Task-phase fMRI in Detection of Improvements in Working Memory Post-Interventions for Carotid Stenosis and Early Alzheimer's Disease

by

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Abstract

Working memory allows for coordination of complex goal-driven behavior. Decline of working memory is linked to severe cognitive disabilities and is an important feature of both severe carotid stenosis and Alzheimer's disease. Functional Magnetic Resonance Imaging (fMRI) can help detect functional brain changes for the evaluation of the impact of standard clinical interventions for both diagnoses. This thesis used fMRI, coupled with cognitive tasks to investigate possible working memory improvements post-standard clinical interventions for both conditions. The study observed post-intervention improvements in task-phase fMRI brain activation patterns together with improvements in task performance. Meanwhile, patients demonstrated complex response patterns associated with disease expression and other individual variability, which were considered with results interpretation. This thesis showed that working memory improvements were possible following standard clinical treatments for both conditions. It also supports for tailoring interventions based on patient peculiarities to maximize treatment effectiveness.

Keywords: Alzheimer's disease; BOLD-fMRI; brain changes; carotid stenosis; task-phase fMRI; working memory

Dedication

This work is dedicated to GOD Almighty - "*And I am certain that God, who began the good work within you, will continue His work until it is finally finished on the day when Christ Jesus returns*" *(Philippians 1:6*); and to my husband, Oladimeji for being a pillar of support in every way, and to my daughter, Toluwanimi, for stretching my capacities in ways I never thought was possible.

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List of Acronyms

3MS	Modified Mini Mental State Exam
3T	3 Tesla
4T	4 Tesla
AD	Alzheimer's Disease
ADAS-Cog	Alzheimer’s Disease Assessment Scale - Cognitive Subscale
BALI	Brain Atrophy and Lesion Index
BMI	Body Mass Index
BOLD	Blood Oxygen Level Dependent
CAS	Carotid Angioplasty and Stenting
CEA	Carotid Endarterectomy
ChEIs	Cholinesterase Inhibitors
CNSVS	Central Nervous System Vital Signs
EPI	Echo Planar Imaging
FAB	Frontal Assessment Battery
FEAT	FMRI Expert Analysis Tool
fMRI	functional Magnetic Resonance Imaging
FSL	FMRIB's Software Library
GOALS	Goal-Oriented Assessment of Lifeskills
ICA	Internal Carotid Arteries
MCI	Mild Cognitive Impairment
MoCA	Montreal Cognitive Assessment

MRI	Magnetic Resonance Imaging
MTL	Middle Temporal Lobe
NASCET	North American Symptomatic Carotid Endarterectomy Trial
NC	Normal Controls
PFC	Prefrontal Cortex
ROI	Region of Interest
RT	Reaction Time

Chapter 1

Introduction

1.1. Statement of Thesis Research

This MSc thesis aimed to use cognitive task-phase functional magnetic resonance imaging (fMRI) to detect improvements in working memory post-standard clinical interventions for severe carotid stenosis and early Alzheimer's disease. The involved fMRI protocols were built on top of standard clinical care.

1.2. Overview

Working memory is a crucial aspect of cognition needed for daily living that allows for coordination of complex goal-driven and guided behavior, usually utilizing information that may be not available in the current setting (D'Esposito & Postle, 2015). Working memory includes the capacity to interactively store information temporarily while allowing room to manipulate such information for decision-making and comprises a core aspect of what is referred to as "executive function" (Baddeley, 2003; Kent, 2016). Decline of working memory has been linked to severe disabilities, including inability to perform functional daily activities of life (Kirova et al., 2015; Wylie et al., 2019). The prefrontal cortex, especially the dorsolateral division, has been implicated for exerting control over the working memory operations (Baddeley, 2003; D'Esposito & Postle, 2015; Kent, 2016).

Working memory decline is an important feature of both carotid stenosis and Alzheimer's disease. In carotid stenosis, working memory decline results from narrowing of the internal carotid arteries with plaque buildup which decreases perfusion to important brain areas (Sztriha et al., 2009). Conversely in Alzheimer's disease, the memory decline is a function of progressive age-related neurodegeneration of the medial temporal lobe (Jack et al., 2018). Standard clinical interventions are normally applied to manage both conditions. However, whether and how such interventions benefit working memory is not well understood. FMRI can help detect functional brain changes for the evaluation of the impact of clinical interventions on working memory. This thesis aimed

to use fMRI, coupled with cognitive tasks that stimulated working memory to sensitively detect whether working memory improvements occurred from standard clinical interventions for both diagnoses.

1.3. Summary of Literature: Carotid Stenosis

Carotid stenosis is characterized by the progressive narrowing of the internal carotid arteries with plaque build-up (Flaherty et al., 2013). The prevalence in the general population is around 3% (de Weerd et al., 2010), but increases drastically to over 18% in individuals with acute ischemic stroke (van Velzen et al., 2021). As a significant risk contributor for ischemic stroke, carotid stenosis contributes greatly to the economic and health burden of ischemic stroke (Mittmann et al., 2012). Carotid stenosis is considered severe when ≥70% as per the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria, and some form of intervention is usually recommended (Moneta et al., 1993). Severe stenosis can either be symptomatic where it is characterized by the presence of transient, chronic neurologic or ischemia-like symptoms or asymptomatic where it is rather much difficult to diagnose on the physical examination by a neurologist as patients appear void of stenosis attributable complaints (Lanzino et al., 2009).

Based on standard clinical care, severe stenosis can be treated by either carotid endarterectomy (CEA) where surgery is performed to remove the plaque or carotid angioplasty and stenting (CAS) in which a mesh-like stent is inserted into the affected artery to improve blood flow (Lanzino et al., 2009). Current clinical standard evaluates primarily the success of the treatment procedure by assessing correct stent placement and presence of perioperative complications, notably the 30-day stroke rate, myocardial infarction rates and death (Higashida et al., 2009). The effects of urgent revascularization treatment have been shown to reduce the risks of adverse ischemic events and stroke by up to 80% especially in younger patients (Halliday et al., 2010; Rothwell et al., 2007).

1.3.1. Carotid Stenosis and Cognitive Impairment

The internal carotid arteries (ICA) branches into the anterior and middle cerebral arteries which comprises the main blood supply for the entire anterior circulation of the forebrain and supply important deep structures such as the internal capsule, thalamus and basal

ganglia (Purves et al., 2001). The anterior circulation (originating from the internal carotid arteries) joins the posterior circulation (originating from the vertebral arteries) at the Circle of Willis to form an integrated cerebral circulation cycle (Purves et al., 2001).

Due to the nature of the cerebral territories supplied by the internal carotid arteries, hypo-perfusion due to severe carotid stenosis can result in substantial and progressive cognitive impairments in several memory domains including the working memory (Sztriha et al., 2009). Seventy percent of studies in a systematic review done on patients with carotid stenosis reported cognitive decline, sometimes even in the absence of visible lesions on MRI (Bakker et al., 2000; Kim et al., 2007; Zheng et al., 2014). Consequently, frontal lobes dysfunction has been observed in studies reporting cognitive decline in carotid stenosis patients even in asymptomatic patients (Bakker et al., 2000; Kim et al., 2007; Zheng et al., 2014). Therefore, working memory recovery is of paramount importance when considering the effect of revascularization interventions for carotid stenosis.

As hypo-perfusion is implied in the mechanism by which carotid stenosis causes memory decline, the extent of memory decline observed in patients can be affected by several factors including the severity and degree of flow limitation of the carotid stenosis, Circle of Willis anatomy and collateral flow to the affected circulation territory and the natural cognitive reserve of patients. Typically, a higher degree of stenosis leads to greater memory decline, whereas levels of cognition can be preserved if the Circle of Willis and collateral blood supply system is not totally compromised (Wei et al., 2019). Hemispheric localization of the stenosis also plays a role as some studies have shown that left ICA stenosis is associated with a greater degree of cognitive impairment compared to right ICA stenosis (Zheng et al., 2014).

1.3.2. The Effects of Carotid Stenosis Interventions on Cognition

The cognitive effects of revascularization of the carotid arteries for treatment of severe ICA has attracted significant research attention over the last few years and has been the subject of multiple review papers (De Rango et al., 2008; Ghogawala et al., 2008; Kolb et al., 2019; Lal, 2007; Plessers et al., 2014). However, the results of these studies have been largely inconclusive, with studies finding either a positive, negative or neutral effect of revascularization (De Rango et al., 2008; Ghogawala et al., 2008; Kolb et al., 2019;

Lal, 2007; Plessers et al., 2014). This may be because most previous research has largely utilized paper-based cognitive tests to study the cognitive impact without directly measuring brain activity, which can be more sensitive and may precede any observable changes with the paper-based tests. Advanced medical imaging methods, such as functional MRI, possess a direct approach to study working memory changes due to its ability to detect brain activity changes arising from the revascularization with high temporal and spatial resolution.

A recent review of literature revealed only a few studies that have utilized fMRI in evaluating the cognitive benefit following revascularization treatment for severe carotid stenosis (Chinda et al., 2021). Majority of the studies were conducted at resting-state and consistently observed improvements in the scale and pattern of functional neural network connectivity and symmetry in several brain regions following treatment which were mostly correlated with improved cognitive performance using paper-based cognitive tests (Cheng et al., 2012; Huang et al. 2018; Lin et al., 2016; Porcu et al., 2019; Tani et al., 2018; Wang et al., 2017). However, even though resting-state fMRI can help understand the general status of functional brain networks through functional connectivity analysis, task-based fMRI is required for identification of the patterns of activation and functional interactions among brain areas, and their alterations, associated with particular cognitive processes. Therefore, task-phase fMRI provides an objective method of evaluating brain activation by pairing the BOLD response following specific fMRI tasks such that cerebral recruitment can be spatially and temporally isolated.

The couple task-phase fMRI studies in the literature utilized a motor task (finger-tapping / hand-gripping exercises) and observed increased strength/level of brain activation and hemispherical symmetry in response to a motor challenge even as early as one day after the revascularization procedure (Jensen et al., 2008; Schaaf et al., 2010). This confirms the known sensitivity of task-fMRI in detecting alterations in the hemodynamic response. However, by employing only finger-tapping / hand-gripping exercises, post-treatment findings were limited primarily to brain activity in the primary motor cortex. Therefore, fMRI tasks designed to test higher level functions such as working memory are more appropriate choices in studying cognitive impairment and should be adapted for understanding cognitive recovery post carotid stenosis interventions.

1.4. Summary of Literature: Alzheimer's Disease

Alzheimer's disease (AD) is a neurodegenerative disease characterized by progressive deterioration leading to dementia (Chandra et al., 2019). It is the most common cause of dementia in older adults: in Canada alone the annual incidence is around 76,000 cases, with a prevalence of over half a million in older adults aged 65 years and above with the numbers estimated to double in 2030 (The Alzheimer Society, n.d).The economic and health burden of dementia in Canada is great, currently costing over $8 billion annually and projected to double in cost by 2031 (Public Health Agency of Canada, 2017).

While normal aging is usually associated with a normal range of decline in some cognitive domains (Salthouse, 2009), AD is usually characterized by a much more rapid and greater loss of cognitive capacities. AD is distinguished from other types of dementia by neuronal and synaptic loss compounded by the presence of extensive and widespread β–amyloid neuritic plaques and neurofibrillary tangles (Chandra et al., 2019; Jack et al., 2018). Several destructive inflammatory and oxidative stress processes leading to widespread neuronal damage are triggered in the AD brain, kindled by abnormally higher levels of hyper-phosphorylated tau and amyloid precursor protein, (Chandra et al., 2019; Jack et al., 2018; Selkoe, 1991) although the timeline and mechanism by which they trigger such damage is not fully understood. However, AD, like most neurodegenerative diseases, is heterogeneous in nature and while several pedagogies exist to explain the disease, the origin and progression cannot be traced to a singular event or component. For instance, several neurotransmitter disparities and deficiencies are typical in AD which are implicated in the pathology of the disease. This includes **decrease in choline acetyltransferase** in the hippocampus and cerebral cortex and multiple imbalances in several monoamine transmitters including dopamine and norepinephrine (Jack et al., 2018; Selkoe, 1991). Further, the cholinergic system plays a major role in AD development, and studies have shown that the severity of cognitive decline in AD significantly correlates with the extent of depletion of choline acetyltransferase activity in cholinergic neurons in the brain (Fu et al., 2004). Therefore, neurotransmitter imbalances have formed the basis of the major pharmacological interventions for clinical management of AD. Cholinesterase inhibitors (ChEIs) for instance are a major class of drugs used to manage AD and they act to counteract

decline in choline acetyltransferase by preventing degradation of acetylcholine (McShane et al., 2019; Patwardhan & Belemkar, 2021).

1.4.1. Cognitive Decline in AD

Brain atrophy in AD is typically first observed in the medial temporal lobe (MTL) structures including the entorhinal cortex and hippocampus, with a volume decrease of up to 40% in AD patients compared to controls (Du et al., 2004). With progression of the disease, atrophy spreads to the rest of the temporal cortex and neocortex, making MTL atrophy a discriminator of whether patients with MCI will convert to AD (Nesteruk et al., 2015). Studies have demonstrated that the spatial distribution of abnormal tau preferentially targets the middle and lateral temporal cortices and limbic lobes, thereby affecting higher level cognitive processes (Hansson et al., 2017). Given this widespread hippocampal atrophy, AD patients present with deficits in executive functioning including working memory and global memory (Kirova et al., 2015; Oosterman et al., 2012; Song et al., 2013). Cognitive impairment in AD typically progresses from impairment in formation of recent memories, ultimately culminating in widespread memory decline that affects performance of activities of daily living (Mayeux & Stern, 2012). Studies have suggested that working memory tasks performance can be used for cognitive capacity surveillance and can be a good indicator of advancement from normal cognition through MCI to full blown AD (Kirova et al., 2015).

Neuro-compensatory mechanisms have been observed in MCI and the prodromal stage of AD and are similar to observations made for normal aging older adults but not younger adults (Gould et al., 2006; Grady et al., 2003; Han et al., 2009). With neuro-compensation, greater brain activation is observed in multiple cerebral regions especially in the prefrontal cortex (PFC) in response to a memory task (Gould et al., 2006; Grady et al., 2003; Han et al., 2009). However, for such processes to be recognized as compensatory, increases in neuronal activity must be correlated with better task performance and/or maintenance of normal levels of cognition (Gregory et al., 2017). Compensatory mechanisms have also been evidenced using several imaging modalities as increased functional network connectivity and anatomical connectivity even in more recent fMRI studies (Behfar et al. 2020; Gould et al., 2006; Gregory et al., 2017; Sheng et al., 2021; Zhang et al., 2021). This may be indicative of adaptive neural plasticity involving the reallocation of cognitive resources from the middle temporal lobe

to the prefrontal cortex which is mostly preserved and only affected at the terminal end of disease progression (Grady et al., 2003). Compensatory mechanisms are generally observed in the prodromal stages of AD just before the severe burden of disease pathology worsens beyond which repair is impossible (Gregory et al., 2017; Hampel et al., 2019). Therefore, the period where compensatory responses occur has been characterized as a treatment window for Alzheimer's disease where changes can be observed (Merlo et al., 2019).

1.4.2. Interventions for AD and Effect on Cognition

Although AD has no definitive cure, current clinical interventions help to slow down the progression of the disease, reduce the effects of neuronal damage and/or relieve symptoms. The major two classes of FDA-approved pharmacological interventions for clinical management of AD are the cholinesterase inhibitors (ChEIs) and N-Methyl-D-aspartic acid (NMDA) antagonists (McShane et al., 2019; Patwardhan & Belemkar, 2021). ChEIs (specifically the FDA-approved Rivastigmine, Donepezil, and Galantamine) act by preventing degradation of acetylcholine while the NMDA antagonists (specifically memantine) act by antagonizing the effect of glutamate-induced toxicity following neuronal death (McShane et al., 2019; Patwardhan & Belemkar, 2021).

The effects of the currently approved pharmacological interventions have been well-researched and the subject of many individual studies, systematic reviews and meta-analyses (Blanco-Silvente et al., 2017; Emre et al., 2008; Knight et al., 2018; Rockwood et al., 2006). The currently FDA-approved ChEI's and NMDA antagonist have all shown to mediate some improvement in cognitive performance, measured using traditional tests of cognition in AD patients, with a strong dose-response correlation, although such improvements vary greatly among individual patients and may be short-lived (Blanco-Silvente et al., 2017; Emre et al., 2008; Knight et al., 2018; Rockwood et al., 2006).

Further, resting-state BOLD fMRI studies have found treatment-related increased functional connectivity in several brain regions including the posterior default mode network, left middle frontal and precentral gyri, and right dorsolateral frontal cortex (Canu et al., 2018; Guo et al., 2018). The brain functional responses were often correlated with cognition. Similarly, task-phase fMRI evaluating the cognitive effects of AD treatments

have employed several tasks including word recognition, attention task, encoding task, matching task, n-back task, facial recognition, and semantic association tasks (Canu et al., 2018; Guo et al., 2018). Post- standard clinical ChEI treatment, fMRI brain activation has been found to increase in response to fMRI task in the left entorhinal cortex, right precuneus, posterior parahippocampal cortex, parietal and prefrontal cortex (Canu et al., 2018; Guo et al., 2018). Post-treatment functional fMRI brain activation decreases in response to tasks were also found in the left dentate gyrus and right fusiform gyrus (Canu et al., 2018; Guo et al., 2018). The fMRI brain activation changes were specific to the brain domain associated with the task and was often correlated with behavioural improvements in task performance although performance did not improve for all tasks and varied on an individual basis (Canu et al., 2018; Guo et al., 2018).

