khalil, B., Blumenkopf, B., Lothman, E. W., & Schwarcz, R. (1993). Preferential neuronal loss in layer III of the entorhinal cortex in patients with temporal lobe epilepsy. *Epilepsy Research*, *16*, 223–233.
- Duffis, E. J. & Fisher, M. (2009). Cardioembolic Stroke. In R. A. Cohen & J. Gunstad (Eds.), *Neuropsychology and Cardiovascular Disease* (pp. 221-232), New York: Oxford University Press.
- Duvernoy, H. M. (2006). *The human hippocampus: Functional anatomy, vascularization, and serial sections with MRI*. New York: Springer Verlag.
- Easton, J. D., Saver, J. L., Albers, G. W., Alberts, M. J., Chaturvedi, S., Feldmann, E., ... Interdisciplinary Council on Peripheral Vascular Disease. (2009). Definition and evaluation of transient ischemic attack: A scientific statement for healthcare professionals from the American Heart Association/American Stroke Association

Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. *Stroke*, 40(6), 2276-2293.

Eichenbaum, H., Mathews, P., & Cohen, N. J. (1989). Further studies of hippocampal representation during odor discrimination learning. *Behavioral Neuroscience*, 103, 1207-1216.

Eichenbaum, H., Pagan, A., Mathews, P., & Cohen, N. (1988). Hippocampal system dysfunction and odor discrimination learning in rats: Impairment or facilitation depending on representational demands. *Behavioral Neuroscience*, 102, 331-339.

Eichenbaum, H., Yonelinas, A. R., Ranganath, C. (2007.) The medial temporal lobe and recognition memory. *Annual Review of Neuroscience*, 30, 123-152.

Eldridge, L. L., Knowlton, B. J., Furmanski, C. S., Bookheimer, S. Y. & Engel, S. A. (2000). Remembering episodes: a selective role for the hippocampus during retrieval. *Nature Neuroscience*, 3, 1149–1152.

Erdogan, M. A., Demirbilek, S., Erdil, F., Aydogan, M. S., Ozturk, E., Tugal, T., & Ersoy, M. O. (2012). The effects of cognitive impairment on anaesthetic requirement in the elderly. *European Journal of Anaesthesiology*, 29, 326-331.

Fanselow, M. S. & Dong, H. W. (2010) Are the dorsal and ventral hippocampus functionally distinct structures? *Neuron*, 65, 7–19.

Fisher, M. (2010). The challenge of mixed cerebrovascular disease. *Annals of the New York Academy of Sciences*, 1207, 18-22.

- Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). Mini Mental State: A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research, 12*, 189–198.
- Fox, N. C., Black, R. S., Gilman, S., Rossor, M. N., Griffith, S. G., Jenkins, L., & Koller, M. (2005). Effects of Abeta immunization (AN1792) on MRI measures of cerebral volume in Alzheimer disease. *Neurology, 64*, 1563–1572.
- Fung, W. K. & Poppas, A. (2009). Overview of Cardiovascular Physiology and Pathology. In R. A. Cohen & J. Gunstad (Eds.), *Neuropsychology and Cardiovascular Disease* (pp. 66-80), New York: Oxford University Press.
- Fuster, V., Moreno, P. R., Fayad, Z. A., Corti, R., & Badimon, J. J. (2005). Atherothrombosis and high-risk plaque: Part I: Evolving concepts. *Journal of the American College of Cardiology, 46*(6), 937-954.
- Gall, F. (1822-1825). *Sur les Fonctions du Cerveau*. Paris: Shoell.
- Gamaldo, A. A., Allaire, J. C., Sims, R. C., & Whitfield, K. E. (2010). Assessing mild cognitive impairment among older African Americans. *International Journal of Geriatric Psychiatry, 25*(7), 748-755. doi: 10.1002/gps.2417.
- Geinisman, Y., deToledo-Morrell, L., Morrell, F., & Heller, R. E. (1995). Hippocampal markers of age-related memory dysfunction: Behavioral, electrophysiological and morphological perspectives. *Progress in Neurobiology, 45*, 223–252.
- Gershberg, F. B. & Shimamura, A. P. (1995). Impaired use of organizational strategies in free recall following frontal lobe damage. *Neuropsychologia, 33*, 1305–1333.

- Gilbert, P. E., Kesner, R. P. & Lee, I. (2001). Dissociating hippocampal subregions: double dissociation between dentate gyrus and CA1. *Hippocampus*, *11*, 626–636.
- Giovannetti, T., Lamar, M., Cloud, B. S., Swenson, R., Fein, D., Kaplan, E., ...Libon, D. J. (2001). Different underlying mechanisms for deficits in concept formation in dementia. *Archives of Clinical Neuropsychology*, *16*(6), 547-560.
- Giovannetti, T., Schmidt, K. S., Gallo, J. L., Sestito, N., & Libon, D. J. (2006). Everyday action in dementia: Evidence for differential deficits in Alzheimer's disease versus subcortical vascular dementia. *Journal of the International Neuropsychological Society*, *12*(1), 45-53.
- Girouard, H., & Iadecola, C. (2006). Neurovascular coupling in the normal brain and in hypertension, stroke, and Alzheimer disease. *Journal of Applied Physiology*, *100*(1), 328-335.
- Glenner, G. G. & Wong, C.W. (1984). Alzheimer's disease: Initial report of the purification and characterization of a novel cerebrovascular amyloid protein. *Biochemical and biophysical research communications*, *120*, 885–890.
- Goldberg, E. (1986). Varieties of perseveration: A comparison of two taxonomies. *Journal of Clinical and Experimental Neuropsychology*, *8*(6), 710-726.
- Goldmann, E. E. (1909). Die äussere und innere Sekretion des gesunden und kranken Organismus im Lichte der 'vitalen Färbung'. *Beiträge zur klinischen Chirurgie*, *64*, 192–265.
- Goldmann, E. E. (1913). Vitalfärbung am Zentralnervensystem. *Abhandlungen der Preussischen Akademie der Wissenschaften Phys.-Math*, *1*, 1–60.

