DISSERTATION

A MULTIDISCIPLINARY ANALYTICAL APPROACH TO THE IDENTIFICATION OF BOTH MODIFIABLE AND NON-MODIFIABLE RISK FACTORS OF DEMENTIA

Submitted by

Kathleen Angela Willoughby

Department of Psychology

In partial fulfillment of the requirements

For the Degree of Doctor of Philosophy

Colorado State University

Fort Collins, Colorado

Summer 2021

Doctoral Committee:

Advisor: Deana Davalos

Don Rojas
Laura Malinin
Jeanette Cleveland

ABSTRACT

A MULTIDISCIPLINARY ANALYTICAL APPROACH TO THE IDENTIFICATION OF BOTH MODIFIABLE AND NON-MODIFIABLE RISK FACTORS OF DEMENTIA

A In recent decades, dementia has become a growing global epidemic. As people are living longer, the number of individuals diagnosed with dementia has risen exponentially. Alzheimer's disease, the most common form of dementia, presently afflicts more that 5.4 million Americans (Thies et al., 2011). Though great strides have been made in dementia research, there is still much to be done to better pin-point disease risk and ameliorate decline and related symptom progression. This dissertation will focus on the efficacy of early intervention and risk factor identification as a first line of defense in staving off dementia progression. Within the B Sharp community-arts engagement program, we will evaluate domain-specific changes in older adult cognition over an acute and extended-duration timespan. Within the Alzheimer's Disease Neuroimaging Initiative, we will identify relevant risk factors associated with the consistent acceleration of cognitive decline as well as the slowing of such decline. As these proactive treatment approaches are more fully understood, better strategies for healthy aging can be implemented at both a generalized and individual level.

ACKNOWLEDGEMENTS

The path toward obtaining my doctoral degree was not forged alone. In addition to my sincerest gratitude towards the faculty and staff of the Psychology department at Colorado State University, I would also like to express my appreciation to the following:

To my advisor, Dr. Deana Davalos, without whom I would not be where I am today. Her wisdom and encouragement have changed me for the better.

To my committee, who generously agreed to work alongside me and offer their expertise and insights over the last year. This dissertation reflects their efforts as much as my own.

To the research teams and undergraduate research assistants I have been so lucky to work with and learn from.

To the Willoughby and Dudley families—it takes an army!

To the two individuals I most admire, my parents, who have led by example in teaching attributes of compassion, humanity, and resilience.

To my dear husband, Richard, who lifts me daily. He is my greatest advocate and truest friend. His support, patience, and love are the sweetest parts of my life.

TABLE OF CONTENTS

LIST OF FIGURES

Chapter 1

INTRODUCTION

Global trends indicate people are living longer than ever. Recent data shows an unprecedented surge in the number of adults over the age of 65. In line with this is an associated increase in the number of older adults with dementia-related diagnoses. Some estimates anticipate the number of active dementia cases at roughly 100 million people globally by 2050 (Kim et al., 2018). While the burden of this increase is observed in higher global public health care costs and economic work force shifts, a more sobering reality is seen in the number of persons affected with each individual diagnosis. The health, financial, and quality of life impact on dementia patients and their loved ones emphasizes the overall urgency to decrease incidences of dementia. The magnitude of these trends has prompted increased exploration into the understanding and detection of the underlying mechanisms found in abnormal aging.

Due to the progressive and irreversible nature of the disease, dementia presents a significant challenge in terms of earlier methods of identification and effective treatment. Presently, no effective treatments for disease-related modification exist. Therefore, the need to further elucidate the etiology and risk factors of dementia cannot be overemphasized. Past research has led to identification of modifiable factors such as smoking, alcohol use, education, and physical activity; as well as inherent risk factors such as age, sex, and other genetic variables (Jiang et al., 2017). While such factors have been studied at length regarding their impact on cognitive decline with age, other potential modifiable risk factors have been underrepresented in the current body of research.

In stride with the detection of risk factors related to accelerated cognitive decline in older adults, other treatments focus on a proactive approach to stave off manifestations of

dementia. Petersen et al., (1998) argues that early intervention is vital when dealing with cognitive decline. To understand the disease's progression, researchers have begun to shift their focus toward the beginning stages of impairment as a way to gain insight into later stages. Perhaps the change in focus to early intervention, rather than symptom management, may have propelled a surge of intervention-directed programs with an aim to intervene early in impairment before significant decline has progressed. Though the efficacy of late-stage intervention has been debated, the view of early amelioration as a tool to buffer cognitive decline and dementia-related disease is shared by most researchers. In combination with the aforementioned identification of meaningful risk factors, a proactive approach to intervention may indeed prove to be the most effective strategy in postponing disease progression.