In general, most of the fMRI studies evaluated whole-brain functional changes in response to AD treatment. However, given that neurocompensation is part of the adaptation response mechanism whereby many AD patients maintain cognitive function in the face of neuronal damage (Gregory et al., 2017; Hampel et al., 2019), it is expedient to also evaluate how interventions for AD affect the neurocompenstaory response overtime. Studies have suggested that while neurocompensatory mechanisms may arise as an attempt to mitigate harmful neurodegenerative conditions, it is not clear whether the final outcome of compensation is positive. Increases in processes like neural activity may even further stress the brain leading to exacerbation of neuronal damage (Merlo et al., 2019). Recent research efforts targeting the effects of medications on the neurocompensatory response are still under research trials and have been experimented mainly on transgenic mice models (Baazaoui & Iqbal, 2018; Jackson et al., 2019). How the currently FDA-approved interventions for AD affect and interact with the neurocompenatory responses deserves further attention.

1.5. Purpose of Thesis

1.5.1. Gap in Literature

For the carotid stenosis research line, there is a need for appropriate working memory fMRI tasks, designed to understand the impact of revascularization treatment on working memory. This is especially crucial as the current clinical standard just evaluates the successful completion of the procedure while previous studies as described above have

only relied on paper-based tests, resting-state fMRI, or motor task-phase fMRI. On the other hand, the literature on AD interventions and cognition have mostly observed general brain activations in response to memory tasks. There is a need to observe how specific adaptive neurocompensatory responses changed with treatment administration in early AD. Lastly, many of the studies were done at lower field strengths of 1.5T with a few at 3T (Canu et al., 2018; Chinda et al., 2021; Guo et al., 2018). Further task-phase fMRI research with higher field strengths for more sensitive detection of treatment effects is warranted.

1.5.2. Research Questions and Goal of Thesis

The general research question probed was: “Do standard clinical interventions for severe carotid stenosis (carotid angioplasty and stenting) and early Alzheimer's disease (Cholinesterase inhibitors) result in improvements in working memory that may be captured using task-phase BOLD fMRI?” Specifically, 1) Are there any improvements in the patterns of fMRI brain activations in response to cognitive tasks following standard clinical interventions for both diagnoses? 2) How do the functional brain activation changes relate to the actual task performance in terms of speed and accuracy? 3) How do the functional brain changes compare to the traditional tests of cognition?

Therefore, the overall goal of this MSc thesis was to investigate possible improvements in working memory post-standard clinical interventions for severe carotid stenosis and early Alzheimer’s disease. To evaluate the research questions and achieve the objectives of this thesis research, task-phase fMRI methodology was selected. The overall methodology evaluated the effect of the standard clinical interventions using a pre-post design. Patients had fMRI paired with cognitive tasks known for stimulating working memory a few weeks prior to standard clinical interventions and again a few weeks post-intervention. The patterns of brain activations were then compared between pre-post interventions and with behavioural performance and traditional cognition tests.

Chapter 2

General Methodology: Functional MRI

2.1. Functional MRI and Applications

2.1.1. The BOLD Signal

The fMRI method acts as a proxy measure of brain activity, often utilizing a natural contrast that is blood oxygen level dependent (BOLD). First explained by Ogawa and colleagues in the early 1990s, the fMRI-BOLD signal arises due to the paramagnetic properties of iron in the deoxygenated hemoglobin during brain activation (Ogawa et al., 1990). Typically, during brain activity, rapid depletion of oxygen occurs as the neurons utilize them during synaptic activities, resulting in an increase of deoxygenated hemoglobin and thus, paramagnetic iron in the surrounding blood vessels (Attwell & Iadecola, 2002; Buxton, 2010; Ogawa et al., 1990). This is then followed within seconds, by a rapid and larger increase in cerebral blood flow and volume, thus resulting in a net reduction of deoxygenated hemoglobin and paramagnetic iron (Attwell & Iadecola, 2002; Buxton, 2010; Ogawa et al., 1990). As paramagnetic iron usually leads to signal loss, a rapid reduction in the amount of deoxygenated hemoglobin is readily detected as a signal change and is what serves as a natural contrast in BOLD fMRI (Attwell & Iadecola, 2002; Buxton, 2010; Ogawa et al., 1990). The BOLD signal is determined and sustained by a balance between blood flow and oxygen extraction by tissues under activity and is heavily reliant on efficient capillary gas exchange and respiration. Therefore, any activity or substance that affects basal metabolism or blood flow to the brain can be noninvasively monitored in real time using the BOLD contrast.

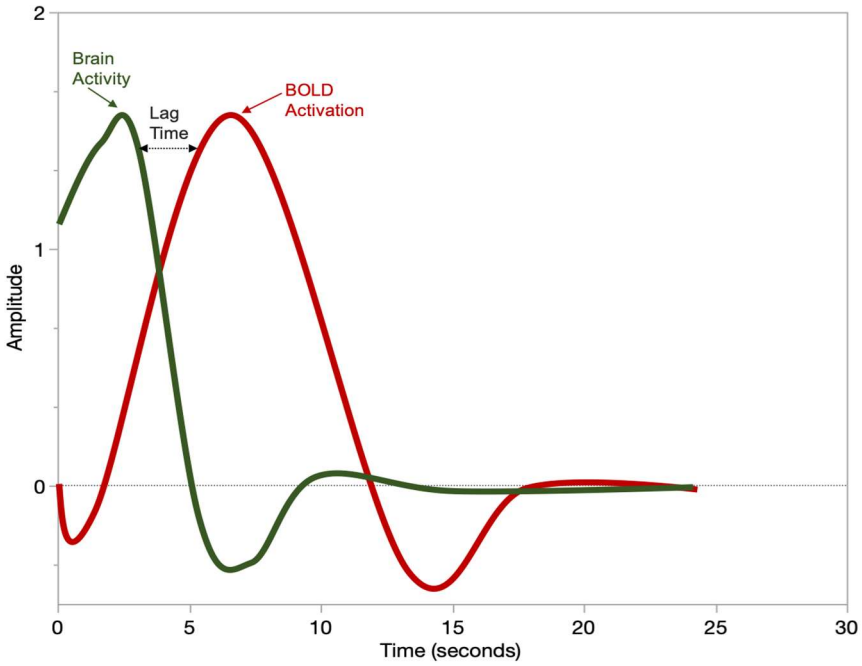


Figure 2.1. A Model of The BOLD Signal / Hemodynamic Response.
The green line shows a burst of neuronal activity, peaking within a few seconds. This is closely followed by an increase in blood supply/oxygen towards the neuron of interest which is interpreted as the BOLD signal (red line). The time between neuronal firing and blood flow increase is the lag time.

Even though the hemodynamic response closely follows the oxygen depletion coupled to brain activity in a matter of seconds, there is still a delay, albeit short, often referred to as the "**lag time**" (Figure 2.1). Therefore, the BOLD signal occursacutely after brain activity and only serves as a proxy estimate of neuronal activity and functional brain changes and does not necessarily refer to "brain activation" per se in this regard. This is one of the sources of the controversies about BOLD fMRI, slowing down its translational potential to clinical applications. The main critiques of BOLD fMRI typically argue that it is an indirect measure of brain activity due to the lag time among other attributing factors and as such, should not be referred to as brain activation (Haller & Bartsch, 2009; Iannetti & Wise, 2007). Also, because the signal is dependent on cerebral blood flow, confounds such as drug ingestion in patients can independently affect the BOLD signal downstream of neuronal activity, which can be erroneously interpreted as brain activity (Haller & Bartsch, 2009; Iannetti & Wise, 2007). Other sources of criticisms surround the experimental design and physiological setup including localised differences in oxygen consumption (e.g. watershed areas), head motion

interferences, signal to noise ratio, and general fMRI analyses and statistical processing (Haller & Bartsch, 2009; Iannetti & Wise, 2007).

Despite the criticisms, BOLD fMRI still offers a unique way to innovatively “see” what happens in the brain when it is at work and has been widely used to probe and understand neuroscience questions. It also cannot currently be replaced by other existing functional neuroimaging modalities due to its sensitivity in detecting brain activation, relatively high spatial and temporal resolutions, and lack of requirement for injection of radioactive substances. In the past few years, several refinements have been suggested to improve the quality of BOLD fMRI research. This includes the addition of control tasks and groups, co-recording of other physiological estimates during scan time to augment results, addition of behavioural data and other imaging results including EEG and inclusion of baseline scans among several others (Iannetti & Wise, 2007). Also, most fMRI is now done utilizing Echo Planar Imaging (EPI), which can collect 2D image data in a very short time snapshot (~60ms) to minimize the interference of head motion and other physiological confounds (Glover, 2011). This debate about BOLD fMRI can only be resolved with continued research, development and refinement in patient-oriented research.

2.1.2. Resting-State and Task-Phase FMRI

Brain functional activity can either be measured when the brain is at rest (i.e resting-state fMRI) or when performing a task (i.e task-phase fMRI). As the name implies, resting-state fMRI activation is observed during ‘task-free’ recordings, where there is no implicit cognitive input/output (participants are usually told to lie still in the MRI scanner, with eyes closed and exert no cognitive effort). With resting-state fMRI, the changes in the pattern of functional connectivity are usually observed over time (Lv et al., 2018). Functional connectivity is the temporal correlation of spontaneous BOLD activations among spatially distributed brain regions at “rest” (Seitzman et al., 2019; Smitha et al., 2017). Functional connectivity is usually studied in clusters of neural cells (called networks) responsible for various brain activities. The common networks analysed typically include the salience, default mode, and sensorimotor networks involved in regulating behavior and brain functions, enabling resting phase and controlling for sensory and motor activities (Seitzman et al., 2019; Smitha et al., 2017).

Resting-state fMRI can help in the understanding of the general status of functional brain networks through connectivity analysis. It is also relatively easy to conduct as participants do not exert any implicit cognitive input/output. Also like most MRI operations, it doesn't require exogenous contrast application and presents as a convenient modality to study brain function, especially in patients. Hence, researchers have explored resting-state fMRI, covering applications such as brain connectivity analysis, identification of abnormal fluctuations of the BOLD signal that are due to pathological changes (Seitzman et al., 2019; Smitha et al., 2017). This has aided in the characterization, diagnosis and prognosis of diseases including Alzheimer's, malignant metastases, epilepsy, and neuropsychiatric conditions such as schizophrenia (Seitzman et al., 2019; Smitha et al., 2017). As such, with further refinement, it holds great promise in aiding treatment by monitoring the functional network architecture of the brain pre/post clinical interventions. However, even though resting-state fMRI has its unique utilities, it cannot replace task-based fMRI which is required in many instances for identification of the patterns of activation and functional interactions among brain areas, and their alterations, associated with particular cognitive processes.

2.1.3. Applications of Task-Phase FMRI to Study Cognition Across Neurological Pathologies

In task-phase fMRI, the detection of brain fMRI activation changes is coupled with specific tasks performed inside the magnet during the scan. Here, the patterns of fluctuation of the BOLD signals are observed in response to the task, allowing for spatial and temporal isolation of cerebral recruitment (Tie et al., 2009). Task-phase fMRI has been extensively used to study several domains of brain activity including working memory and executive functioning and across diverse pathologies and populations including children (Table 2.1). Many traditional paper-based cognitive tasks (e.g. Delayed match-to-sample, Stroop test, N-back test, Go/No-Go) have also been adapted for performance in the scanner, leading to an increase in their applications in task-phase fMRI studies (McDonald et al., 2018).

Table 2.1. Recent Studies Utilizing Task-Phase FMRI Task to Study Cognition Across Neurological Pathologies

First Author (Year)	Pathology Studied	Population/Sample	fMRI Task	Main Conclusions
Barch DM (2016)	Schizophrenia	Adults; 60 schizophrenic patients	N-back (0-back and 2-back) sequential-letter memory task; word encoding task	Task-phase fMRI is a useful tool for the evaluation of pharmacological interventions for treatments of cognitive injury in schizophrenia
Nagano-Saito A (2016)	Parkinson's Disease (PD) with Mild Cognitive Impairment (MCI)	Older adults; 12 PD with MCI patients; 12 PD without MCI patients	Wisconsin Card Sorting task	Task-phase fMRI can be used to show longitudinal alterations in brain function that differentiates between cognitive decline in PD patients with and without MCI.
Metin B (2018)	Attention Deficit Hyperactivity Disorder (ADHD)	Children; 19 ADHD patients; 16 healthy controls	Cued spatial attention task	Task-phase fMRI can be used to show deficits in the attentional networks, suggesting impairments in reward and feedback processing in children with ADHD.
Saddiki N (2018)	Epilepsy	Adults; 35 epileptic patients	Face/words encoding and retrieval task	Task-phase fMRI can delineate the roles of the hippocampus in memory encoding and retrieval in patients with varying presentations of epilepsy
Corriveau-Lecavalier N (2019)	Mild Cognitive Impairment (MCI)/ Alzheimer's Disease (AD)	Older Adults; 26 MCI patients; 14 healthy controls	Words encoding task	Task-phase fMRI can identify patterns of abnormal brain functional activation that distinguish MCI patients who fully progressed to Alzheimer's dementia.
Wu SJ (2020)	Traumatic Brain Injury (TBI)	Adults; 20 TBI patients	Face/scene matching 1-back fMRI task	Attentional task-phase fMRI can acutely model neural plasticity in selective attention post-trauma in TBI patients

First Author (Year)	Pathology Studied	Population/Sample	fMRI Task	Main Conclusions
Chinda B (2021)	Carotid Stenosis	Adults; 2 Carotid Stenosis patients	Delayed match to sample task	Task-phase fMRI can show cognitive changes in working memory following revascularization treatment for severe internal carotid stenosis.
Xiao Q (2021)	Bipolar Disorder	Adolescents; 16 Mania Bipolar patients; 18 Euthymic Bipolar patients; 17 healthy controls	Emotional Go/Nogo face recognition task	Task-phase fMRI can distinguish between functional correlates of manic and euthymic bipolar disorder in a pediatric population.

One advantage of task-phase fMRI is its versatility. Almost any physiological or psychological topic of interest can be studied once an appropriate and valid fMRI-compatible task can be designed. Stimuli can range from visual, tactile to auditory, and different levels of difficulties can be created and controlled for. Common designs like the block design allow for stimuli to be alternated between a rest and experimental periods such that activation can be inferred from a baseline comparison (Glover, 2011). In addition, because of the absence of radiation or the need for intravenous contrast, participants can be studied on a longitudinal basis without any foreseeable side effects.

However, task-phase fMRI presents its own unique challenges including the selection, design, and implementation of appropriate fMRI tasks for detecting specific brain functions in specific brain regions, procurement of MRI-compatible task presentation and response devices and engaging and instructing patient participants in performing the tasks at all experimental sessions. There is also the requirement of making sure attention is sustained throughout the experiment, especially in populations where such attention can be compromised (Glover, 2011). Also, test-retest variability in task fMRI can be poor, especially when measures are not carefully put in place to reduce confounds and ensure that testing is done systematically (Bennett & Miller, 2013; Casey et al., 1998). Despite these challenges, task-phase fMRI still presents a unique way to capture brain function with great spatial and temporal resolution and cannot currently be replaced by any other existing method (Logothetis, 2008). Many of the challenges can be tackled through thorough task design and implementation, and taking proper care during study conductance, while making sure data analyses factor as many confounders as possible (Glover, 2011).

2.2. Rationale for Choice of General Methodology

FMRI presented as an appropriate choice to study working memory improvements following standard clinical interventions for early Alzheimer's disease and severe carotid stenosis. This is because the deoxyhaemoglobin which is responsible for the BOLD signal is influenced by various physiological parameters including cerebral blood flow and the neuronal metabolic rate of oxygen. Therefore, pathologies influencing any of these physiological parameters will affect the magnitude of the BOLD signal and can be studied using task-phase fMRI. In carotid stenosis, narrowing of the internal carotid arteries with plaque buildup decreases perfusion to important brain areas and results in

cognitive impairments if left untreated (Sztriha et al., 2009). Here, the BOLD signal will be impacted from the alterations in the cerebral blood flow, such that task-phase fMRI can be used to study changes pre/post treatment. Conversely in early Alzheimer's disease, progressive age-related neurodegeneration of the medial temporal lobe results in cognitive impairments (Jack et al., 2018). In this case, the BOLD signal is impacted from the neuronal metabolic rate, as there are fewer neurons partaking in brain activity where the neurodegeneration occurs. Though happening through differing mechanisms, the consequence of both severe carotid stenosis and early Alzheimer's disease results in fluctuations in the magnitude of the BOLD signal observed. This serves as the rationale for using task-phase fMRI to study the effects of routine clinical interventions on working memory in these two diagnoses.

Chapter 3

Carotid Stenosis Study

3.1. Hypotheses

The aim of this study was to evaluate using a working memory task-phase BOLD fMRI, the improvements in working memory following revascularization using carotid angioplasty and stenting (CAS) for treatment of severe carotid stenosis. Patients with severe carotid stenosis were evaluated pre-and 2 months post-CAS. The following hypotheses (H) were tested:

H1: The task-phase fMRI can distinguish brain activation patterns indicative of working memory recovery in severe ICA stenosis patients undergoing revascularization interventions.

H2: The fMRI findings will be correlated to traditional cognitive assessments for working memory.

3.2. Experimental Design

3.2.1. General Study Design

The study employed a repeated-measures longitudinal design built on top of the standard clinical care for patients with carotid stenosis. Study participants had an MRI scan and neurocognitive assessment two weeks before (baseline) and two months' after (follow-up) their clinically scheduled CAS intervention (Figure 3.1). Each research appointment lasted 2 hours, consisting of 1 hour of MRI scan and 1 hour of computerized neurocognitive assessment.