- Goldstein, K., and Scheerer, M. (1941). Abstract and concrete behavior. *Psychological Monographs*, 53, 329-401.
- Golomb, J., Deleon, M. J., Kluger, A., George, A. E., Tarshish, C., & Ferris, S. H. (1993). Hippocampal atrophy in normal aging: An association with recent memory impairment. *Archives of Neurology*, 50, 967–973.
- Graf, P. & Schacter, D. L. (1985). Implicit and explicit memory for new associations in normal and amnesic subjects. *Journal of experimental psychology: Learning, memory, and cognition*, 11, 501–518.
- Graham, N. L., Emery, T., & Hodges, J. R. (2004). Distinctive cognitive profiles in Alzheimer’s disease and subcortical vascular dementia. *Journal of Neurology, Neurosurgery & Psychiatry*, 75, 61–71.
- Greenberg, S. M., Rebeck, G. W., Vonsattel, J.P., Gomez-Isla, T., & Hyman, B.T. (1995). Apolipoprotein E epsilon 4 and cerebral hemorrhage associated with amyloid angiopathy. *Annals of Neurology*, 38, 254–259.
- Gutierrez, J., & Williams, O. A. (2014). A decade of racial and ethnic stroke disparities in the United States. *Neurology*, 82(12), 1080-1082. doi: 10.1212/WNL.0000000000000237.
- Hachinski, V. C., Potter, P., & Merskey, H. (1987). Leuko-araiosis. *Archives of Neurology*, 44(1), 21-23.
- Haist, F., Shimamura, A., & Squire, L. R. (1992). On the relationship between recall and recognition. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, 18(4), 691-702.

- Haller, C. S., Stone, W. S., & Walder, B. (2012). Small but continuous progress in the research of preoperative and postoperative cognitive dysfunction. *European Journal of Anaesthesiology*, 29, 307-308.
- Hardy, J. A. & Higgins, G.A. (1992). Alzheimer's disease: The amyloid cascade hypothesis. *Science*, 256, 184–185.
- Hatzinikolaou-Kotsakou, E., Kartasis, Z., Tziakas, D., Stakos, D., Hotidis, A., Chalikias, G., ... Hatseras, D. I. (2005). Clotting state after cardioversion of atrial fibrillation: A haemostasis index could detect the relationship with the arrhythmia duration. *Thrombosis Journal*, 3(1), 2.
- Helzner, E. P., Luchsinger, J. A., Scarmeas, N., Cosentino, S., Brickman, A.M., Glymour, M.M., & Stern, Y. (2009). Contribution of vascular risk factors to the progression in Alzheimer disease. *Archives of Neurology*, 66, 343–348.
- Hirono, N., Yasuda, M., Tanimukai, S., Kitagaki, H., Mori, E. (2000). Effect of the apolipoprotein E epsilon4 allele on white matter hyperintensities in dementia. *Stroke*, 31, 1263–1268.
- Hogue, C. W., Hershey, T., Dixon, D., Fucetola, R., Nassief, A., Freedland, K. E., . . . Schechtman, K. (2006). Preexisting cognitive impairment in women before cardiac surgery and its relationship with C-reactive protein concentrations. *Anesthesia and Analgesia*, 102, 1602–1608.
- Holtzman, D. M., Fagan, A.M., Mackey, B., Tenkova, T., Sartorius, L., Paul, S. M., & Hyman, B. T. (2000). Apolipoprotein E facilitates neuritic and cerebrovascular

- plaque formation in an Alzheimer's disease model. *Annals of Neurology*, 47, 739–747.
- Honig, L. S., Kukull, W. & Mayeux, R. (2005). Atherosclerosis and AD: Analysis of data from the US National Alzheimer's Coordinating Center. *Neurology*, 64, 494–500.
- Hsia, A. Y., Masliah, E., McConlogue, L., Yu, G. Q., Tatsuno, G., Hu, K., ... Mucke, L. (1999). Plaque-independent disruption of neural circuits in Alzheimer's disease mouse models. *Proceedings of the National Academy of Science, U. S. A.*, 96, 3228–3233.
- Hudetz, J. A., Patterson, K. M., & Pagel, P. A. Comparison of pre-existing cognitive impairment, amnesic mild cognitive impairment, and multiple domain mild cognitive impairment in men scheduled for coronary artery surgery. (2012). *European Journal of Anaesthesiology*, 29, 320-325.
- Hylek, E. M., & Singer, D. E. (1994). Risk factors for intracranial hemorrhage in outpatients taking warfarin. *Annals of Internal Medicine*, 120, 897-902.
- Irani, F. (2009). Cardiac Output and Ejection Fraction: Impact on Brain Structure and Function. In R. A. Cohen & J. Gunstad (Eds.), *Neuropsychology and Cardiovascular Disease* (pp. 233-239), New York: Oxford University Press.
- Ishai, A., Ungerleider, L. G. & Haxby, J. V. (2000). Distributed neural systems for the generation of visual images. *Neuron*, 28, 979–990.
- Issa, A. M., Rowe, W., Gauthier, S., & Meaney, M. J. (1990). Hypothalamic–pituitary–adrenal activity in aged and cognitively unimpaired rats. *Journal of Neuroscience*, 10, 3247–3254.