Background

Rather than a single disease, dementia acts as a classification of disorders with a variety of potential underlying causes, characterized by chronic and progressive neuronal decline (Velkers et al., 2018). Dementia as a term encompasses a broad range of disorders, often characterized by progressive neurological degeneration and accompanied by an atypical decline in cognitive, behavioral, emotional, occupational, or interpersonal functioning. Three common types of dementia presentation include Alzheimer's disease (AD), vascular dementia, and dementia with Lewy bodies; with Alzheimer's disease estimated to account for 50-56% of all dementia diagnoses (Jiang et al., 2017). This dissertation will focus on mild cognitive impairment (MCI), a precursor to dementia, and Alzheimer's disease (AD), the most common form of dementia.

Levels of impairment can vary greatly between a cognitively healthy older adult and one with dementia. An intermediate step between these categorizations is classified as mild

cognitive impairment (MCI), with MCI acting as a precursor for dementia. Individuals with MCI typically have noticeable cognitive decline when compared to healthy aging adults but are still able to independently perform activities of daily living (Velkers et al., 2018). A diagnosis of dementia is typically given when cognitive impairments are severe enough to compromise basic activities for daily living.

Behaviorally, AD presents most commonly with short-term memory loss, followed by increased difficulty in cognitive domains such as problem solving, language, and emotion. As these newfound deficits persist, neuronal atrophy typically spreads to different areas in the brain, eventually resulting in the loss of critical bodily functions including walking, efficient breathing, and swallowing. Over time, this functional decrease may lead to the death of those with AD (Velkers et al., 2018).

Early Intervention Efficacy

A shift in focus to early intervention, rather than symptom management, has increased the utilization of intervention-directed programs to ameliorate accelerated cognitive decline in older adults. Social engagement programs may act as a viable option to consider when designing efficacious interventions for individuals with dementia.

A pilot study, conducted by researchers at Colorado State University from 2015-2016, reported the positive impact of a community-based music engagement program known as B Sharp Arts Engagement®, on cognition in individuals with MCI and dementia (Davalos, et al., 2019). The B Sharp Arts Engagement pilot study assessed the impact of this nonpharmacological intervention on cognition in individuals with varying stages of MCI and dementia. Two of the three articles proposed in this dissertation, acting as an extension of the 2015-2016 pilot, will aim to replicate and expand findings of previous B Sharp Arts

Engagement examinations in hopes to further elucidate trends in cognition among older adults with MCI and AD diagnoses.

The proposed studies will focus on analyzing previously collected cognitive information from participants with dementia-type disorders who attended the B Sharp Arts Engagement program at the Fort Collins Symphony by way of neuropsychological testing over the span of the full concert season. Changes in cognition between varying cognitive domains have the potential to shed light on areas of cognition expected to receive greatest benefit from this type of intervention program. Participants in this study included individuals living in and around Fort Collins, Colorado, who were able to attend three or more performances provided by the Fort Collins Symphony over a given symphony season. Participants needed to be over 50 years of age and show some degree of age-related cognitive impairment. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), a gold standard in the assessment of cognitive decline for its domain specificity, short duration, and high test-retest reliability through the use of parallel testing forms. This assessment was administered by trained undergraduate and graduate students. RBANS testing was completed before and after the concert season as well as before and after each concert event. This testing paradigm allows for the assessment of both extended and acute domain changes in cognition. In addition to 5 RBANS index scores, 12 standardized subtest scores will be calculated, allowing for a holistic view of overall cognitive functioning taken from multiple cognitive domains of interest. Applicable subtests will be grouped into broader categories reflecting cognition.

Extended duration testing was conducted on 35 individuals with varying degrees of cognitive decline over a single 10-month concert season timespan between 2015 and 2019 (2015-2016, N=6; 2016-2017, N=8; 2017-2018, N=13; 2018-2019, N=8). Differences in

domain-specific pre-season and post-season RBANS scores will be evaluated using paired t tests. Differences in acute pre- and post-event scores on domain-specific subtests and broader cognitive domains were compiled across all symphony seasons occurring between 2017 and 2020 (2017-2018, N=22; 2018-2019, N=20; 2019-2020, N=13), resulting in 116 pre and post domain-specific subtest comparisons before and after an individual symphony performance. Between domain-specific subtests, rate of change comparisons will be analyzed for pre- and post-event comparisons of change using paired t tests.