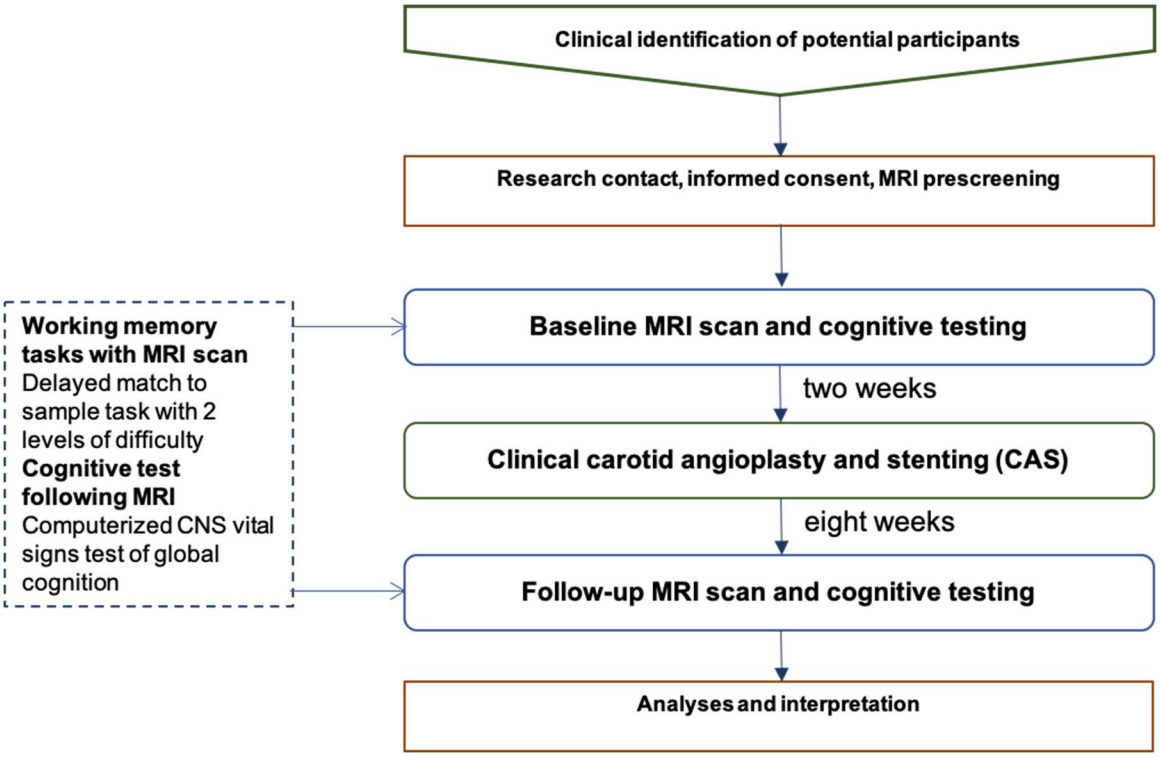


Figure 3.1. Carotid Stenosis Study Design and Clinical-Research Interaction Flowchart.
This shows the movement of patients within the study, from baseline MRI to the clinical CAS procedure and back for follow-up MRI.

3.2.2. Ethics

The study obtained harmonized research ethics board (REB) approval from Simon Fraser University, Fraser Health Authority and the University of British Columbia (FHREB 2018-058 | H18-02495). The study was conducted on-top of standard clinical care without any other additional experimental intervention provided during the research appointment and presented with minimal risk to participants. All study participants provided written informed consent to participate in the study and were always free to withdraw.

3.2.3. Participants Recruitment

Participants were identified by physicians at the Royal Columbian Hospital and were referred for contact. As ***inclusion criteria***, study participants were 19-90 years of age with a diagnosis of severe cervical carotid artery stenosis that could be treated by carotid angioplasty and stenting, could provide written informed consent, pass the MRI safety

screening, were fluent in English, and with normal or corrected vision and hearing abilities. Patients were ***excluded*** if they had any contraindication to MRI based on safety screening, were unable to have the stenting procedure completed or were unable to complete any aspect of the research study.

Upon identification and referral of a suitable patient for CAS with potential research participation by the treating physician, they were recruited and provided with research information to obtain informed consent. Then the patient participants were scheduled for their initial research MRI scans (Figure 2.1). The follow-up scans were scheduled after patients successfully completed CAS.

3.2.4. MRI Acquisition

The MRI scans were conducted using a whole-body Philips Ingenia 3.0T CX Quasar Dual MRI system equipped with a 32-channel dStream head coil and operated by Release 5.3 (Philips Medical Systems Nederland B.V.) located at the SFU ImageTech Lab. At each MRI scan, patients completed two task-phase fMRI sessions that lasted for approximately 5 minutes each. The fMRI scan utilized an echo planar imaging (EPI) sequence (TR/TE=2000/30ms, flip angle=90◦, field of view = 240x240mm, voxel size = 3x3x3 mm3 voxels covering the whole brain). High-resolution anatomical T1 images (for co-registration) were also acquired.

3.2.5. MRI Scan/Study Procedures

Prior to research enrolment, identified prospective participants referred by the physicians were pre-screened for MRI suitability and other inclusion/exclusion criteria. Upon successful enrolment, each patient provided written informed consent and was scheduled for baseline research appointments falling within 2 weeks prior to the CAS intervention.

At each research visit, participants had one hour of MRI scan and 30-45 minutes of neurocognitive testing. On arrival, participants were prepared for MRI safety which included a full MRI screening and removal of ferromagnetic objects they carried. They then changed into MRI-safe hospital pajamas. Before entering the MR scanner, participants practiced a demonstration of the fMRI task they performed (Figure 2.2) on a

computer outside the scanner under supervision to ensure they understood the task. Once the MRI scan was done, participants proceeded to perform the computerized neuropsychological assessment which is described in more detail below. They were compensated $25 for their time and were then scheduled for follow-up MRI scans within 2 months after their CAS procedure.

3.3. Methodology

3.3.1. Study Participants

Two case studies were recruited in this study (Figure 3.2). Case 1 was a 65-year-old man of South Asian origin with a severe pre-occlusive right carotid stenosis (>95%, determined using North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria. He had a history of myocardial infarction treated by coronary bypass surgery, type 2 diabetes, hypertension and hypercholesterolemia and is a previous smoker. The circle of Willis anatomy showed a patent anterior communicating artery and a small right posterior communicating artery. He received the CAS procedure (a Medtronic Protégé tapered 8/6mmx30mm nitinol stent with distal protection using an EV3 Spider filter device) to restore flow in the affected right carotid artery 13 days after his baseline MRI scan. There were no complications, and the post-CAS stenosis rate was <20%. He undertook the second MRI scan 86 days post-CAS.

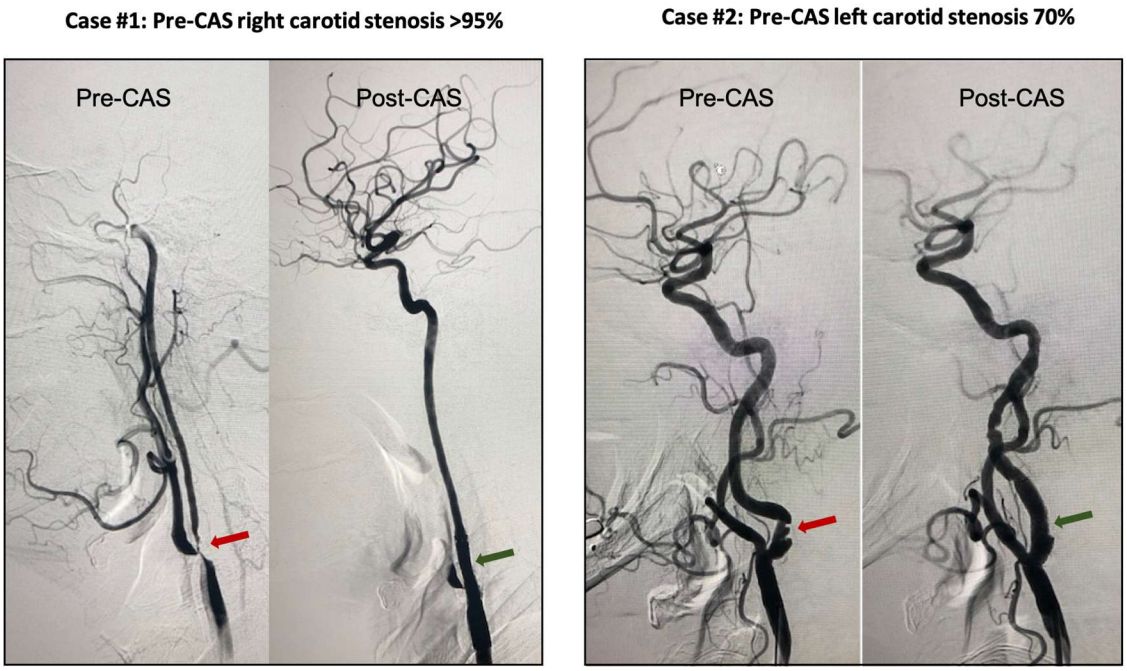


Figure 3.2. Pre-Post CAS Carotid Angiograms of Carotid Stenosis Case Studies. This figure shows Case 1 with pre-CAS right carotid stenosis of >95% (left panel) and Case 2 with pre-CAS left carotid stenosis of 70% (right panel). Red arrows point to regions of narrowing pre-CAS while green arrows point to restored vessels post-CAS.

Case 2 was an 81-year-old man of Caucasian origin with significant symptomatic left carotid stenosis (70%, determined using NASCET criteria). He had a series of transient ischemic attacks, consisting of episodes of aphasia and amaurosis fugax and a history of coronary stenting. The circle of Willis anatomy showed a hypoplastic A1 segment of the left anterior cerebral artery and bilateral hypoplastic posterior communicating arteries. He received the CAS procedure (a Medtronic Protégé tapered 8/6mmx30mm nitinol stent with distal protection using an EV3 Spider filter device) to restore the affected left carotid artery 2 days after his baseline MRI scan. There were no complications, and the post-CAS stenosis rate was <20%. He undertook the second MRI scan 81 days post-CAS.

3.3.2. FMRI Task

The fMRI task used in this study was the well-known and validated “delayed match to sample” task (Daniel et al., 2016). The task began with presentation of the study stimulus (encoding), followed by a delay, and then a response time in which participants were instructed to correctly select the study stimulus when it was presented together

with a distractor image (Figure 3.3). The task was adapted with modification for the study with two levels of task complexity: a simple (3*3 grid) and a difficult (5*5 grid) task (Figure 3.3). Each participant had 2 BOLD-fMRI scans to perform both levels of the task. The task was presented in a block design with 5 blocks and 6 rest phases. Each block contained 6 stimuli such that a total of 30 responses were collected in each fMRI scan session.

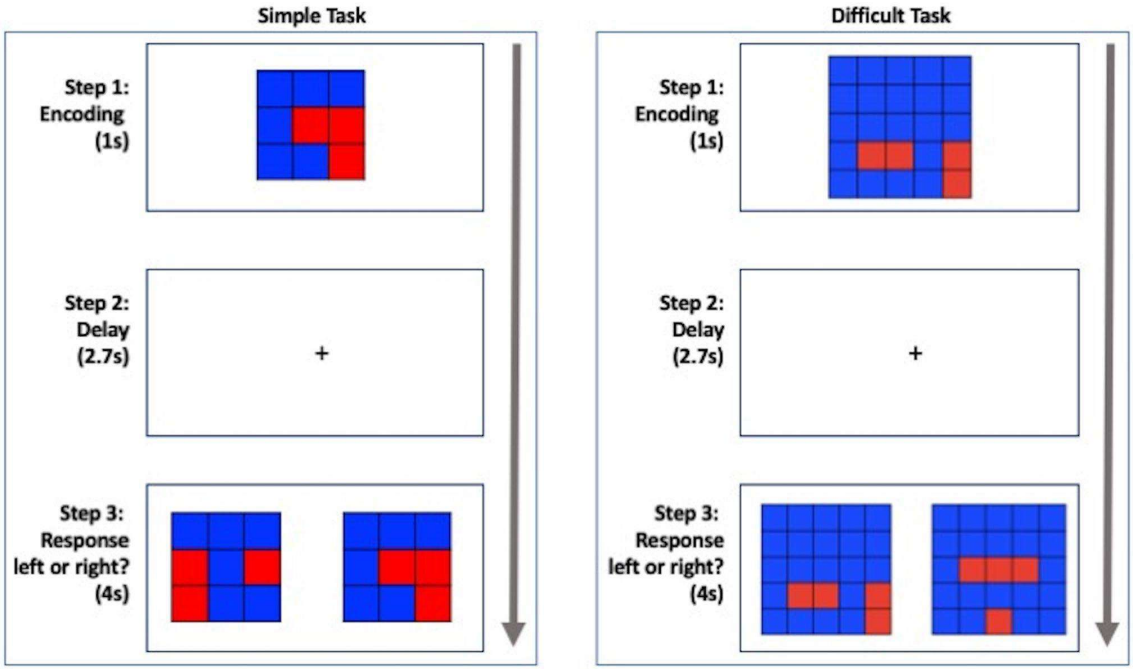


Figure 3.3. Delayed Match to Sample fMRI Task Employed in the CAS Study. The task began with presentation of the study stimulus (encoding), followed by a delay, and then a response time in which participants had to correctly select the study stimulus when presented together with a distractor image. The simple (3x3 grid) and difficult (5x5 grid) variations are shown.

The delayed match to sample task was chosen as it has been well-validated for testing working memory and executive functioning (Daniel et al., 2016), i.e., cognitive domains important for coordination of goal-driven, complex, and guided behavior (D'Esposito & Postle, 2015), representing impacted areas often observed in carotid stenosis patients (Sztriha et al., 2009). Basically, in the delay period, participants must actively maintain the original stimulus long enough to make a correct decision among distractors; this relies heavily on an intact working memory. The task was also easy to understand/perform by the patients; this is important considering that the study population may already have some form of cognitive impairment. Also, it was easy to manipulate many aspects of the task to allow performance in the MR scanner including

task complexity, encoding and delay time and response choice programming. The experiment was designed and presented to participants using the template provided by Presentation® software (Presentation, n.d.)

3.3.3. Cognitive Testing

Computerized neuropsychological testing of global cognition was done for each patient using the Central Nervous System Vital Signs (CNSVS). CNSVS is a computerized assessment tool adapted from conventional paper-based cognitive tests (Gualtieri & Johnson, 2006). The CNSVS tests comprised several tasks that evaluated various cognitive domains including complex attention, working memory and executive function. The psychometric properties of CNSVS have been tested and validated in many studies and have the advantage of being completely automated, preventing manual scoring afterwards and reducing inter-rater variabilities (Gualtieri & Johnson, 2006). At the end of the test, the results generated include an accuracy and speed score as well as the percentile rating based on the general population. The results were compared to fMRI scans and behavioural performance pre-and post-CAS.

3.3.4. MRI and Statistical Analyses

FMRI data processing and analyses were performed using FEAT (FMRI Expert Analysis Tool) Version 6.00, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl) following the standard processing procedures. Several pre-processing steps were applied including non-brain tissue (e.g skull) removal, motion correction, spatial smoothing (5mm), grand-mean intensity normalization of the entire 4D dataset, and highpass temporal filtering (50s) (Beckmann & Smith, 2004; Jenkinson et al., 2002; Smith, 2002; Woolrich et al., 2001; Worsely, 2001). Functional data were co-registered to high resolution structural (T1-weighted) and standard space (MNI152 1mm) images. Time-series statistical analysis was carried out using FILM with local autocorrelation correction, fitting to the GLM ($Z>2.0$ at $P<0.05$ cluster-corrected). Higher-level analysis was carried out using a fixed effects model in FLAME, applying contrasts to compare between tasks (i.e., simple vs. difficult) and time points (i.e., pre-vs. post CAS). For each fMRI scan/task, region of interest (ROI) analyses was also performed to evaluate brain regions known to be important for working memory and attention (e.g middle temporal

lobes), comparing pre-post CAS on the filtered time series and percentage of activated voxels within the ROI using Featquery.

Performance accuracy and reaction time (RT) in response to fMRI tasks were examined using pair-wised t-tests ($p<0.05$). Changes in brain fMRI activation and behavioral performance were compared for each patient pre/post CAS.

3.4. Results

3.4.1. FMRI Task Behavioural Performance

Case 1 (with pre-CAS right carotid stenosis >95%) had poor fMRI cognitive performance pre-CAS, which significantly improved post-CAS (Table 3.1). Pre-CAS, difficulties were encountered in task completion as seen by a very high miss rate (80% missing in the simple task; 86% missing in the difficult task) and poor performance in terms of accuracy (67% simple, 50% difficult). Post-CAS, there were improvements in both task completion rate (43% missing in the simple task; 13% missing in the difficult task) and accuracy (71% simple, 77% difficult). However, reaction times increased slightly post-CAS compared to pre-CAS (simple t=-0.78, p=0.459 two-tailed; difficult t= -0.77, p=0.448)

In contrast, Case 2 (with pre-CAS left carotid stenosis of 70%[L SEP]) had excellent baseline cognitive performance (> 90% accuracy, mean missing = 0.8%) pre-CAS across both the simple and difficult tasks, and this did not change or improved further after the CAS procedure (Table 3.1). There was a slight increase in reaction time post CAS for the difficult task (simple t=-0.04, p=0.970; difficult t=1.96, p=0.028).