- Jefferson, A. (2010). Cardiac output as a potential risk factor for abnormal brain aging. *Journal of Alzheimer's Disease*, *20*, 813-821.
- Jellinger, K. A. (2008). Morphologic diagnosis of “vascular dementia” — a critical update. *Journal of Neurological Science*, *270*, 1–12.
- Jernigan, T. L., Archibald, S. L., Berhow, M. T., Sowell, E. R., Foster, D. S., & Hesselink, J. R. (1991). Cerebral structure on MRI, part I. Localization of age-related changes. *Biological Psychiatry*, *29*, 55–67.
- Jetter, W., Poser, U., Freeman, R. B., & Markowitsch, J. H. (1986). A verbal long term memory deficit in frontal lobe damaged patients. *Cortex*, *22*, 229-242.
- Kalaria, R. N. (2002). Small vessel disease and Alzheimer's dementia: Pathological considerations. *Cerebrovascular Disease*, *13*, (Suppl 2), 48–52.
- Koch, S., & Gonzalez, N. (2013). Preconditioning the Human Brain: Proving the Principle in Subarachnoid Hemorrhage. *Stroke*, *44*, 1748-1753.
- Koch, S., Della-Morte, D., Dave, K. R., Sacco, R. L., & Perez-Pinzon, M. A. (2014). Biomarkers for ischemic preconditioning: finding the responders. *Journal of Cerebral Blood Flow & Metabolism*, *34*(6), 933-941.
- Kokubo, Y., Chowdhury, A. H., Date, C., Yokoyama, T., Sobue, H., & Tanaka, H. (2000). Age dependent association of apolipoprotein E genotypes with stroke subtypes in a Japanese rural population, *Stroke*, *31*, 1299–1306.
- Kontiola, P., Laaksonen, R., Sulkava, R. & Erkinjuntti, T. (1990). Pattern of language impairment is different in Alzheimer's disease and multi-infarct dementia. *Brain and Language*, *38*, 364-83.

- Kopelman, M. D., Bright, P., Buckman, J., Fradera, A., Yoshimasu, H., Jacobson, C., Colchester, A. C. (2007.) Recall and recognition memory in amnesia: Patients with hippocampal, medial temporal, temporal lobe or frontal pathology. *Neuropsychologia*, *45*, 1232-1246.
- Korf, E. S., Scheltens, P., Barkhof, F., & de Leeuw, F. E. (2005). Blood pressure, white matter lesions and medial temporal lobe atrophy: closing the gap between vascular pathology and Alzheimer's disease? *Dementia and Geriatric Cognitive Disorders*, *20*, 331–337.
- Kramer, J. H., Delis, D. C., Blusewicz, M. J., Brandt, J., Ober, B. A., & Strauss, M. (1988). Verbal memory errors in Alzheimer's and Huntington's dementias. *Developmental Neuropsychology*, *4*, 1-15.
- Kriete, A., Sokhansanj, B. A., Coppock, D. L., & West, G. B. (2006). Systems approaches to the networks of aging. *Ageing Research Reviews*, *5*, 434–448.
- Kuller, L. H., & Lopez, O. L. (2011). Dementia and Alzheimer's disease: A new direction. The 2010 Jay L. Foster Memorial Lecture. *Alzheimer's and Dementia*, *7*(5), 540-50. doi: 10.1016/j.jalz.2011.05.901
- Kuller, L. H., Lopez, O. L., Jagust, W. J., Becker, J. T., DeKosky, S. T., Lyketsos, C., . . . Dulberg, C. (2005). Determinants of vascular dementia in the Cardiovascular Health Cognition Study. *Neurology*, *64*(9), 1548-1552.
- Laakso, M. P., Partanen, K., Riekkinen, P., Lehtovirta, M., Helkala, E. L., Hallikainen, M., . . . Soininen, H. (1996). Hippocampal volumes in Alzheimer's disease,

Parkinson's disease with and without dementia, and in vascular dementia: An MRI study. *Neurology*, 46(3), 678-681.

LADIS Study Group. (2011). 2001–2011: A Decade of the LADIS (Leukoaraiosis And DISability) Study: What Have We Learned about White Matter Changes and Small-Vessel Disease? *Cerebrovascular Diseases*, 32, 577–588. doi: 10.1159/000334498

Lafosse, J. M., Reed, B. R., Mungas, D., Sterling, S. B., Wahbeh, H., & Jagust, W. J. (1997). Fluency and memory differences between ischemic vascular dementia and Alzheimer's disease. *Neuropsychology*, 11, 514-522.

Lahoz, C., Schaefer, E. J., Cupples, L. A., Wilson, W., Levy, D., Osgood, D., ...Ordovas, J. M. (2001). Apolipoprotein E genotype and cardiovascular disease in the Framingham Heart Study. *Atherosclerosis*, 154, 529–537.

Lamar, M., Catani, M., Price, C. C., Heilman, K. M. & Libon, D. J. (2008). The impact of region specific leukoaraiosis on working memory deficits in dementia. *Neuropsychologia*, 46, 2597-2601.

Lamar, M., Podell, K., Carew, T. G., Cloud, B. S., Resh, R., Kennedy, C., ...Libon, D. J. (1997). Perseverative behavior in Alzheimer's disease and subcortical ischemic vascular dementia. *Neuropsychology*, 11(4), 523-534.

Lamar, M., Price, C. C., Davis, K. L., Kaplan, E., & Libon, D. J. (2002). Capacity to maintain mental set in dementia. *Neuropsychologia*, 40(4), 435-445.

- Lamar, M., Price, C. C., Libon, D. J., Penney, D. L., Kaplan, E., Grossman, M., & Heilman, K. M. (2007). Alterations in working memory as a function of leukoaraiosis in dementia. *Neuropsychologia*, *45*, 245-254.
- Lamar, M., Swenson, R., Kaplan, E., & Libon, D. J. (2004). Characterizing alterations in executive functioning across distinct subtypes of cortical and subcortical dementia. *The Clinical Neuropsychologist*, *18*(1), 22-31.
- Lao, Z., Shen, D., Liu, D., Jawad, A. F., Melhem, E. R., Launer, L. J., ... Davatzikos, C. (2008). Computer-assisted segmentation of white matter lesions in 3D MR images using support vector machine. *Academic Radiology*, *15*(3), 300-313.
- Lashley, K. S. (1950). In search of the engram. Society of Experimental Biology Symposium No. 4: Physiological mechanisms in animal behaviour (pp. 454-482). Cambridge, England: Cambridge University Press.
- Launer, L. J., Petrovitch, H., Ross, G. W., Markesbery, W., & White, L. R. (2008). AD brain pathology: Vascular origins? Results from the HAAS autopsy study. *Neurobiology of Aging*, *29*, 1587-1590.
- Lee, D. Y., Fletcher, E., Martinez, O., Ortega, M., Zozulya, N., Kim, J., . . . DeCarli, C. (2009). Regional pattern of white matter microstructural changes in normal aging, MCI, and AD. *Neurology*, *73*(21), 1722-1728.
- Lee, I., Yoganasimha, D., Rao, G., & Knierim, J. J. (2004). Comparison of population coherence of place cells in hippocampal subfields CA1 and CA3. *Nature*, *430*, 456-459.

- Leutgeb, J. K., Leutgeb, S., Moser, M. B. & Moser, E. I. (2007). Pattern separation in the dentate gyrus and CA3 of the hippocampus. *Science*, *315*, 961–966
- Leutgeb, S., Leutgeb, J. K., Treves, A., Moser, M. B. & Moser, E. I. (2004). Distinct ensemble codes in hippocampal areas CA3 and CA1. *Science*, *305*, 1295–1298.
- Lewandowsky, M. (1900). Zur Lehre der Cerebrospinalflüssigkeit. *Zeitschrift für Klinische Medizin*, *40*, 480–494.
- Libon, D. J., Bogdanoff, B., Bonavita, J., Skalina, S., Cloud, B. S., Resh, R., ...Ball, S. K. (1997). Dementia associated with periventricular and deep white matter alterations: A subtype of subcortical dementia. *Archives of Clinical Neuropsychology*, *12*(3), 239-250.
- Libon, D. J., Bogdanoff, B., Cloud, B. S., Skalina, S., Giovannetti, T., Gitlin, H. L., & Bonavita, J. (1998). Declarative and procedural learning, quantitative measures of hippocampus, and subcortical white alterations in Alzheimer's disease and ischaemic vascular dementia. *Journal of Clinical & Experimental Neuropsychology*, *20*, 30– 41.
- Libon, D. J., Malamut, B. L., Swenson, R., & Cloud, B. S. (1996a). Further analyses of clock drawings among demented and non-demented subjects. *Archives of Clinical Neuropsychology*, *11*, 193-211.
- Libon, D. J., Mattson, R. E., Glosser, G., Kaplan, E., Malamut, M., Sands, L. P., . . . Cloud, B. S. (1996b). A nine word dementia version of the California Verbal Learning Test. *The Clinical Neuropsychologist*, *10*, 237-244.

- Libon, D. J., Price, C. C., Davis Garrett, K., & Giovannetti, T. (2004). From Binswanger's disease to leukoaraiosis: What we have learned about subcortical vascular dementia. *Clinical Neuropsychologist, 18*(1), 83-100.
- Libon, D. J., Price, C. C., Giovannetti, T., Swenson, R., Bettcher, B. M., Heilman, K. M., & Pennisi, A. (2008). Linking MRI hyperintensities with patterns of neuropsychological impairment: Evidence for a threshold effect. *Stroke, 39*(3), 806-813.
- Lich, K. H., Tian, Y., Beadles, C. A., Williams, L. S., Bravata, D. M., Cheng, E. M., . . . Matchar, D. B. (2014). Strategic Planning to Reduce the Burden of Stroke Among Veterans: Using Simulation Modeling to Inform Decision Making. *Stroke, 45*, 2078-2084.
- Lister, J. P. & Barnes, C. A. (2009). Neurobiological changes in the hippocampus during normative aging. *Archives of Neurology, 66*(7), 829-33.
- Longstreth, W. T., Jr., Manolio, T. A., Arnold, A., Burke, G. L., Bryan, N., Jungreis, C. A., . . . Fried, L. (1996). Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people. The Cardiovascular Health Study. *Stroke, 27*(8), 1274-1282.
- Lorente de Nó, R. (1934). Studies on the structure of the cerebral cortex II. Continuation of the study of the ammonic system. *Journal für Psychologie und Neurologie, 46*, 113–117

- Lukatela, K., Malloy, P., Jenkins, M., & Cohen, R. (1998). The naming deficit in early Alzheimer's and vascular dementia. *Neuropsychology, 12*, 565-572.
- Luria, A. R. (1980). *Higher cortical functions in man* (2nd ed.). New York, NY: Basic Books Inc.
- MacKinnon, D., & Squire, L. R. (1989). Autobiographical memory in amnesia. *Psychobiology, 17*, 247-256.
- Maguire, E. A., Gadian, D. G., Johnsrude, I. S., Good, C. D., Ashburner, J., Frackowiak, R. S. J., Frith, C. D. (2000). Navigation-related structural change in the hippocampi of taxi drivers. *Proceedings of the National Academy of Sciences of the United States of America, 97*, 4398–4403.
- Manns, J. R. & Eichenbaum, H. (2006). Evolution of declarative memory. *Hippocampus, 16*(9), 795-808.
- Marinković, S., Gibo, H., Milisavljević, M., Četković, M. (2001). Anatomic and clinical correlations of the lenticulostriate arteries. *Clinical Anatomy, 14*(3), 190-195.
- Marr, D. (1971). Simple memory: A theory for archicortex. *Philosophical Transactions of the Royal Society of London Series B: Biological Sciences, 262*, 23–81.
- Marti-Vilalta, J. L., Arboix, A., & Mohr, J. P. (2004). Lacunes. In J. P. Mohr, D. W. Choi, J. C. Grotta, B. Weir, & P. A. Wolf (Eds.), *Stroke: Pathophysiology, diagnosis, and management* (4th ed.) (pp. 275-300). Philadelphia: Elsevier Health Sciences.
- Massman, P. J., Delis, D. C., Butters, N., Levin, B., & Salmon, D. P. (1990). Are all subcortical dementias alike?: Verbal learning and memory in Parkinson's and Huntington's disease patient's. *Journal of Clinical and Experimental Neuropsychology, 12*, 729-744.

- McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., & Stadlan, E. M. (1984). Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*, *34*(7), 939-944.
- McNaughton, B.L. and Morris, R.G. (1987). Hippocampal synaptic enhancement and information storage within a distributed memory system. *Trends in Neurosciences*, *10*, 408–415
- Meek, W H., Church, R. M., & Olton, D. S. (1984). Hippocampus, time and memory. *Behavioral Neuroscience*, *98*, 3-22.
- Meng, X., & D'Arcy, C. (2012). Education and dementia in the context of the cognitive reserve hypothesis: A systematic review with meta-analysis and qualitative analysis. *PLoS ONE*, *7*(6). doi:10.1371/journal.pone.0038268
- Meyers, J. E., & Meyers, K. R. (1995). Rey complex figure test and recognition trial: Professional manual. PAR, Inc.
- Miller, I. N., Haynes, W. G., & Moser, D. J. (2009). Systemic Vascular Function and Cognitive Function. In R. A. Cohen & J. Gunstad (Eds.), *Neuropsychology and Cardiovascular Disease* (pp. 240-263). New York: Oxford University Press.
- Mishkin, M. (1978). Memory in monkeys severely impaired by combined but not by separate removal of amygdala and hippocampus. *Nature*, *273*, 297-298.
- Mishkin, M., Malamut, B., & Bachevalier, J. (1984). Memories and habits: Two neural systems. In G. Lynch, J. L. McGaugh, & N. M. Weinberger (Eds.), *Neurobiology of learning and memory* (pp. 65-77). New York: Guilford Press.

- Mooradian, A. D. (1988). Effect of aging on the blood-brain barrier. *Neurobiology of Aging*, 9, 31-39.
- Morris, J. C. & Price, A. L. (2001). Pathologic correlates of nondemented aging, mild cognitive impairment, and early-stage Alzheimer's disease. *Journal of Molecular Neuroscience*, 17, 101–118.
- Moser, M. B. & Moser, E. I. (1998). Functional differentiation in the hippocampus. *Hippocampus*, 8, 608–619.
- Moyer V. A., & U.S. Preventive Services Task Force. (2014). Screening for cognitive impairment in older adults: U.S. Preventive services task force recommendation statement. *Annals of Internal Medicine*, 160(11), 791-7.
- Mungas, D., Jagust, W. J., Reed, B. R., Kramer, J. H., Weiner, M. W., Schuff, N., . . . Chui, H. C. (2001). MRI predictors of cognition in subcortical ischemic vascular disease and Alzheimer's disease. *Neurology*, 57(12), 2229-2235.
- Muthén, L. K., & Muthén, B. O. (1998-2012). Mplus User's Guide. Fifth Edition. Los Angeles, CA: Muthén & Muthén.
- Nadel, L. & Moscovitch, M. (1997). Memory consolidation, retrograde amnesia and the hippocampal complex. *Current Opinion in Neurobiology*, 7, 217-227.
- Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS). (2001). Pathological correlates of late-onset dementia in a multicentre, community-based population in England and Wales. *Lancet*, 357, 169–175.

- Nilsson, S. E., Read, S., Berg, S., Johansson, B., Melander, A., & Lindblad, U. (2007). Low systolic blood pressure is associated with impaired cognitive function in the oldest old: Longitudinal observations in a population-based sample 80 years and older. *Aging clinical and experimental research*, *19*(1), 41-47.
- Nylund, K. L., Asparouhov, T., & Muthén, B. O. (2007a). Deciding on the number of classes in latent class analysis and growth mixture modeling: A Monte Carlo simulation study. *Structural Equation Modeling*, *14*, 535–569.
- Nylund, K., Bellmore, A., Nishina, A., & Graham, S. (2007b). Subtypes, severity, and structural stability of peer victimization: What does latent class analysis say? *Child Development*, *78*, 1706-1722.
- Nyquist, P. A., Bilgel, M. S., Gottesman, R., Yanek, L. R., Moy, T. F., Becker, L. C., . . . Vaidya, D. (2014). Extreme deep white matter hyperintensity volumes are associated with African American race. *Cerebrovascular Diseases*, *37*(4), 244-250. doi: 10.1159/000358117.
- Oler, J. A., Fox, A. S., Shelton, S. E., Rogers, J., Dyer, T. D., Davidson, R. J., . . . Kalin, N.H. (2010). Amygdalar and hippocampal substrates of anxious temperament differ in their heritability. *Nature*, *466*, 864–868.
- Overman, W. H., Ormsby, G., & Mishkin, M. (1990). Picture recognition vs. picture discrimination learning in monkeys with medial temporal removals. *Experimental Brain Research*, *79*, 18-24.
- Pantoni, L. (2010). Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. *Lancet Neurology*, *9*(7), 689-701.

- Pantoni, L., & Garcia, J. H. (1997). Cognitive impairment and cellular/vascular changes in the cerebral white matter. *Annals of the New York Academy of Sciences*, 826, 92-102.
- Penfield, W. & Perot, P. (1963). The brain's record of auditory and visual experience. *Brain*, 86, 595–696.
- Phares, T. W., Kean, R. B., Mikheeva, T., Hooper, D. C. (2006). Regional differences in blood-brain barrier permeability changes and inflammation in the apathogenic clearance of virus from the central nervous system. *Journal of Immunology*, 176(12), 7666–7675.
- Price, C. C., Garrett, K. D., Jefferson, A. L., Cosentino, S., Tanner, J., Penney, D. L., Swenson, R., Giovannetti, T., Bettcher, B. M, and Libon, D. J. (2009). The role of leukoaraiosis severity on learning and memory in dementia: Performance differences on a 9-word list learning test. *The Clinical Neuropsychologist*, 23, 1-18.
- Price, C. C., Jefferson, A. L., Merino, J. G., Heilman, K. M., & Libon, D. J. (2005). Subcortical vascular dementia: Integrating neuropsychological and neuroradiologic data. *Neurology*, 65(3), 376-382.
- Price, C. C., Mitchell , S. M., Brumback, B., Tanner, J. J ., Schmalfluss, I., Lamar, M., . . . Libon, D. J. (2012). MRI-leukoaraiosis thresholds and the phenotypic expression of dementia. *Neurology*, 79(8), 734-740. doi: 10.1212/WNL.0b013e3182661ef6
- Price, J. L. & Morris, J. C. (1999). Tangles and plaques in nondemented aging and “preclinical” Alzheimer's disease. *Annals of Neurology*, 45, 358–368.