Table 3.1. Delayed Match to Sample FMRI Task Performance Pre-and Post CAS for the Carotid Stenosis Case Studies

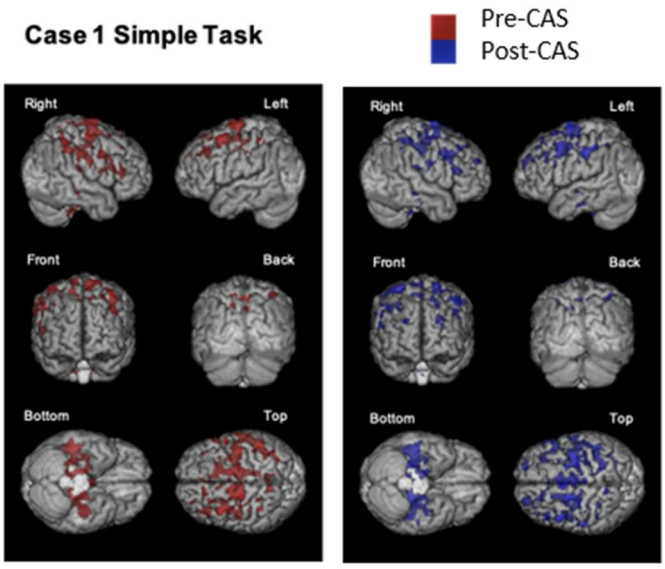
	Pre-CAS			Post CAS		
Task Type	Reaction Time (ms)	Accuracy (%)	Missed (%)	Reaction Time (ms)	Accuracy (%)	Missed (%)
			CASE 1			
Simple	1974.9 ± 869.6	66.7	80.0	2295.1 ± 857.1	70.5	43.3
Difficult	1712.2 ± 1336.0	50.0	86.7	2042.2 ± 706.9	77.0	13.3
			CASE 2			
Simple	1277.0 ± 267.7	96.7	0.0	1280.1 ± 361.0	93.3	0
Difficult	1546.2 ± 474.8	100.0	3.3	1321.4 ± 405.0	90.0	0

3.4.2. FMRI Brain Activation

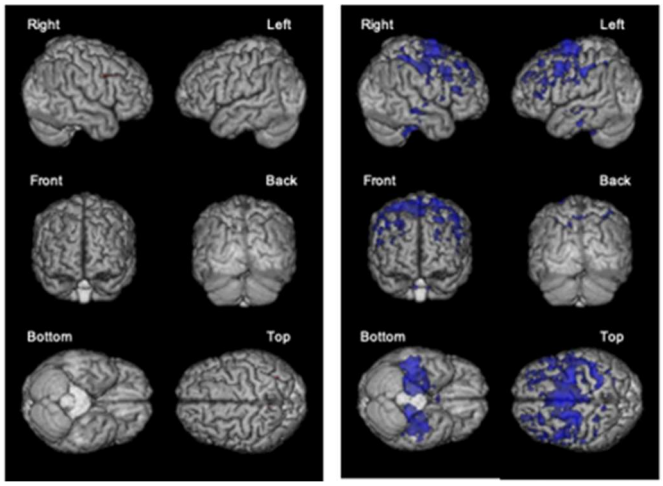
The fMRI brain activation maps for Case 1 showed no observable fMRI brain activation for the difficult task while some activations were observed for the simple task in the dorsolateral frontal lobes. Post-CAS, there were increased activations in the treated right anterior circulation territory, especially in the frontal and temporal lobes for both tasks, but especially for the difficult tasks post-CAS (Figure 3.4).

For Case 2, decreased activations in the contralateral right hemisphere to the treated side and mild increased activation in the left anterior circulation territory, namely in the left temporal lobe were observed post-CAS (Figure 3.4).

Case 1 Simple Task



Case 1 Difficult Task



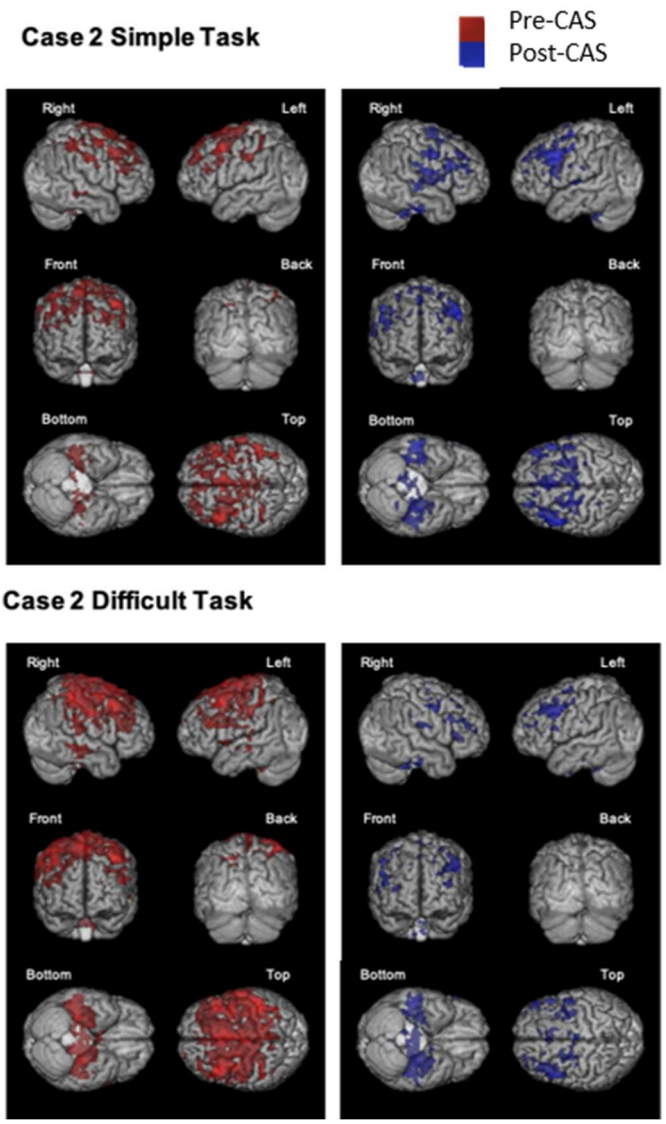
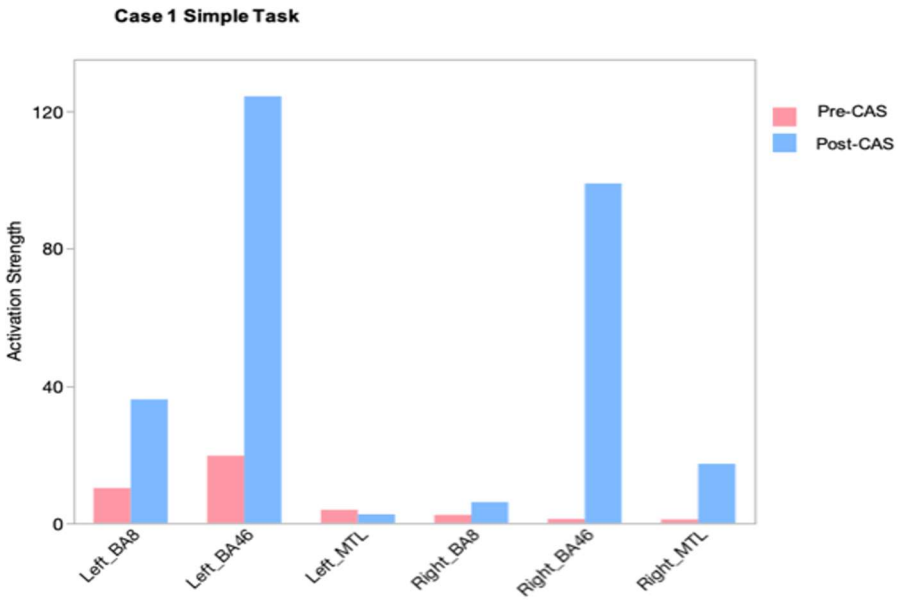
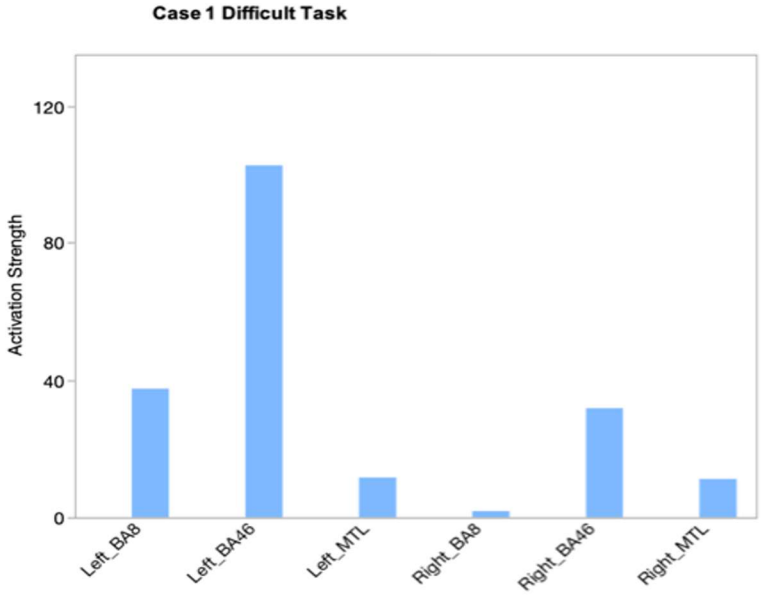


Figure 3.4. FMRI Activation Maps Pre/Post CAS for the Caroid Stenosis Case Studies.
These figures show Z statistic images, thresholded Non-parametrically using clusters determined by Z>2 (p= 0.05), and rendered on high resolution T1 images. The red maps refer to baseline activation while the blue refer to the follow-up activation for the simple (top panels) and difficult (bottom panels) tasks respectively. The top figure represents Case 1 while the bottom figure represents Case 2.

Query into activations in specific brain regions showed a corresponding increased activations post-CAS (Figure 3.5) in the medial temporal lobes and the dorsal frontal cortical network (Brodmann Areas 8 and 46) for Case 1. For Case 2, query into activation strength in medial temporal lobes and the dorsal frontal cortical network did not show increments with CAS (Figure 3.5).


Case 1 Simple Task
Activation Strength
120
80
40
0
Left_BA8
Left_BA46
Left_MTL
Right_BA8
Right_BA46
Right_MTL
Pre-CAS
Post-CAS


Case 1 Difficult Task
Activation Strength
120
80
40
0
Left_BA8
Left_BA46
Left_MTL
Right_BA8
Right_BA46
Right_MTL

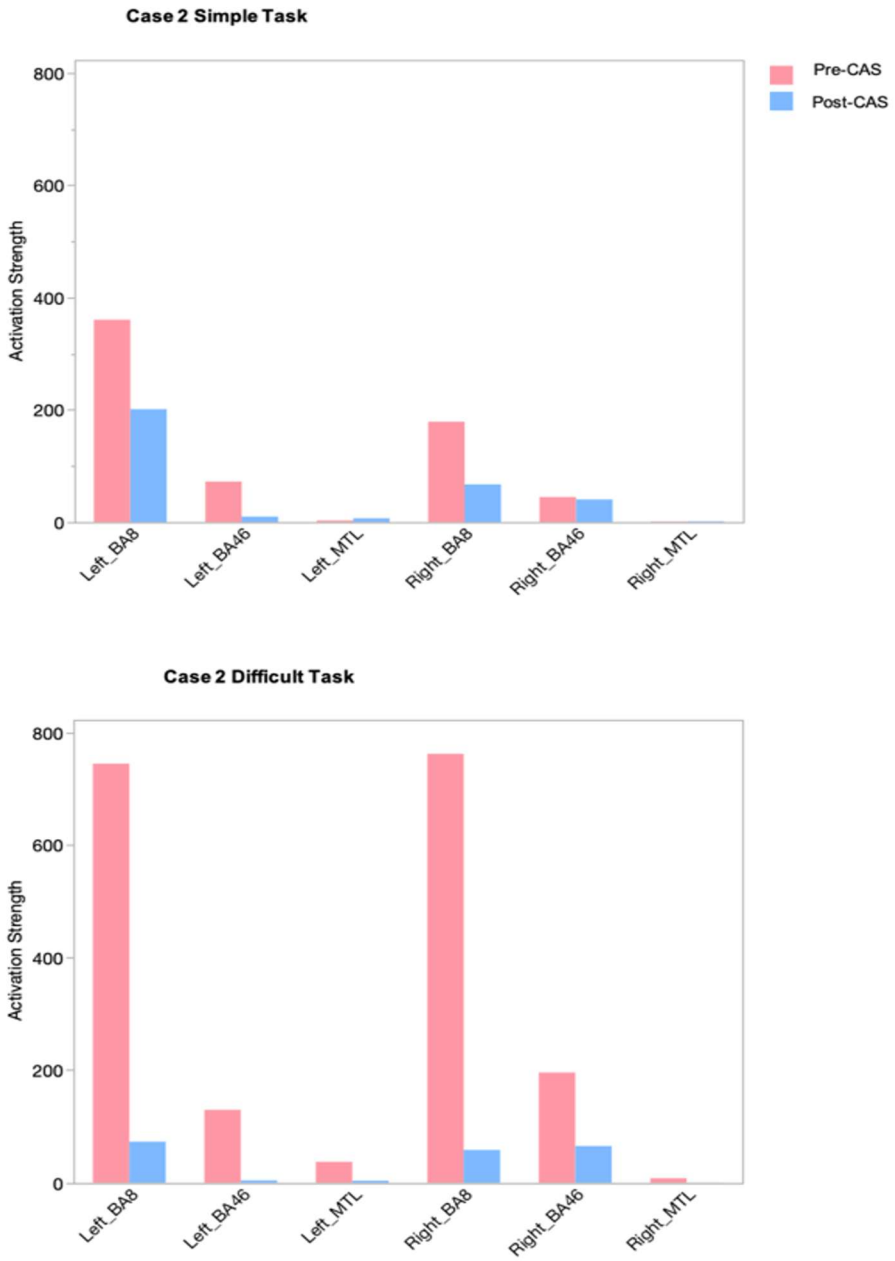


Figure 3.5. Strength of fMRI Brain Activation in Regions Associated with Working Memory Pre/Post CAS.
This figure shows a query into the dorsal frontal cortical network (BA 8 and 46) as well as the medial temporal lobes for both cases on the simple and difficult tasks pre (red) and post (blue) CAS. The bars represent the strength of fMRI activation generated by multiplying the mean value and number of the z-thresholded voxel clusters (z>2, p=0.05).

3.4.3. Neuropsychological Performance

Post-CAS, the CNSVS scores for Case 1 indicated a decrease in global cognition (neurocognition index) and several other cognitive domains (Table 3.2). Increases were observed only in the cognitive domains of processing speed and reaction time post-CAS. Case 2 also had a slight decline in global cognition (neurocognition index) and several other cognitive domains but showed an increase in psychomotor speed, cognitive flexibility, motor speed, processing speed and executive function post-CAS (Table 3.2).

Table 3.2. Computerized Cognitive Performance Pre-and Post-CAS for the Carotid Stenosis Case Studies

	CASE 1		CASE 2	
	Pre-CAS *Score*	**Post-CAS *Score***	**Pre-CAS *Score***	**Post-CAS *Score***
Neurocognition Index	64	54	96	93
Composite Memory	88	80	90	76
Verbal Memory	47	41	47	44
Visual Memory	41	39	43	32
Psychomotor Speed	101	40	124	132
Reaction Time	1198	1058	812	862
Complex Attention	29	32	26	24
Cognitive Flexibility	-15	-20	-1	4
Processing Speed	11	21	22	31
Executive Function	-11	-81	4	8
Simple Attention	40	40	40	39
Motor Speed	88	19	99	101

3.5. Interpretation

Task-fMRI was able to distinguish between pre-and post-CAS, showing that improved cerebral perfusion to areas supplied by carotid arteries following CAS is correlated with

improved cognitive function in working memory performance along with increased fMRI activations in the re-perfused vascular territory. Pre-CAS, fMRI activations are generally more prominent in the contralateral frontal and temporal lobes, areas that have been shown to be important in working memory and decision-making (Sallet et al., 2013). Post-CAS, fMRI activations are more prominent in the treated frontal and temporal lobes and reduced in the contralateral hemisphere. In Case 1, the reaction time increased post-CAS for both tasks; and was associated with higher-level task performance and may infer that the patient had paid more attention to the task Post-CAS. Case 1 had increased activations in the queried brain regions covering the medial temporal lobes and Brodmann Areas 8 and 46 (part of the dorsal frontal cortical network). These networks have been shown to be areas involved in working memory performance (Sallet et al., 2013), suggesting cognitive improvement resulting from the clinical procedure with re-established cerebral circulation and perfusion. While post-CAS improvements in the CNSVS performance was consistently observed in processing speed in both cases, variability existed in several domains, presumably reflecting the complexity and lesser sensitivity of the subjective test, compared to directly “viewing” the functional brain activation on MRI, especially given the relatively short follow-up time.

There was considerable individual variability between the two cases that impacted the fMRI brain cognitive changes observed post-CAS. One of these variations is the severity and degree of flow limitation of the stenosis. The degree of cognitive impairment is affected by the rate of hypo-perfusion and silent embolization in the affected area, often dependent on the integrity of the artery (Zuccala et al., 2001). This could explain why Case 1 (with >95% flow-limiting stenosis Pre-CAS) had more cognitive improvements post-CAS compared to Case 2 (with only 70%). Another source of variation surrounds the Circle of Willis anatomy and collateral flow to the affected circulation territory pre-and post CAS. Typically, patients with very severe ICA stenosis can present with normal levels of cognition if the collateral blood supply system is not compromised (Wei et al., 2019). For Case 1, the Circle of Willis consisted of a small right posterior communicating artery (PCOMM) and a small anterior communicating artery (ACOMM). Prior to the right carotid stenting, the reduced collateral flow via the right PCOMM and ACOMM was likely enough to prevent infarction but impeded full function of the neurons in the compromised territory affected by the severe flow-limiting carotid stenosis. Hence, the fMRI activation showed dampened activity in the right MCA

territory pre-CAS but demonstrated increased fMRI activity after restoring blood flow to the territory post-CAS. For case 2, the Circle of Willis consisted of a hypoplastic left PCOMM and a slightly hypoplastic A1 segment of the left anterior cerebral artery limiting collateral circulation. However, since the severe left carotid stenosis was not flow limiting, the left middle cerebral artery was theorized to receive adequate blood flow pre-CAS; hence, there was no dramatic clinical and fMRI improvement demonstrated post-CAS.

Chapter 4

Early Alzheimer's Disease Study

4.1. Hypotheses

The aim of this study was to evaluate, using an encoding and retrieval working memory task-phase BOLD fMRI, the improvements in working memory following cholinesterase inhibitors (ChEI's) treatment for early Alzheimer's disease. Early AD patients were evaluated pre-and 6 months' post-intervention, comparing them to a group of age and sex-matched normal controls. The following hypotheses (H) were tested:

H1: In response to a working memory task, early AD patients will demonstrate greater neuro-compensatory responses compared to normal controls.