- Raz, N. (1999). Aging of the brain and its impact on cognitive performance: Integration of structural and functional findings. In F. I. M. Craik & T. A. Salthouse (Eds.), *Handbook of aging and cognition—II*, (pp. 1–90). Mahwah, NJ: Erlbaum.
- Raz, N. (2005). The Aging Brain Observed in Vivo: Differential Changes and Their Modifiers. In R. Cabeza, L. Nyberg, & D. Park (Eds.), *Cognitive neuroscience of aging: Linking cognitive and cerebral aging* (pp. 19-57). New York: Oxford University Press, Inc.
- Raz, N., Rodrigue, K. M., Kennedy, K. M., & Land, S. (2009). Genetic and vascular modifiers of age-sensitive cognitive skills: Effects of COMT, BDNF, ApoE, and hypertension. *Neuropsychology*, 23(1), 105-116.
- Reed, B. R., Mungas, D. M., Kramer, J. H., Ellis, W., Vinters, H. V., Zarow, C., ... Chiu, H. C. (2007). Profiles of neuropsychological impairment in autopsy-defined Alzheimer's disease and cerebrovascular disease. *Brain*, 130, 731-739.
- Reitan, R. M. (1958). Validity of the trail making test as an indicator of organic brain damage. *Perceptual and Motor Skills*, 8, 271-276.
- Rey, A. (1941). Psychological examination of traumatic encephalopathy. *Archives de Psychologie*, 28, 286-340; sections translated by J. Corwin, & F.W. Bylsma. (1993). *The Clinical Neuropsychologist*. 4–9.
- Rigs, H. E., & Rupp, C. (1963). Variation in form of Circle of Willis. The relation of the variations to collateral circulation: Anatomic Analysis. *Archives of Neurology*, 8, 8-14.

- Rinne, J. O., Brooks, D. J., Rossor, M. N., Fox, N. C., Bullock, R., Klunk, W. E., Mathis, C.A.,... Grundman, M., (2010). 11C-PiB PET assessment of change in fibrillar amyloid-beta load in patients with Alzheimer's disease treated with bapineuzumab: A phase 2, double-blind, placebo-controlled, ascending-dose study. *Lancet Neurology*, 9, 363–372.
- Ritman, E. L., & Lerman, A. (2007). The dynamic vasa vasorum. *Cardiovascular Research*, 75(4), 649-658.
- Roher, A. E., Chaney, M. O., Kuo, Y. M., Webster, S. D., Stine, W. B., Haverkamp, L. J., ... Emmerling, M. R. (1996). Morphology and toxicity of Abeta-(1–42) dimer derived from neuritic and vascular amyloid deposits of Alzheimer's disease, *Journal of Chemical Biology*, 271, 20631–20635.
- Rolls, E.T. (1996). Theory of hippocampal function in memory. *Hippocampus*, 6, 601–620.
- Roman, G. C. (1987). Senile dementia of the Binswanger type. A vascular form of dementia in the elderly. *JAMA*, 258(13), 1782-1788.
- Roman, G. C. (2003). Vascular Dementia: A Historical Background, *International Psychogeriatrics*, 1, Suppl. 1, 11-13.
- Roman, G. C., Tatemichi, T. K., Erkinjuntti, T., Cummings, J. L., Masdeu, J. C., Garcia, J. H., et al. (1993). Vascular dementia: Diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. *Neurology*, 43(2), 250-260.

- Rowe, C. C., Ellis, K. A., Rimajova, M., Bourgeat, P., Pike, K. E., Jones, G., ... Villemagne, V. L. (2010). Amyloid imaging results from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging. *Neurobiology of Aging*, *31*, 1275–1283.
- Rudy, J. W. & Sutherland, R. W. (1989). The hippocampal formation is necessary for rats to learn and remember configural discriminations. *Behavioral Brain Research*, *34*, 97-109.
- Ryan, C. M., Freed, M. I., Rood, J. A., Cobitz, A. R., Waterhouse, B. R., & Strachan, M.W. (2006). Improving metabolic control leads to better working memory in adults with type 2 diabetes. *Diabetes Care*, *29*, 345–351.
- Salloway, S., Sperling, R., Gilman, S., Fox, N. C., Blennow, K., Raskind, M., ... Grundman, M. (2009). A phase 2 multiple ascending dose trial of bapineuzumab in mild to moderate Alzheimer disease. *Neurology*, *73*, 2061–2070.
- Saunders, R. C., & Weiskrantz, L. (1989). The effects of fornix transection and combined fornix transection, mammillary body lesions and hippocampal ablations on object-pair association memory in the rhesus monkey. *Behavioral Brain Research*, *35*, 85-94.
- Schuur, M., Henneman, P., van Swieten, J. C., Zillikens, M. C., de Koning, I., Janssens, A. C., . . . van Duijn, C. M. (2010). Insulin-resistance and metabolic syndrome are related to executive function in women in a large family-based study. *European Journal of Epidemiology*, *25*, 561–568.
- Schwarcz, R. & Witter, M. P. (2002). Memory impairment in temporal lobe epilepsy: The role of entorhinal lesions. *Epilepsy Research*, *50*, 161–177.

- Schwartz, G. (1978). Estimating the dimension of a model. *Annals of Statistics*, 6, 461–464.
- Sclove, S. L. (1987). Application of model-selection criteria to some problems in multivariate analysis. *Psychometrika*, 52, 333–343.
- Seidel, G. A., Giovannetti, T., & Libon, D. J. (2012). Cerebrovascular disease and cognition in older adults. In M. W. Bondi (Ed.), *Current Topics in Behavioral Neurosciences: Aging*. New York: Springer.
- Seidel, G. A., Giovannetti, T., Price, C. C., Tanner, J., Mitchell, S., Eppig, J., & Libon, D. J. (2013). Neuroimaging correlates of everyday action in dementia. *Journal of Clinical and Experimental Neuropsychology*, 35(9), 993-1005. doi: 10.1080/13803395.2013.844773
- Seidel, G.A., Giovannetti, T., & Libon, D.J. (2012). Cerebrovascular disease and cognition in older adults. In M.W. Bondi & M-C Pardon (Eds.), *Behavioral Neurobiology of Aging* (213-241), New York: Springer.
- Sharma, M., Clark, H., Armour, T., et al. (2005). *Acute Stroke: Evaluation and Treatment. Evidence Reports/Technology Assessments, No. 127*. Rockville, MD: Agency for Healthcare Research and Quality (US).
- Silbert, B. S., Scott, D. A., Evered, L. A., Lewis, M. S., & Maruff, P. T. (2007). Preexisting cognitive impairment in patients scheduled for elective coronary artery bypass graft surgery. *Anesthesia and Analgesia*, 104, 1023-1028.

- Small, S. A., Schobel, S. A., Buxton, R. B., Witter, M. P., & Barnes, C. A. (2011). A pathophysiological framework of hippocampal dysfunction in ageing and disease. *Nature Reviews: Neuroscience*, *12*(10), 585-601. doi: 10.1038/nrn3085.
- Snowdon, D. A., Greiner, L. H., Mortimer, J. A., Riley, K. P., Greiner, P.A., & Markesbery, W.R. (1997). Brain infarction and the clinical expression of Alzheimer disease. The nun study. *JAMA*, *277*, 813–817.
- Solomon, P. R., & Moore, J. W (1975). Latent inhibition and stimulus generalization of the classically conditioned nictitating membrane response in rabbits (*Oryctolagus cuniculus*) following dorsal hippocampal ablation. *Journal of Comparative and Physiological Psychology*, *59*, 1192-1203.
- Spielberger, C. D., Gorsuch, R. L., & Lushene. R. E. (1970). *Manual for the State-Trait Anxiety Inventory*. Palo Alto, CA: Consulting Psychologists Press.
- Spielberger, C. D., Reheiser, E. C., Ritterband, L. M., Sydeman, S. J., & Unger, K. K. (1995). Assessment of Emotional States and Personality Traits: Measuring Psychological Vital Signs. In Butcher, J.N. (Ed.) *Clinical Personality Assessment: Practical Approaches*. New York: Oxford University Press.
- Spren, O., & Strauss, E. (1998). A compendium of neuropsychologist tests: Administration, norms, and commentary, New York: Oxford University Press.
- Squire, L. R. & Wixted, J. T. (2011). The Cognitive Neuroscience of Human Memory Since H.M. *Annual Review of Neuroscience*, *34*, 259-288. doi: 10.1146/annurev-neuro-061010-113720

- Squire, L. R. (1979). The hippocampus, space, and human amnesia. *Behavioral and Brain Sciences*, 2, 514-515.
- Squire, L. R. (1992). Memory and the hippocampus: A synthesis from findings with rats, monkeys, and humans. *Psychological Review*, 99(2), 195-231.
- Sultzer, D., Mahler, M., Cummings, J., Van Gorp, W., Hinkin, C., & Brown, C. (1995). Cortical abnormalities associated with subcortical lesions in vascular dementia. *Archives of Neurology*, 52, 773-780.
- Sutherland, R. W., & McDonald, R. J. (1990). Hippocampus, amygdala, and memory deficits in rats. *Behavioral Brain Research*, 37,57-79.
- Szabo, K., Forster, A., Jager, T., Kern, R., Griebe, M., Hennerici, M. G., ...Gass, A. (2009). Hippocampal lesion patterns in acute posterior cerebral artery stroke: Clinical and MRI findings. *Stroke*, 40(6), 2042-2045.
- Taylor, E. M. (1959). Psychological appraisal of children with cerebral deficits, Cambridge, MA: Harvard University Press.
- Thomas, T., Thomas, G., McLendon, C., Sutton, T., & Mullan, M. (1996). beta-Amyloidmediated vasoactivity and vascular endothelial damage, *Nature* 380 (1996) 168–171.
- Thoonsen, H., Richard, E., Bentham, P., Gray, R., van Geloven, N., De Haan, R. J., ... Nederkoorn, P. J. (2010). Aspirin in Alzheimer's disease: Increased risk of intracerebral hemorrhage: Cause for concern? *Stroke*, 41(11), 2690-2692.

- Tierney, M. C., Black, S. E., Szalai, J. P., Snow, G., Fisher, R. H., Nadon, G & Chui, H. C. (2001). Recognition memory and verbal fluency differentiate probable Alzheimer's disease from subcortical ischemic vascular dementia. *Archives of Neurology*, 58, 1654-1659.
- Tombaugh, T. N. (2004). Trail Making Test A and B: Normative data stratified by age and education. *Archives of Clinical Neuropsychology*, 19, 203–214.
- van der Flier, W. M., Barkhof, F., & Scheltens, P. (2007). Shifting paradigms in dementia: Toward stratification of diagnosis and treatment using MRI. *Annals of the New York Academy of Sciences*, 1097, 215–224.
- van der Flier, W. M., van Straaten, E. C., Barkhof, F., Ferro, J. M., Pantoni, L., Basile, A. M., . . . LADIS Study Group. (2005). Medial temporal lobe atrophy and white matter hyperintensities are associated with mild cognitive deficits in non-disabled elderly people: the LADIS study. *Journal of Neurology, Neurosurgery, and Psychiatry*, 76, 1497-1500.
- van Dijk, E. J., Prins, N. D., Hofman, A., van Duijn, C. M., Koudstaal, P. J., & Breteler, M. M. (2007). Plasma beta amyloid and impaired CO₂-induced cerebral vasomotor reactivity. *Neurobiology of Aging*, 28, 707–712.
- van Dijk, E. J., Prins, N. D., Vermeer, S. E., Hofman, A., van Duijn, C. M., Koudstaal, P. J., & Breteler, M. M. (2004). Plasma amyloid beta, apolipoprotein E, lacunar infarcts, and white matter lesions. *Annals of Neurology*, 55, 570–575.
- Van Hoesen, G. W. (1982). The parahippocampal gyrus. *Trends in Neurosciences*, 5, 345-350.