H2: Treatment with ChEI's will modulate fMRI brain activation in early AD patients, reducing the need for neurocompensatory responses together with improvement in cognitive and fMRI behavioural responses.

H3: Individual variability in AD patients will moderate the magnitude and level of fMRI brain activation and improvements observed.

4.2. Experimental Design

4.2.1. General Study Design

This study only involved secondary analyses of a portion of the fMRI data shared by an original study with complete information. The study employed a repeated-measures longitudinal design built on top of the standard clinical care for patients with early Alzheimer's disease (Figure 4.1). Early AD patients had an MRI scan at baseline and six months' after (follow-up) their clinical administration of cholinesterase inhibitors (ChEIs), as normally prescribed by their doctors. Age, sex, and education matched normal controls without AD diagnosis just had baseline and 6-month follow up scans without any intervention in between. At each appointment, the functional MRI scan lasted for 1 hour.

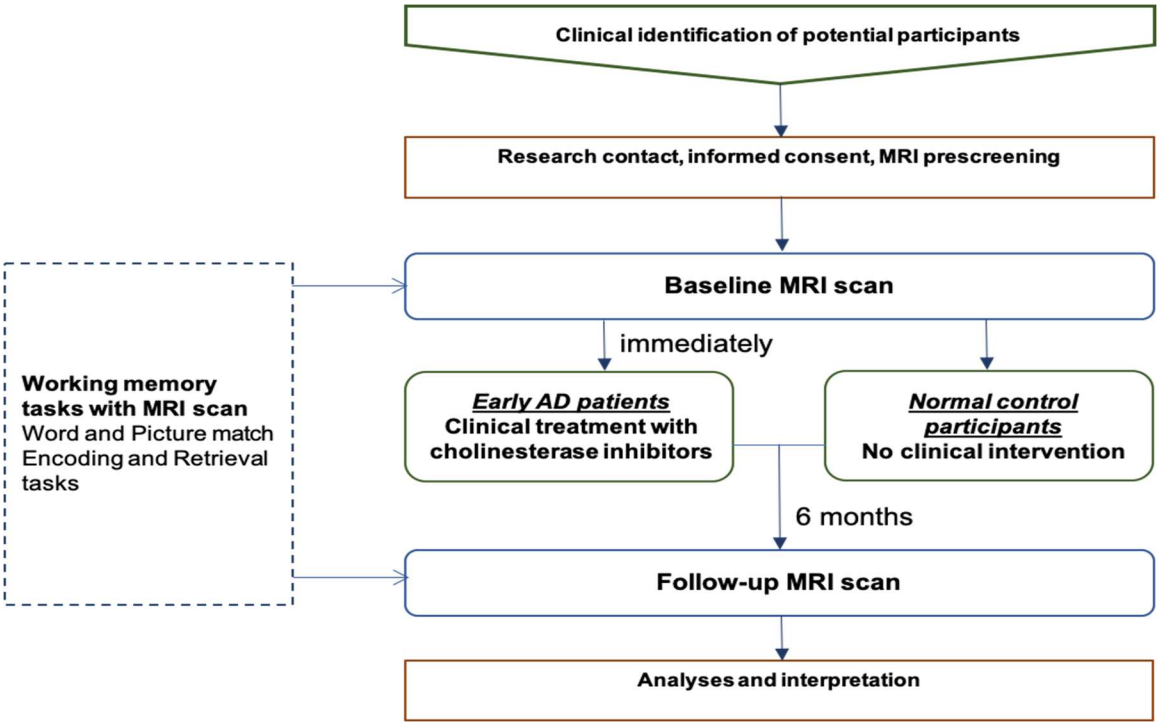


Figure 4.1. Early Alzheimers Disease Study Design and Clinical-Research Interaction Flowchart
This shows the movement of participants within the study, from baseline MRI to the clinical ChEI treatment procedure (AD patients only) and back for follow-up MRI.

4.2.2. Ethics

The study was conducted on-top of standard clinical care without any other additional experimental intervention provided during the research appointment and presented with minimal risk to participants. The study obtained harmonized research ethics board (REB) approval from the National Research Council Research Ethics Board, Health Canada, and the Capital Health District Authority Research Ethics Board (WREB2005-03 | CDHA-RS/2005-224). Additional approval for secondary data analyses were received from Fraser Health Research Ethics Board (FHREB #2014-084; FHREB #2015-030).

4.2.3. Participants Recruitment

Participants including AD patients and healthy controls were identified by physicians at the QEII Health Sciences Centre for Elderly Care and were referred for contact. As ***inclusion criteria***, study participants were older adults (65 to 90 years old), and either cognitively healthy (normal controls) or have mild Alzheimer's disease but no other major

cognitive impairments. Participants could communicate fluently in English and have normal vision or corrected-to-normal vision, could provide written informed consent and could pass the 4T MRI safety screening. Participants were ***excluded*** if they had any contraindication to 4T MRI scanning based on safety screening, were diagnosed with neurological or psychiatric disorders other than, or in addition to, mild AD, and if they were treated with cholinesterase inhibitors within 30 days prior to the start of the study.

Upon identification and referral of a suitable patient or normal control, participants were recruited and provided with research information to obtain informed consent. Then participants were screened for 4T MRI safety and neurological or psychiatric disorders and were scheduled for their initial research MRI scans. Participants were re-screened for MRI safety and neurological state at the 6 months' follow-up to ensure they were still eligible for the study.

4.2.4. MRI Acquisition

The MRI scans were performed on a 4T Varian INOVA MRI (Oxford Magnet Technology human imaging system; INOVATM console from Varian Inc.; 35 mT/m imaging gradients from Tesla Engineering). A standard EPI sequence was used for whole brain fMRI (TR/TE= 2000/40ms, flip angle=60o, Resolution 64×64, FOV=240mm, slice thickness = 5mm). High-resolution T1-weighted images were also acquired (3D MP-FLASH) for co-registration of functional images for localization purposes when data are analyzed.

4.2.5. MRI Scan Procedures

Identified prospective participants referred by the physicians were pre-screened for MRI suitability and other inclusion/exclusion criteria prior to enrolment and baseline scanning. Between the scans, AD patients only had their clinical administration of cholinesterase inhibitors (ChEIs), as normally prescribed by their doctors. The medical and MR screening were performed again at six months, before the follow-up fMRI and neurocognitive testing. The normal controls were also re-screened at the time of follow-up to ensure that they remained cognitively healthy and had not taken cholinesterase inhibitors. Participants also had baseline and follow-up cognitive assessments including the Montreal Cognitive Assessment (MoCA; maximum score of 30) (Nasreddine et al., 2005), the Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog;

maximum score of 70) (Kueper et al., 2018), Modified Mini Mental State Exam (3MS; maximum score of 100) (Teng & Chui, 1987), and the Frontal Assessment Battery (FAB; maximum score of 18) (Dubois et al., 2000).

4.3. Methodology

4.3.1. Study Participants

The participants evaluated included 7 early AD patients (79.6 ± 9.1 years) and an equal ratio of age, sex and handedness-matched normal controls (76.4 ± 7.8 years) without AD diagnosis (Table 4.1).

4.3.2. FMRI Task

The fMRI task used a mixed event-related/block design to test episodic memory including encoding and retrieval. Picture-word matching (Snodgrass & Vanderwart, 1980; Song et al., 2008) were adapted for fMRI, consisting of black-line drawings of common objects and words representing the names of these objects, presented on a white background (Figure 4.2). For the encoding tasks, a word beneath an object appeared on the screen while participants were instructed to decide whether the pictures match the word. For the retrieval tasks, similar stimuli (i.e. picture-word pairs) were displayed on the screen (with 50% probability of being seen) and participants were instructed to decide whether each picture-word pair had appeared previously (Figure 4.2). The fMRI task contained 10 blocks (i.e., 5 encoding blocks and 5 retrieval blocks), and each block consisted of 10 trials each and a rest period. Each trial had a 2-second stimulus and 1-second fixation duration.

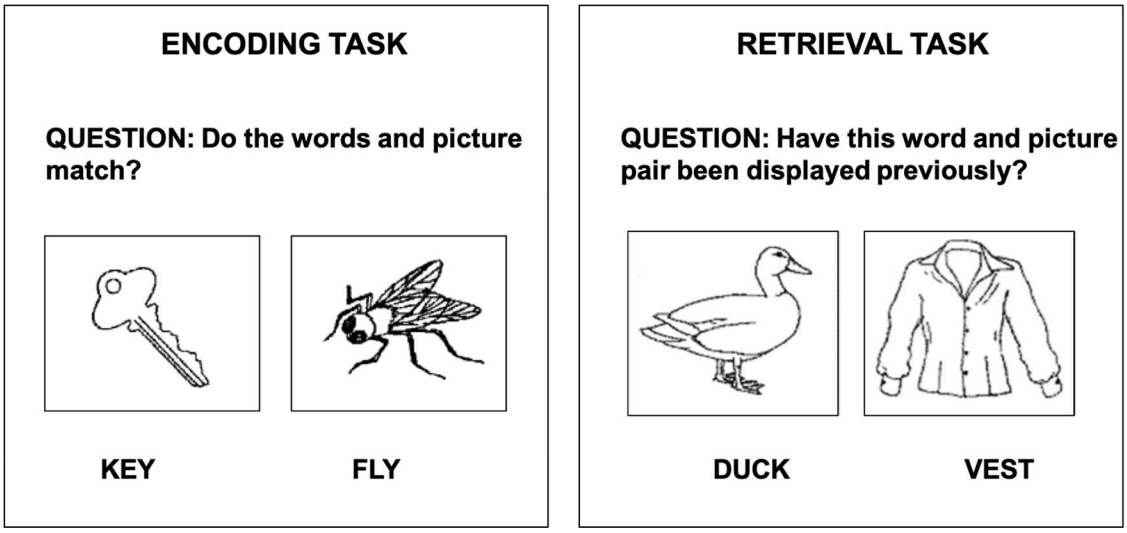


Figure 4.2. Encoding and Retrieval Working Memory FMRI Task Employed in the Early AD Study.
For the encoding task, participants were instructed to decide about whether the pictures match the word. For the retrieval task, participants were instructed to decide about whether each picture-word pair had appeared previously.

The visual stimuli were presented using Avotec MR video goggles (Avotec Inc, Stuart, FL) inside the magnet and a 14-inch CRT computer monitor outside the magnet for practice sessions. All stimuli were presented using E-Prime ® (Psychology Software Tools, Sharpsburg, PA, USA) while behavioural responses (accuracy and reaction time) were measured using a standard MR-compatible response pad.

The fMRI task was appropriate for the study. Prior research has shown that Alzheimer patients in general show lower accuracy rates and longer reaction time than healthy controls when performing similar memory tasks (Chandra et al., 2019). Therefore, the task allowed for sufficient cognitive discrimination between patients and normal control, and between baseline and follow-up post-treatment in patients.

4.3.3. MRI and Statistical Analyses

FMRI data processing and analyses were performed using FEAT (FMRI Expert Analysis Tool) Version 6.00, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl) following the standard processing procedures. Several pre-processing steps were applied including non-brain tissue (e.g skull) removal, motion correction, spatial smoothing (5mm), grand-mean intensity normalization of the entire 4D dataset, and highpass temporal filtering (50s) (Beckmann & Smith, 2004; Jenkinson et al., 2002;

Smith, 2002; Woolrich et al., 2001; Worsely, 2001). Functional data were co-registered to high resolution structural (T1-weighted) and standard space (MNI152 1mm) images. Time-series statistical analysis was carried out using FILM with local autocorrelation correction, fitting to the GLM ($Z>2.3$ at $P<0.05$ cluster-corrected). Higher-level analysis was carried out using a fixed effects model in FLAME, applying contrasts to compare between tasks (i.e., simple vs. difficult) and time points (i.e., pre-vs. post CAS). For each fMRI scan/task, region of interest (ROI) analyses was also performed to evaluate brain regions known to be important for memory encoding and retrieval (e.g middle temporal lobes, prefrontal cortex), comparing pre-post CAS on the filtered time series and percentage of activated voxels within the ROI using Featquery.

Performance accuracy and reaction time (RT) in response to fMRI tasks were examined using pair-wised t-test ($p<0.05$). Changes in brain fMRI activation and behavioral performance were compared for each participant at baseline and follow-up, and between the early AD patients and normal controls. Brain activation strength was computed by multiplying the mean value and number of the z-thresholded voxel clusters, and comparisons were made between baseline and follow-up and between patients and normal controls with significance testing at $p<0.05$.

4.4. Results

4.4.1. Participants Characteristics

There was perfect matching of sex (57.1% females) and handedness (85.7% right-handed) between early AD patients and normal controls (Table 4.1). There were insignificant differences between early AD patients and normal controls in other demographic data including age (79.6 ± 9.1 vs 76.4 ± 7.8 years), BMI (24.0 ± 3.8 vs 22.9 ± 3.6), and BALI scores (11.1 ± 4.3 vs 10.6 ± 2.2).

Table 4.1. Early AD Patients and Normal Controls Participant Demographic Information

	Early AD Patients	Matched Normal Controls	T statistics (AD vs NC)	P > |t|
N (%)	7 (100)	7 (100)	-	-
Age Range, Years	65 - 90	66 - 88	-	-
Age, Years (mean ± SD)	79.6 ± 9.1	76.4 ± 7.8	-0.69	0.5014
Female, N (%)	4 (57.1)	4 (57.1)	-	-
BMI (mean ± SD)	24.0 ± 3.8	22.9 ± 3.6	-0.53	0.6035
BALI range	6 - 16	7 - 13	-	-
BALI (mean ± SD)	11.1 ± 4.3	10.6 ± 2.2	-0.31	0.7585
Right Handedness (%)	6 (85.7)	6 (85.7)	-	-
Education, Years (mean ± SD)	15.1 ± 3.7	14.6 ± 1.5	-0.38	0.7129
Living alone (%)	3 (42.9)	2 (28.6)	-	-
> 2 diseases (%)	4 (57.1)	2 (28.6)	-	-
> 2 prescriptions (%)	4 (57.1)	3 (42.9)	-	-
GOALS (mean ± SD)	67.4 ± 8.9	68.3 ± 7.6	0.19	0.8501
Exercise Total score (mean ± SD)	20.6 ± 2.8	18.3 ± 4.6	-1.12	0.2849

AD= early Alzheimer's disease patient, BALI = Brain Atrophy and Lesion Index, GOALS = Goal-Oriented Assessment of Lifeskills, max score of 80, NC = normal controls

Structural Brain Differences

The early AD patients showed marked middle temporal lobe atrophy and overall temporal lobe atrophy, as an expected feature of the disease, compared to the normal controls (Figure 4.3). Marked atrophy was also associated with abnormal lateral ventricle enlargement in early AD patients compared to the normal controls.

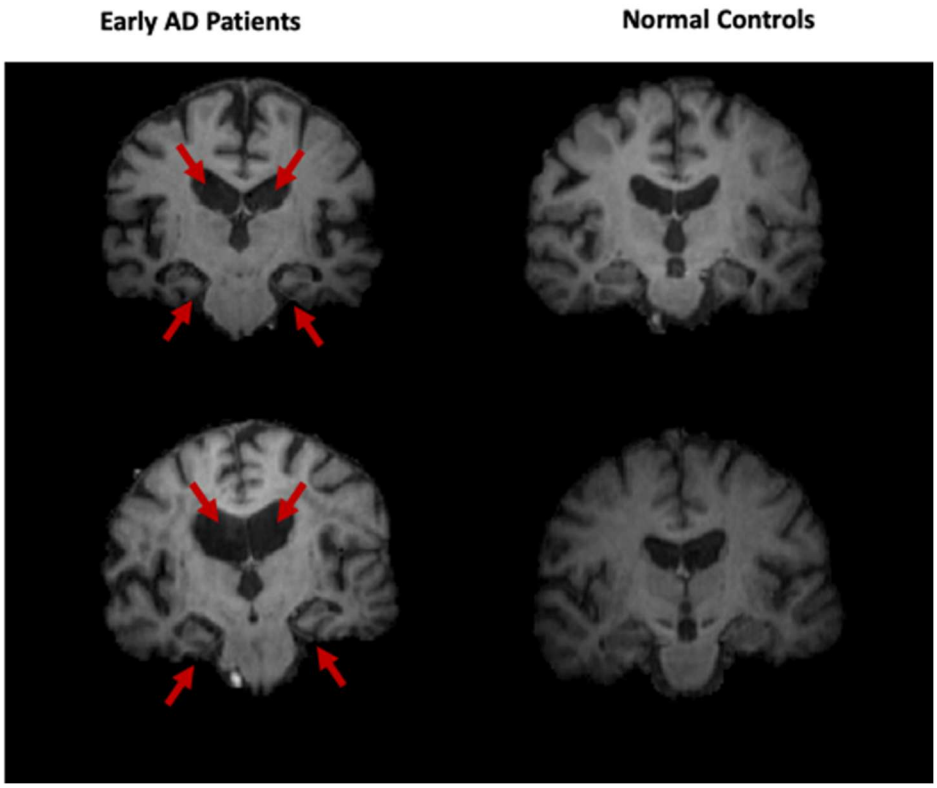


Figure 4.3. Coronal T1-Weighted Images Showing Middle Temporal and General Atrophy in Early AD.
Red arrows point to regions of visible middle temporal lobe atrophy and lateral ventricle expansion in AD patients (left panels) compared to age and sex-matched normal controls (right panels). Further atrophy in other regions can also be seen in AD patients.

4.4.2. Cognitive Assessments

The major and significant difference between early AD patients and the NC were in the several cognitive measures i.e. MoCA, ADAS-Cog, 3MS and FAB (Table 4.2). At both baseline and follow-up, normal controls performed better on all tests of cognition compared to AD patients and the difference was significant at $p<0.05$ (Table 4.2).