- van Norden, A. G., van Dijk, E. J., de Laat, K. F., Scheltens P., Olderrikkert M. G., & de Leeuw, F. E. (2012). Dementia: Alzheimer pathology and vascular factors: From mutually exclusive to interaction. *Biochimica et biophysica acta*, 1822(3), 340-9.
- Vasilevko, V., Passos, G. F., Quiring, D., Head, E., Kim, R. C., Fisher, M., Cribbs, D. H. (2010). Aging and cerebrovascular dysfunction: contribution of hypertension, cerebral amyloid angiopathy, and immunotherapy. *Annals of the New York Academy of Sciences*, 1207, 58-70.
- Vidal, M. (2009). A unifying view of 21st century systems biology. *FEBS Letters*, 583, 3891-3894.
- Vidal, R., Calero, M., Piccardo, P., Farlow, M. R., Unverzagt, F. W., Mendez E., ...Ghetti, B. (2000). Senile dementia associated with amyloid beta protein angiopathy and tau perivascular pathology but not neuritic plaques in patients homozygous for the APOE-epsilon4 allele. *Acta Neuropathologica*, 100, 1-12.
- Wahlund, L. O. & Blennow, K. (2003). Cerebrospinal fluid biomarkers for disease stage and intensity in cognitively impaired patients. *Neuroscience Letters*, 339, 99-102.
- Walsh, D. M., Klyubin, I., Fadeeva, J. V., Cullen, W. K., Anwyl, R., Wolfe, M. S., ...Selkoe, D. J. (2002). Naturally secreted oligomers of amyloid beta protein potently inhibit hippocampal long-term potentiation in vivo, *Nature*, 416, 535-539.
- Warrington, E. K. & Weiskrantz, L. (1974). The effect of prior learning on subsequent retention in amnesic patients. *Neuropsychologia*, 12, 419-428.

- Wechsler, D. (1945). A standardized memory scale for clinical use. *Journal of Psychology, 19*, 87-95.
- Wechsler, D. (1997). *Wechsler Adult Intelligence Scale* (3rd ed.). San Antonio, TX: Psychological Corporation.
- Weiskrantz, L., & Warrington, E. K. (1979). Conditioning in amnesic patients. *Neuropsychologia, 17*, 187-194.
- White, L., Small, B. J., Petrovitch, H., Ross, G. W., Masaki, K., Abbott, R. D., Hardman, J., ...Markesbery, W. (2005). Recent clinical-pathologic research on the causes of dementia in late life: update from the Honolulu-Asia Aging Study. *Journal of Geriatric Psychiatry and Neurology, 18*(4), 224-227.
- Wixted, J. T. & Squire, L. R. (2010). The role of the human hippocampus in familiarity-based recognition memory. *Behavioral Brain Research, 215*, 197-208.
- Wolf, P. A., Mitchell, J. B., Baker, C. S., Kannel, W. B., & D'Agostino, R. B. (1998). Impact of atrial fibrillation on mortality, stroke, and medical costs. *Archives of Internal Medicine, 158*(3), 229-234.
- Wolf, P. A., D'Agostino, R. B., Belanger, A.J., & Kannel, W. B. (1991). Probability of stroke: A risk profile from the Framingham Study. *Stroke, 22*, 312-318.
- Wu, W., Brickman, A. M., Luchsinger, J., Ferrazzano, P., Pichiule, P., Yoshita, M., ...Small, S. A. (2008). The brain in the age of old: The hippocampal formation is targeted differentially by diseases of late life. *Annals of Neurology, 64*, 698-706.
- Yaffe, K. (2007). Metabolic syndrome and cognitive disorders: Is the sum greater than its parts? *Alzheimer Disease and Associated Disorders, 21*(2), 167-171.

- Yassa, M. A. & Stark, C. E. (2011). Pattern separation in the hippocampus. *Trends in Neurosciences*, 34(10), 515-25.
- Yesavage, J. A., Brink, T. L., Rose, T. L., Lum, O., Huang, V., Adey, M., & Leirer, V. O. (1983). Development and validation of a geriatric depression screening scale: A preliminary report. *Journal of Psychiatric Research*, 17(1), 37-49.
- Yip, A. G., McKee, A. C., Green, R. C., Wells, J., Young, H., Cupples, L. A., & Farrer, L. A. (2005). APOE, vascular pathology, and the AD brain. *Neurology*, 65, 259–265.
- Zieren, N., Duering, M., Peters, N., Reyes, S., Jouvent, E., Hervé, D., . . . Dichgans, M. (2013). Education modifies the relation of vascular pathology to cognitive function: Cognitive reserve in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. *Neurobiology of Aging*, 34, 400-407.
- Zlokovic, B. V. (2004). Clearing amyloid through the blood-brain barrier. *Journal of Neurochemistry*, 89, 807-811.
- Zlokovic, B. V. (2008). The blood-brain barrier in health and chronic neurodegenerative disorders. *Neuron*, 57(2), 178-201.
- Zola-Morgan, S., & Squire, L. R. (1984). Preserved learning in monkeys with medial temporal lesions: Sparing of motor and cognitive skills. *Journal of Neuroscience*, 4, 1072-1085.
- Zola-Morgan, S., & Squire, L. R. (1990). Identification of the memory system damaged in medial temporal lobe amnesia. In L. R. Squire & E. Lindenlaub (Eds.), *The biology of memory* (pp. 509-521). Stuttgart, Germany: F. K. Schattauer Verlag.

- Zola-Morgan, S., Squire, L. R., & Amaral, D. G. (1986). Human amnesia and the medial temporal region: Enduring memory impairment following a bilateral lesion limited to field CA1 of the hippocampus. *Journal of Neuroscience*, *6*, 2950-2967.
- Zola-Morgan, S., Squire, L. R., & Amaral, D. G. (1989a). Lesions of the hippocampal formation but not lesions of the fornix or the mammillary nuclei produce long-lasting memory impairment in monkeys. *Journal of Neuroscience*, *9*, 898-913.
- Zola-Morgan, S., Squire, L. R., & Amaral, D. G. (1989b). Lesions of the amygdala that spare adjacent cortical regions do not impair memory or exacerbate the impairment following lesions of the hippocampal formation. *Journal of Neuroscience*, *9*, 1922-1936.