AD patients improved on all scores of cognitions at follow-up, by an average of about 2 points, but only the increase in MoCA scores was significant ($p = 0.0388$). The normal controls also performed better on all scores of cognitions at follow-up, although none was significant (Table 4.2).

Table 4.2. Baseline and Follow-Up Neurocognitive Assessment for Early AD Patients and Normal Controls

	Early AD Patients		Normal Controls	
	Baseline	Follow-up	Baseline	Follow-up
ADAS-Cog (M ± SD)	17.8 ± 5.2	15.9 ± 3.4	5.8 ± 3.4	4.3 ± 3.3
3MS (M ± SD)	73.1 ± 6.2	75.6 ± 8.1	94.9 ± 6.1	96.0 ± 5.9
FAB (M ± SD)	12.6 ± 2.4	14.0 ± 3.2	17.0 ± 1.5	17.0 ± 1.0
MoCA (M ± SD)	16.7 ± 3.2	18.6 ± 2.1	25.6 ± 3.6	26.4 ± 3.6

Significance Testing

	AD vs NC - baseline	AD vs NC - follow-up	BL vs FL_AD	BL vs FL_NC
ADAS-Cog T stat (p-value)	5.10 (0.0003)	6.40 (0.00003)	0.96 (0.3758)	1.84 (0.1157)
3MS T stat (p-value)	6.62 (0.00003)	5.39 (0.0002)	1.02 (0.3467)	1.25 (0.2563)
FAB T stat (p-value)	4.15 (0.0013)	2.39 (0.0339)	1.83 (0.1177)	0.00 (1.0000)
MoCA T stat (p-value)	4.83 (0.0004)	5.01 (0.0003)	*2.64 (0.0388)*	1.00 (0.3559)

ADAS-Cog = The Alzheimer's Disease Assessment Scale–Cognitive Subscale; 3MS = Modified Mini Mental State Exam, >77/100 is normal cognition; FAB = Frontal Assessment Battery, max score of 18, higher score better; MoCA = Montreal Cognitive Assessment, >26/30 is normal cognition. M = mean, SD = standard deviation, BL = baseline, FL = follow-up, AD = early Alzheimer's disease patients, NC = normal controls. All t-statistics are double-sided at $p<0.05$.

4.4.3. FMRI Task Behavioural Performance

Both early AD patients and normal controls performed better (i.e., had higher accuracy and greater speeds) in the encoding task compared to the more difficult retrieval task at both baseline and follow-up (Table 4.3). Early AD patients and NCs alike had greater speed at ALL tasks in the follow-up testing, but this was a trade-off at the expense of accuracy which dropped for all tasks (except the patient follow-up retrieval). Mild AD patients had higher accuracy in the follow-up retrieval task (Table 4.3).

Normal controls had higher accuracy compared to mild AD patients in ALL tasks and at ALL time-points, although only the difference in retrieval accuracy was significant (p = 0.0091 and 0.0148 at retrieval baseline and follow-up respectively) (Table 4.3, Table A.1). Normal controls also had greater speeds compared to mild AD patients in ALL tasks and at ALL time-points, although only the speed difference in baseline retrieval and follow-up encoding was significant (p = 0.0481 and 0.0180 respectively). Mild AD patients had much greater variability in the results (reflected by much higher standard deviations) in their task performances at each timepoint (Table 4.3, Table A.1).

Table 4.3. Baseline and Follow-Up FMRI Task Behavioural Performance for Early AD Patients and Normal Controls

Task	Early AD Patients		Normal Controls	
	Baseline	Follow-up	Baseline	Follow-up
		Accuracy, % (M ± SD)		
Encoding	91.4 ± 11.5	87.1 ± 12.1	99.6 ± 1.1	98.1 ± 2.6
Retrieval	56.7 ± 22.7	62.9 ± 18.6	89.1 ± 15.7	88.6 ± 15.0
		Reaction Time, ms (M ± SD)		
Encoding	1614.9 ± 477.6	1540.6 ± 479.6	1219.5 ± 403.3	1006.3 ± 191.6
Retrieval	2675.6 ± 798.7	2246.0 ± 773.6	1953.3 ± 341.9	1673.6 ± 522.6

Significance Testing

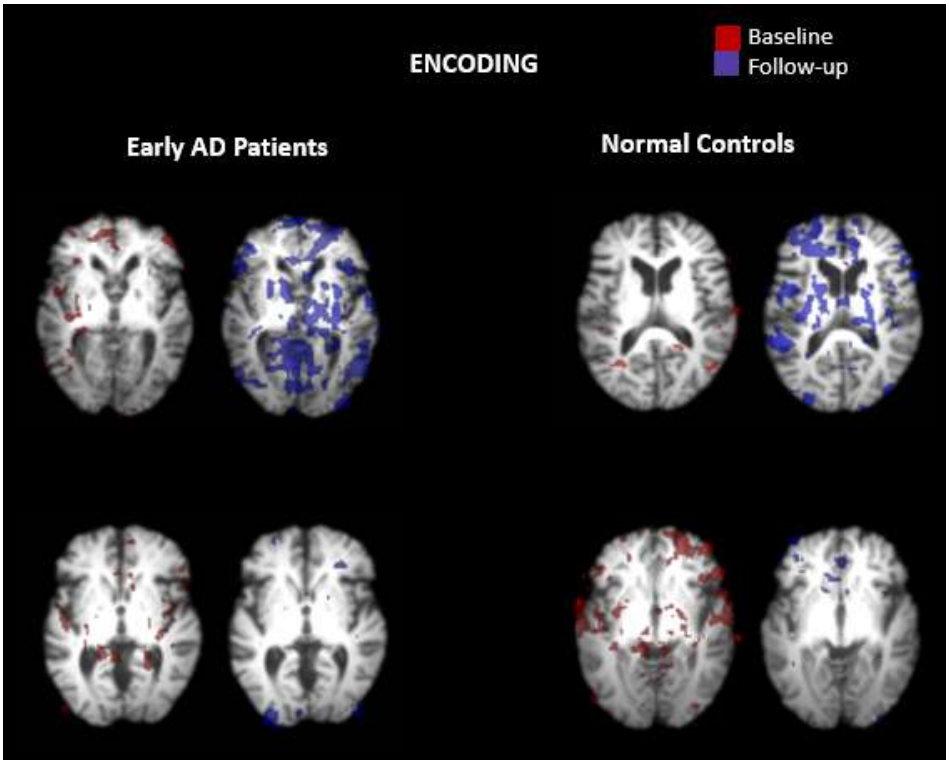
	AD vs NC - baseline	AD vs NC - follow-up	BL vs FL_AD	BL vs FL_NC
		Accuracy - T stat (p-value)		
Encoding	1.86 (0.0876)	1.99 (0.0715)	-1.88 (0.1096)	-2.11 (0.0796)
Retrieval	3.11 (0.0091)	2.84 (0.0148)	0.83 (0.4370)	-0.19 (0.8546)
		Reaction Time - T stat (p-value)		
Encoding	-1.67 (0.1201)	-2.74 (0.0180)	-0.32 (0.7582)	-1.45 (0.1964)
Retrieval	-2.20 (0.0481)	-1.62 (0.1308)	-2.99 (0.0243)	-2.33 (0.0584)

M = mean, SD = standard deviation. BL = baseline, FL = follow-up, AD = early Alzheimer's disease patients, NC = normal controls. All t-statistics are double-sided at p<0.05.

4.4.4. FMRI Brain Activation

General Brain Activation

There was individual variability in general fMRI brain activation in both early AD patients and normal controls alike across tasks and time points. Some participants saw increased activation at baseline compared to follow-up, while some saw the reverse wherein follow-up brain activation was greater than baseline (Figure 4.4).



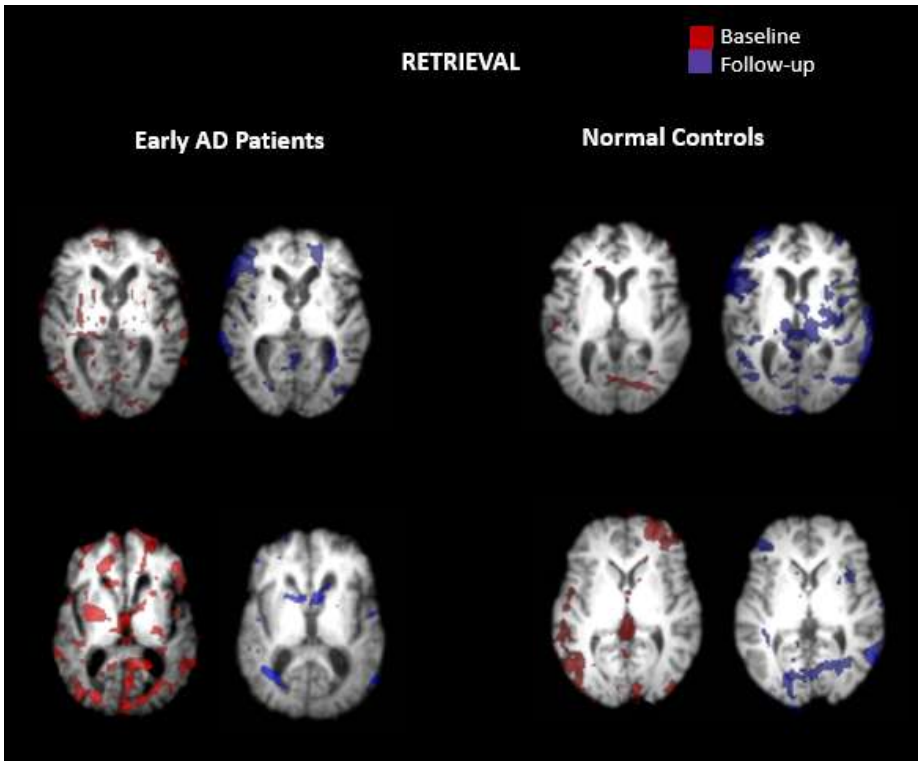
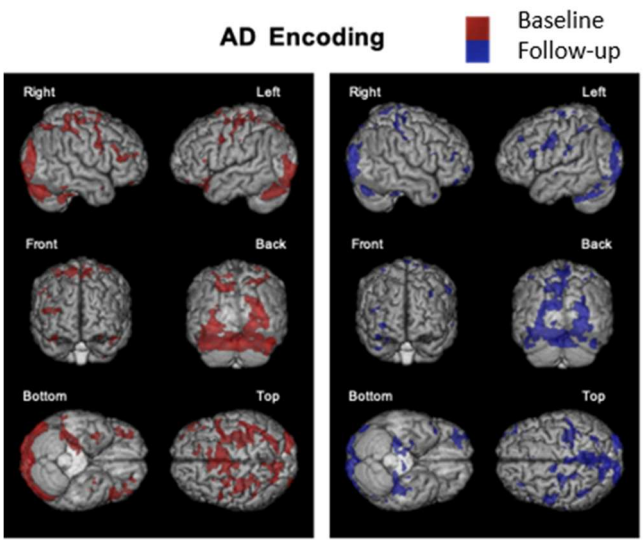


Figure 4.4. Individual FMRI Brain Activation Contrast Maps for Early AD Patients and Normal Controls.
These figures show Z statistical images, thresholded non-parametrically using clusters determined by Z>2.3 (p= 0.05) at baseline (red maps) and follow-up (blue maps). A sample of both early AD patients (left panels) and normal controls (right panels) are chosen to illustrate the individual variability within fMRI brain activation. For both tasks, some participants saw greater activation at follow-up compared to baseline (top panels); while some others had greater general brain activation at baseline compared to follow-up (bottom panels).

At the group level, at baseline, AD patients had a more lateralized pattern of brain activation in the right prefrontal and dorsomedial frontal and parietal cortices across the encoding and retrieval tasks. At follow-up, there was decrease in the lateralized right activation across both tasks (Figure 4.5). Normal controls also saw a pattern of right dorsolateral frontal activation at baseline, but only for the retrieval task. At follow-up, much of the right frontal activation remained, but coupled with an increase in left dorsolateral prefrontal cortex especially in the encoding task (Figure 4.5). In general, normal controls had greater mean activation than the early AD patients, especially in the bilateral prefrontal cortex at follow-up.


AD Encoding
Baseline
Follow-up
Right
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Front
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Bottom
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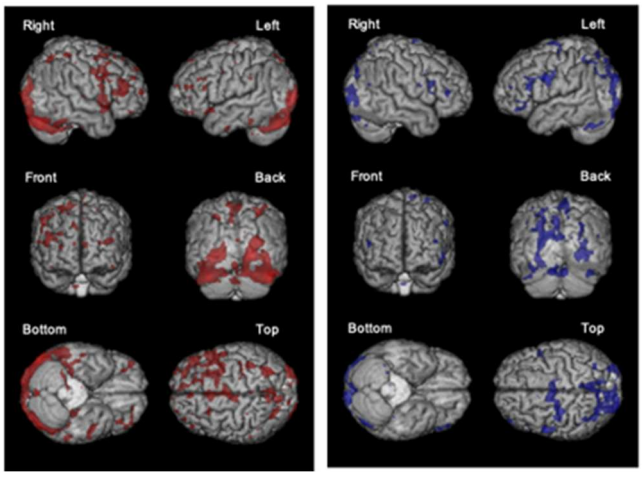
AD Retrieval
Right
Left
Front
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Bottom
Top
Right
Left
Front
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Bottom
Top

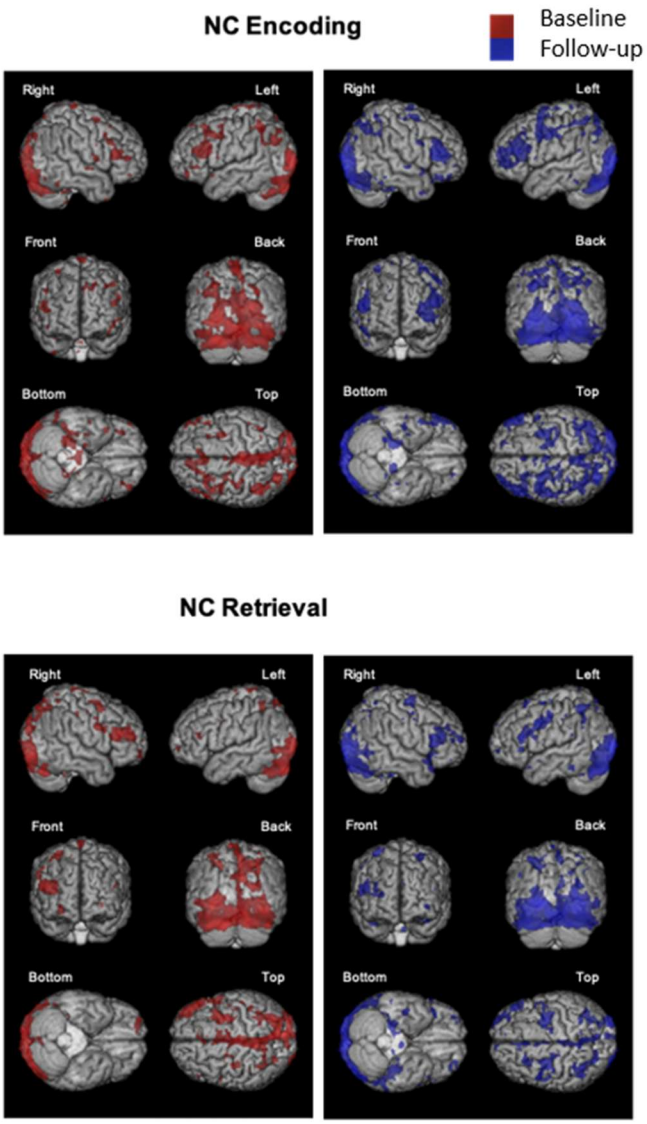

Figure 4.5. FMRI Group Activation Maps for Early AD Patients and Normal Controls.
These figures show group Z statistic images, thresholded non-parametrically using clusters determined by Z>2.3 (p= 0.05) and rendered on high resolution T1 images. The red maps refer to baseline group activation while the blue refers to the follow-up group activation for the encoding (top panels) and retrieval (bottom panels) tasks respectively. The left figure represents the early AD patients (AD) while the right figure represents the normal controls (NC).

Individual ROI Analyses: Prefrontal Cortex Neurocompensation

There was great individual variability in the pattern of strength of activation across time points in the prefrontal cortex for both the early AD patients and normal controls alike. Some patients displayed neuro-compensation while some did not (Figure 4.6). For the encoding task, left prefrontal cortex hyperactivation was observed in AD3 at baseline.

The compensatory activity decreased at follow-up but was not associated with increased accuracy (73% BL vs 67% FL accuracy).

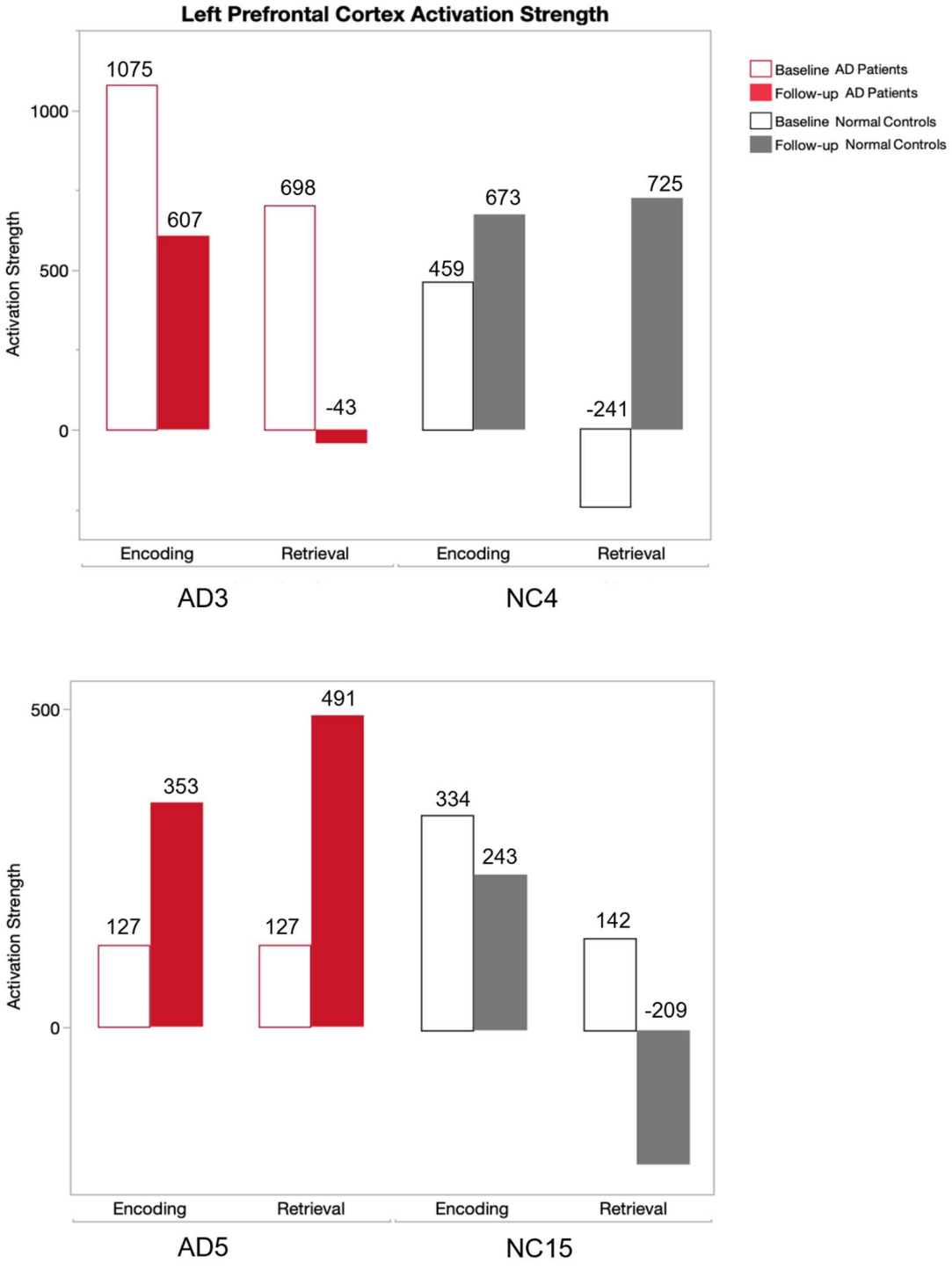

Figure 4.6. Strength of Prefrontal Cortex Activation in Response to Working Memory Task in Early AD Patients and Normal Controls
This figure shows a query into the left prefrontal cortex (LPFC), illustrating individual variation in a sample of the AD patients (red) and normal controls (grey) across baseline (clear bars) and follow-up (colored bars). The bars represent the strength of fMRI activation generated by multiplying the mean value and number of the z-thresholded activated voxel clusters (z> 2.3, p=0.05). Some patients showed great prefrontal cortex hyperactivation (e.g AD3) compared to age-matched controls, while some did not (e.g AD5).

For the retrieval task, left prefrontal cortex hyperactivation was also found in the same patient (e.g AD3) at baseline, and reduced at follow-up post-treatment, but was not associated with improved accuracy (63% BL vs 60% FL accuracy) (Appendix A.2). Patients in general had a greater strength of activation in the right prefrontal cortex at baseline compared to follow-up (Fig 4.6). However, some normal controls (e.g NC4) showed prefrontal hyperactivation in both the left and right prefrontal cortices for the retrieval task, especially at follow-up (Appendix).

Group ROI Analyses: Prefrontal Cortex and Middle Temporal Lobe

For the encoding task, early AD patients had increased strength of activation in both the left and right middle temporal lobes (MTL) at follow-up post-treatment. In addition, the strength of activation in the left and right prefrontal cortex (PFC) decreased at follow-up post-treatment (Table 4.4). In contrast, normal controls had decreased strength of activation in both the left and right middle temporal lobes (MTL), and right prefrontal cortex at follow-up with increased strength of activation in only the left PFC at follow-up for the encoding task. None of the differences between timepoints was significant statistically at $p<0.05$.

Table 4.4. Strength of FMRI Brain Activation in Prefrontal and Middle Temporal Cortices for Early AD Patients and Normal Controls

ROI	Early AD Patients		Normal Controls	
	Baseline	Follow-up	Baseline	Follow-up
		Encoding (M ± SD)		
LMTL	159.6 ± 116.2	178.9 ± 116.7	221.8 ± 271.7	204. 5 ± 196.6
RMTL	92.8 ± 167.4	176. 0 ± 54.5	237.1 ± 237.7	220.4 ± 131.2
LPFC	267.1 ± 458.0	232.4 ± 259.2	476.4 ± 158.2	583.7 ± 320.0
RPFC	307.1 ± 159.0	395.5 ± 293.8	227.0 ± 122.2	342.4 ± 203.3
		Retrieval (M ± SD)		
LMTL	200.3 ± 120.6	48.4 ± 72.4	132.6 ± 59.7	244.8 ± 257.6
RMTL	144.1 ± 148.2	107.3 ± 117.8	59.7 ± 90.7	184.9 ± 234.8
LPFC	263.0 ± 330.3	233.9 ± 285.4	81.2 ± 198.7	246.6 ± 395.0
RPFC	401.5 ± 173.2	132.9 ± 146.6	303.9 ± 271.6	390.9 ± 525.4

Significance Testing

ROI	AD vs NC - baseline	AD vs NC - follow-up	BL vs FL_AD	BL vs FL_NC
		Encoding - T stat (p-value)		
LMTL	0.47 (0.6505)	0.25 (0.8091)	0.30 (0.7800)	-0.22 (0.8332)
RMTL	1.11 (0.2984)	0.70 (0.5047)	1.12 (0.3244)	-0.18 (0.8639)
LPFC	0.97 (0.3624)	1.91 (0.0929)	-0.30 (0.7796)	1.33 (0.2536)
RPFC	0.59 (0.5703)	1.09 (0.3085)	-1.48 (0.2118)	-0.47 (0.6656)
		Retrieval - T stat (p-value)		
LMTL	-1.12 (0.2933)	1.64 (0.1395)	*-5.14 (0.0068)*	1.07 (0.3439)
RMTL	-0.44 (0.6750)	1.11 (0.2985)	-1.19 (0.3006)	0.75 (0.4936)
LPFC	-1.05 (0.3225)	-0.06 (0.9548)	-0.15 (0.8858)	0.67 (0.5388)
RPFC	-0.68 (0.5172)	1.06 (0.3211)	*-5.09 (0.0070)*	0.31 (0.7693)

M = mean, SD = standard deviation, BL= Baseline, FL= follow-up, LMTL = left middle temporal lobe, LPFC = left prefrontal cortex, NC= normal controls, RMTL = right middle temporal lobe, ROI = region of interest, RPFC = right prefrontal cortex

For the retrieval task, early AD patients had decreased strength of activation in both the left and right MTL and PFC at follow-up in response to treatment. Only the decreased strength of activation in the left MTL (t= -5.14, p= 0.0068) and right PFC (t= -5.09, p= 0.0070) at follow-up were significant at $p<0.05$ (Table 4.4). Normal controls in contrast had increased strength of activation in both the left and right MTL and PFC at follow-up, although the differences were not significant at $p<0.05$. (Table 4.4)

4.5. Interpretation

The baseline fMRI behavioural performance showed that early AD patients had poorer accuracy and slower reaction times compared to the normal controls. Only the difference in the retrieval fMRI task was statistically significant (accuracy t= 3.11, p= 0.0091; reaction time t= -2.20, p= 0.0481) and is reflective of the more mental effort required for accurate memory recollection, which is dependent on the middle temporal lobe infrastructure. Following ChEI treatment, fMRI behavioural performance of AD patients improved, with increase in retrieval accuracy and a significant reduction in retrieval reaction time (p= 0.0243) (Table 4.3). In addition, the difference in performance between the normal controls and AD patients for the retrieval tasks was reduced post-treatment, showing some intervention mediated improvements in working memory.

Whole-brain fMRI activation for AD patients at the group level showed a pattern of lateralization in the right dorsolateral PFC, across the encoding and retrieval tasks, confirmed by ROI analyses (Figure 4.5). However, normal controls only showed right lateral activation for the retrieval task. There is evidence in support for right lateralization of object identification (McAuliffe & Knowlton, 2001), and results of this study may confirm such hypothesis. At the individual level, there was variability in whole brain fMRI activation across both tasks, with some individuals seeing greater activation at baseline compared to follow-up, while the reverse was the case for others (Figure 4.4).This was also consistent with the individual ROI analyses. AD patients revealed individual variations in the responses; only select AD patients experienced hyperactivation of the left prefrontal cortex, which was however not correlated with higher accuracy or speed (Figure 4.5, Figure A1). Normal controls also had variations in their fMRI brain activation responses; and follow-up assessment revealed prefrontal cortex hyperactivity in one control (Appendix A; Figure A2).

Group ROI analyses in the middle temporal lobe (MTL) showed that at baseline, normal controls had greater activation strength in the left and right MTL compared to early AD patients for the encoding task, while AD patients had greater strength of activation in both left and right MTL for the retrieval task (Table 4.4). For the less mentally demanding encoding task involving object identification, differences between AD and NC in MTL strength of activation may just be reflective of the state of middle temporal lobe atrophy (i.e neuronal density). However, for the more mentally demanding retrieval task relying on information recollection, the difference between AD and NC may reflect the extra effort by AD patients to recall information using a MTL undergoing atrophy compared to NC who do not need to expend such effort. This is supported by the correlation with the fMRI behavioural data, wherein extra MTL efforts did not result in higher accuracy or reaction time in the retrieval task (Table 4.3). Following treatment with ChEI, AD patients saw increases in the activation strength in the left and right MTL across the encoding task, associated with improvement in speed. Decreases in the MTL activation strength was observed for the retrieval task together with working memory improvements in speed and accuracy. This may be indicative of a treatment-induced improvement in the response of the MTL to the cognitive load.

For the prefrontal cortex (PFC), AD patients had a much-exaggerated strength of activation across the left and right PFC for the retrieval task compared to normal controls at baseline (Table 4.4). This PFC hyperactivation was only observed for the more complex retrieval task that presents more cognitive load to the degenerating middle temporal cortex. This is only partly consistent with the literature on neuro-compensation; because while cognitive resources were reallocated to the prefrontal cortex (PFC), it did not result in a corresponding sustenance of cognitive performance (Grady et al., 2003). However, following treatment, AD patients showed a decrease in activation strength of the right and left PFC associated with improvements in working memory performance, demonstrated by increases in task accuracy and speed for the retrieval task (Table 4.4). This showed that AD patients had treatment-mediated improvements in working memory, reducing the need for prefrontal cortex neuro-compensatory behaviour post-treatment and increasing response with the MTL (which in fact increased in activation strength post-treatment) in response to cognitive load.

Chapter 5

Discussion and Conclusion

5.1. Discussion

5.1.1. Evaluation of Hypotheses

For the carotid stenosis study, the hypotheses were only partly supported. The first hypothesis was supported as brain activation patterns indicative of working memory recovery in severe ICA stenosis patients undergoing revascularization intervention were evidenced using task phase fMRI. Improved cerebral perfusion to areas supplied by carotid arteries following CAS were correlated with improved cognitive function in working memory performance along with increased fMRI activations in the re-perfused vascular territory and reduced in the contralateral frontal and temporal lobes. However, the second hypothesis was only partly supported as the fMRI findings correlated well with only a subset of the traditional cognitive assessments for working memory. Both patients experienced a decrease in global cognition (neurocognition index) and several other cognitive domains (Table 3.2) while improvements were also observed in select cognitive domains including processing speed and reaction time (Case 1), and psychomotor speed, cognitive flexibility, motor speed, processing speed and executive function (Case 2). The findings with the traditional cognitive testing are consistent with the previous research in this line using paper-based tests which has mostly yielded inconclusive results (De Rango et al., 2008; Plessers et al., 2014). However, these findings further emphasized the known sensitivity of task-phase BOLD fMRI in detecting improvements in brain activation patterns in the acute phase, long before improvements on global tests of cognition may be observed.

For the AD study, the hypotheses were only partly supported as well. The first hypothesis was not supported. Baseline prefrontal cortex hyperactivation was found only in select AD patients, and for only the retrieval working memory task at the group level. However, such responses could not be regarded as neuro-compensatory (Gregory et al., 2017) as they were not associated with maintenance of working memory performance (i.e. poor task accuracy and speed). The second hypothesis was supported for the

retrieval task only. Treatment with ChEI's in early AD patients, was associated with reduction in the prefrontal cortex hyperactivation in both individual patients and overall, correlated with improvement in working memory fMRI behavioural responses (higher accuracy and speed). The third hypothesis was supported the most as individual variability in AD patients moderated the magnitude and level of fMRI brain activation and improvements observed.

5.1.2. Individual Variability as a Factor

Overall, the standard clinical interventions for both AD and severe carotid stenosis resulted in improvements in working memory in patients. However, such improvements were not generalizable. A central theme in the studies evaluated is the impact of individual variability in response to the treatment and in patterns of fMRI brain activation. This variability itself arises from the peculiarity of individuals ranging from medical, cognitive, lifestyle and other factors. In the AD study, great individual variability was observed in the pattern of fMRI activation and response to treatment in the AD patients. Even in the supposedly cognitively "healthy" normal controls, variation was found in their fMRI brain activation responses; and follow-up assessment revealed prefrontal cortex hyperactivity in one control (Appendix A). Whether this is a neurocompensatory mechanism signalling beginning of cognitive decline in that subject deserves further attention. However, while some patterns were found in the overall general brain activation, the individual peculiarity observed prevents generalizability to the broader population

Further, while the genetic and physiological heterogeneity of AD has been established for a while, it was also interesting to see that such heterogeneity also applied to the carotid stenosis study. For example, variations in the severity and degree of flow limitation of the stenosis, pre-CAS Circle of Willis anatomy and collateral flow to the affected circulation territory and baseline cognitive between the two cases impacted the effect of treatment and consequent fMRI brain cognitive changes observed post-CAS as well.

5.2. Scientific Contributions

The carotid stenosis study addressed the gap of designing and applying an appropriate working memory fMRI task to directly measure the cognitive impact of CAS for the treatment of severe carotid stenosis while the AD study also examined how neurocompensatory responses to cognitive load in AD was affected and modulated by treatment. The carotid stenosis study showed that revascularization treatment favourably improved brain activation pattern in correlation with behavioural data in the acute phase, long before improvements on global tests of cognition may be observed and is a testament to the known sensitivity of task-phase BOLD fMRI. The AD study showed that the neurocompensatory response is a function of task difficulty and cognitive load, and is modulated by routine ChEI intervention for AD.

Taken together, both studies showed that, while the relevant clinical interventions for the diagnoses were related with improvements in working memory, the effects of individual variability interfere with strength of such treatment significance and is a deterrent to generalizability. To improve clinical treatment outcomes, it may be better to approach care plans from a patient-oriented individualized angle. Recent reviews on current and novel therapies for AD are consistent with these findings, tagged as the future of “precision medicine” (Strac et al., 2021; Yu et al., 2021). Using the precision medicine approach, appropriate interventions are selected based on personal characteristics in order to achieve the best possible effect with the most minimal harm and adverse effects (Strac et al., 2021; Yu et al., 2021). This thesis lends support to design and implementation of personalized interventions for AD and carotid stenosis with possibility of extension into other neurological conditions. Such treatment outcomes can be sensitively monitored using task-phase fMRI.

5.3. Challenges and Mitigation Strategies

One caveat to consider while interpreting the results of this study is that the findings were based on small samples, which showed considerable individual variability. Therefore, the generalizability of the results requires further investigations. Even so, the follow-up nature of the study allowed each patient to have duplicate scans for pre-post comparison and provides individual patient-oriented evidence of the impact of treatment

on cognition. This is also coupled with the known sensitivity of fMRI data that allows changes in functional brain activations to be observed even for a smaller set of data.

Further, the individual variations as revealed by these small samples is an important contribution to the field and lends support for the need for individualized patient-oriented care to better improve treatment outcomes. Enlightened by these cases, further research can be conducted with increased sample size, and more follow-up sessions, while also accounting for individual variability.

In addition, in both studies, fMRI imaging analyses and cognitive assessments were not blinded to diagnostic information (i.e severity of carotid stenosis, whether a participant was an AD patient or normal control) and other demographic information, therefore leaving room for bias. Blinding, although important, was difficult to achieve in the current setting due to the limitation in personnel (i.e., singular person involved in data collection, storage, retrieval, and analyses). However, the results from the analyses are consistent with previous research in the field, including those done with a double-blinded design (Canu et al., 2021; Chinda et al., 2021; Guo et al., 2018). Therefore, while the risk of bias in analyses and interpretation is present, the results underscore the actual differences that have been found post revascularization in carotid stenosis patients and post- ChEI treatment in AD patients.

Lastly, the AD study involved secondary analyses of already collected data. Therefore, data quality was dependent on the original collection and was subject to unknown errors at that time. However, time-series observation of fMRI data in relation to task design was used to evaluate data and remove data showing no response or questionable patterns, while the data quality was accessed by one of the original collectors.

5.4. Future Directions

Future research directions in this field should aim to increase the sample size and the amount of follow-up sessions. Given the high likelihood of a progressive course of functional brain recovery, having a baseline and more than one follow-up fMRI session at intervals during the first six to twelve months would allow a better understanding of the short- and medium- term cognitive benefits of the treatment. In addition, for the carotid

stenosis study, future investigations should include a comparison metric of a matched healthy control group to help with the interpretation of fMRI findings. By comparing data between patients and matched controls, a baseline standard is set, to control for possible confounding factors and to comparatively evaluate the level of recovery.

More importantly, future studies and data analyses should also be performed blinded to diagnostic information or treatment conditions to eliminate risks of bias in results interpretation. Future directions should also aim to link the functional brain activations with long-term outcome data i.e morbidity and mortality. Also, the role of variations in structural brain health in patient outcomes involving complex cognitive tasks warrants further attention and could be expanded for future research. Multimodal fMRI should also be employed in future studies used to evaluate the effects of treatment from various angles. As individualized treatments become implemented in the future, fMRI can be applied to sensitively monitor the treatment effects.

5.5. Conclusion

This thesis research found that improvements in task-phase fMRI brain activation patterns together with improvements in task accuracy and speed were observed in a large portion of participants following standard clinical interventions (i.e., carotid angioplasty and stenting for severe carotid stenosis and cholinesterase inhibitors treatment for early Alzheimer's disease). Meanwhile, patients demonstrated complex response patterns associated with disease status, expression, and other individual variability. This thesis contributes task-phase fMRI evidence in establishing the impact of standard clinical interventions in helping patient’s memory following neurological trauma. It also highlights the uniqueness of individuals patients, even though they may be classified with the same diagnoses. Recognizing individual uniqueness at the point of care through developing and implementing tailored treatment plans has the potential to increase the effectiveness of standard clinical interventions and improve patients well-being.

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Appendix A.

Pairwise Individualized fMRI Behavioural Data for AD Patients and Normal Controls

Table A.1. Individualized FMRI Behavioral Data for Early AD Patients and Normal Controls

	Encoding				Retrieval			
	Baseline		Follow-up		Baseline		Follow-up	
ID	Accuracy (%)	Reaction Time (ms)	Accuracy (%)	Reaction Time (ms)	Accuracy (%)	Reaction Time (ms)	Accuracy (%)	Reaction Time (ms)
AD1	96.7	2167.6	96.7	1786.3	76.7	2443.4	53.3	2607.8
NC11	100.0	1071.3	96.7	1008.1	80.0	1658.3	90.0	1808.3
AD2	100.0	1183.1	90.0	2341.9	10.0	4181.5	37.0	3549.3
NC8	100.0	966.2	97.0	718.1	96.7	1992.2	90.0	1637.4
AD3	73.3	1944.0	66.7	1501.2	63.3	1727.7	60.0	1714.2
NC4	100.0	1417.8	100.0	1207.1	96.7	2006.9	96.7	1277.2
AD4	100.0	1091.1	100.0	815.0	76.7	2534.1	80.0	1904.5
NC14	100.0	1026.2	100.0	959.1	96.7	1860.2	86.7	1699.4

	Encoding				Retrieval			
	Baseline		Follow-up		Baseline		Follow-up	
ID	Accuracy (%)	Reaction Time (ms)	Accuracy (%)	Reaction Time (ms)	Accuracy (%)	Reaction Time (ms)	Accuracy (%)	Reaction Time (ms)
AD5	76.6	2185.6	80.0	1491.3	53.3	2963.1	46.7	2618.6
NC15	97.0	1026.9	93.3	1263.9	56.7	2654.9	56.7	2725.2
AD7	100.0	1216.9	96.7	1179.5	53.3	2883.1	86.7	2186.0
NC16	100.0	965.1	100.0	842.9	96.6	1635.4	100.0	1122.8
AD10	93.3	1515.8	80.0	1669.3	63.3	1996.5	76.6	1141.5
NC17	100.0	2063.0	100.0	1044.7	100.0	1865.1	100.0	1444.9

AD = early Alzheimer's disease patients, NC = normal controls

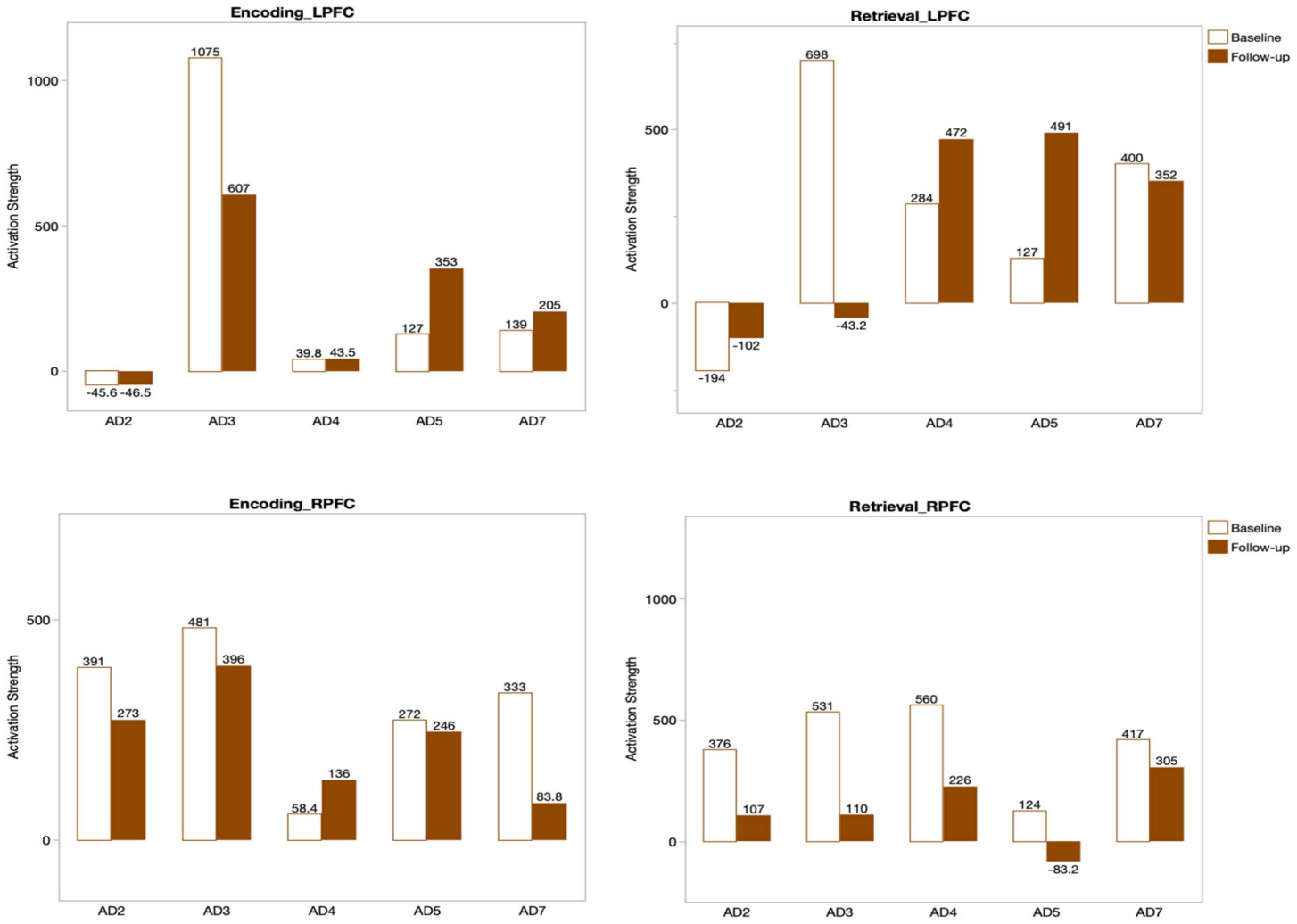
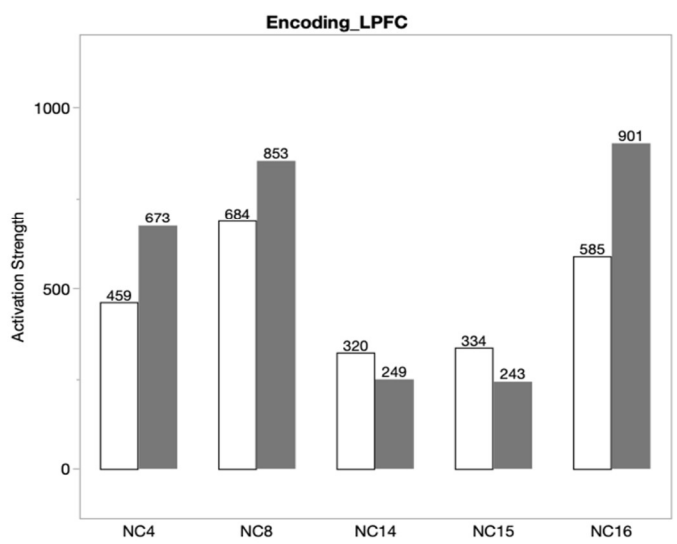
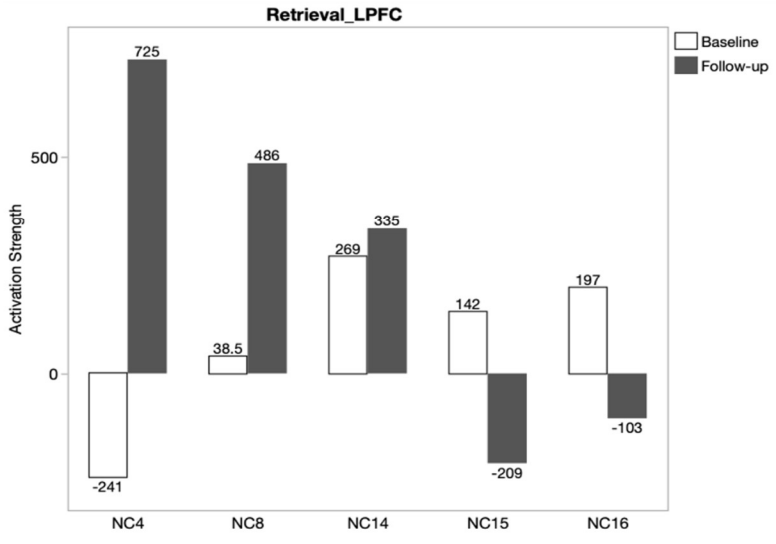
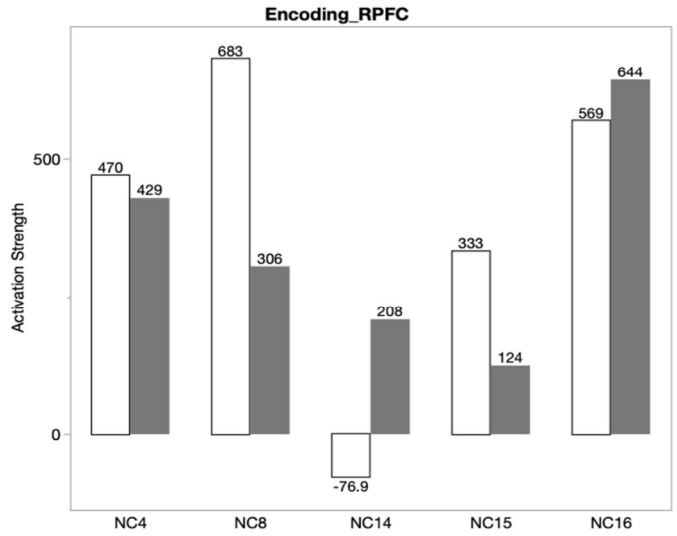


Figure A.1. Individualized early AD patients' strength of brain activation in response to encoding and retrieval working memory tasks in the prefrontal cortex across baseline (clear bars) and follow-up (colored bars) .

This figure shows a query into the left and right prefrontal cortex (LPFC), illustrating individual variation in all the AD patients. The bars represent the strength of fMRI activation generated by multiplying the mean value and number of the z-thresholded activated voxel clusters (z> 2.3, p=0.05). Some patients showed great prefrontal cortex hyperactivation (e.g AD3) while some did not (e.g AD5).


Encoding_LPFC
Activation Strength
1000
500
0
459
673
684
853
320
249
334
243
585
901
NC4
NC8
NC14
NC15
NC16


Retrieval_LPFC
Baseline
Follow-up
Activation Strength
500
0
-241
725
38.5
486
269
335
142
-209
197
-103
NC4
NC8
NC14
NC15
NC16


Encoding_RPFC
Activation Strength
500
0
470
429
683
306
-76.9
208
333
124
569
644
NC4
NC8
NC14
NC15
NC16

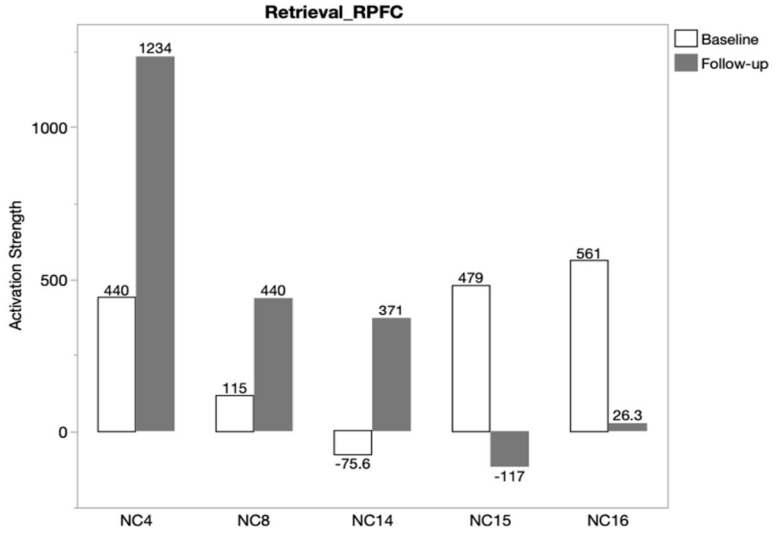

Retrieval_RPFC
Baseline
Follow-up
Activation Strength
1000
500
0
440
1234
115
440
-75.6
371
479
-117
561
26.3
NC4
NC8
NC14
NC15
NC16

Figure A.2. Individualized normal controls' strength of brain activation in response to encoding and retrieval working memory tasks in the prefrontal cortex across baseline (clear bars) and follow-up (colored bars) .
This figure shows a query into the left and right prefrontal cortex (LPFC), illustrating individual variation in the normal controls. The bars represent the strength of fMRI activation generated by multiplying the mean value and number of the z-thresholded activated voxel clusters (z> 2.3, p=0.05).

Appendix B

List of Scholarly Publications Arising from MSc Research

Arab, A., **Chinda, B.,** Medvedev, G., Siu, W., Guo, H., Gu, T., ... & Song, X. (2020). A fast and fully-automated deep-learning approach for accurate hemorrhage segmentation and volume quantification in non-contrast whole-head CT. *Scientific Reports*, *10*(1), 1-12

Chinda, B., Liang, S., Siu, W., Medvedev, G., & Song, X. (2021). Functional MRI evaluation of the effect of carotid artery stenting: a case study demonstrating cognitive improvement. *Acta Radiologica Open*, *10*(2), 2058460120988822.

Chinda, B., Tran, K. H., Doesburg S., Siu, W., Medvedev, G., Liang, S., Brooks-Wilson, A., & Song, X. (2021) Functional MRI evaluation of cognitive effects of carotid stenosis revascularization. *Brain and Behavior*, (Submitted under review).

Chinda, B., Medvedev, G., Siu, W., Ester, M., Arab, A., Gu, T., ... & Song, X. (2018). Automation of CT-based haemorrhagic stroke assessment for improved clinical outcomes: study protocol and design. *BMJ Open*, *8*(4), e020260.

Chinda, B., Sarveswaran, S., Rockwood, K., Brooks-Wilson, A., & Song, X. (2021) Frailty in healthy oldest old: characterizing the frailty index of Super-Seniors. (Manuscript in preparation).

Sepehri, K., Braley, M. S., **Chinda, B.,** Zou, M., Tang, B., Park, G., ... & Song, X. (2020). A computerized frailty assessment tool at points-of-care: development of a standalone electronic comprehensive geriatric assessment/frailty index (eFI-CGA). *Frontiers in Public Health*, *8*, 89

List of Conference Presentations Arising from MSc Research

Arab, A., **Chinda, B.,** Medvedev, G., Siu, W., Guo, H., Gu, T., ... & Song, X. (2020). A fully-automated convolutional neural network with deep supervision approach for haemorrhage segmentation and volume quantification in CT scans. *American Society of Neuroradiology Annual Meeting*.

Chinda, B., Liang, S., Siu, W., Medvedev, G., & Song, X. (2021). Task-phase fMRI evidencing cognitive improvement post carotid angioplasty and stenting (CAS) – initial findings of a follow-up study. *International Society for Magnetic Resonance in Medicine (ISMRM) Annual Meeting and Exhibition*.

Chinda, B., Liang, S., Siu, W., Medvedev, G., & Song, X. (2020). Monitoring of changes in cognitive function and carotid blood flow post carotid angioplasty and stenting using functional and quantitative flow MRI: Preliminary results. *American Society of Neuroradiology Annual Meeting*.

Chinda, B., Sepehri, K., Zou, M., Braley, M., Garm, A., Park, G., ... & Song, X. (2019). The electronic frailty index based on the comprehensive geriatric assessment: development and testing. *Innovation in Aging*, *3*(Supplement_1), S685-S686

Chinda, B., Song, X., Sarveswaran, S., Rockwood, K., & Brooks-Wilson, A. (2019). Frailty in healthy oldest old: characterizing the frailty index of Super-Seniors. *Innovation in Aging*, *3*(Suppl 1), S913.

Zou, M., Kelly, R., **Chinda, B.,** Braley, M., Zhang, T., Arvan, T., ... & Song, X. (2019). The effects of frailty, polypharmacy, and cognition on health outcomes: a study on INTERRAI residential care data. *Innovation in Aging*, *3*(Supplement_1), S86-S86.

Zhang, E. D., Kelly, R., Arvan, T., **Chinda, B. N.,** Low, H., & Song, X. (2020). Polypharmacy in long-term care residents: Prevalence and relationships with age and dementia: Health services research/Policy and plans. *Alzheimer's & Dementia*, *16*, e038664.