For the purposes of this dissertation, visuospatial and auditory-verbal domains will be evaluated for both acute and extended changes in cognition as a way to gain insight into domain specific effects of social intervention in older adults. We are interested in whether music-based interventions lead to specific benefits in cognition (e.g. auditory-verbal and visuospatial). If present, this distinction will allow for the implementation of social interventions tailored to cognitive deficits most vulnerable to decline. Although preliminary, we anticipate cognitive function as measured by the Repeatable Battery for Assessment of Neuropsychological Status (RBANS; Randolph et al., 1998) to improve to varying degrees in both visuospatial and auditory-verbal domains both in an acute (pre-and post-concert event) and extended (pre-and post-season) trajectory. Differences in change between acute and extended durations of time may be useful in making applied conclusions for dementia intervention efficacy.

Risk Factor Identification

A topic of growing interest regards why some individuals with MCI will progress on to AD while others will not. Related variables contributing to accelerated cognitive decline require greater attention. A way to evaluate these variables of interest has become possible by means of the Alzheimer's Disease Neuroimaging Initiative (ADNI). This initiative, started in

2004 and is funded by the National Institutes of Aging and other community partners, aimed to allow for the widespread evaluation of relevant predictors for AD prevention in a population of 822 adults between 50 and 90 years of age with varying levels of normal cognitive decline. Measures include a range of neuropsychological, lumbar puncture-based CSF, 3T MRI and FDG PET methods to assess variables of interest. Identifying these factors as either contributors to or buffers against progression into dementia is invaluable in allowing for the use of identifying profiles of high and low risk for dementia.

Due to the lack of feasibility in collecting various costly and painful biomarker measures, the ADNI database serves as a useful tool for which to explore factors of interest for our research question. In the B Sharp Arts Engagement program, the RBANS was used to help us better understand cognitive deficits in our participants and how these cognitive deficits responded to a music-based community intervention. However, given limitations in the B Sharp Arts Engagement study, we were not able to collect data to better understand the biological substrates of the cognitive deficits observed.

Using the RBANS as a frame of reference, we are able to evaluate similar cognitive subtests within ADNI in addition to genetic APOE and protein-based biomarkers. Cognitive screener assessments of interest include the Alzheimer's Disease Assessment Scale (ADAS) and the Montreal Cognitive Assessment (MOCA), both of which are widely used for their increased sensitivity in the detection of cognitive changes in older adults. In addition, we will incorporate measures of depression, post-traumatic stress disorder, and traumatic brain injury. Genetic variables of interest include individual compositions of APOE allele variations, as well as Aβ, Aβ 38, Aβ 40, Aβ 42, CSF t-tau, and CSF p-Tau. Though 822 participants were recruited as part of the Alzheimer's Disease Neuroimaging Initiative database, a significant portion of

individuals did not consent to have lumbar punctures or other assessments performed. After accounting for these limitations, 97 individuals with data for all variables of interest will be included in the proposed analyses.

In lieu of a linear analysis approach, a non-linear analysis approach was chosen for the elucidation of relationships between variables of interest at baseline for its specificity in identifying complex and interconnected variable contributions. The CART analysis method was identified as the most appropriate way to study these underlying interactions, in that they are useful when evaluating complex relationships between predictor and response variables. This approach allows for a more in-depth interpretation of existing correlations between a wide breadth of physiological and psychological factors present and their relationship to cognition in two commonly utilized assessments (MOCA and ADAS) for the evaluation of cognitive decline in older adults.

We expect to see a relationship between poor relative cognitive assessment scores and an interaction of APOE compositions, elevated protein accumulations, psychological status, and traumatic brain injury. This expanded snapshot view can help elucidate variables are present in those with AD when compared to those without, allowing for exploration into potentially relevant trends in cognitive measures and biomarkers for AD. A future step, out of the scope of this dissertation's purview, may be to compare extended-duration progressions of dementia over time to variable levels at varying time points.

Conceptual Framework for the Study

This multifaced approach to a proactive line of treatment evaluates alternative methods for identifying high risk cognitive and genetic profiles and using this information to intervene in the cognitive decline trajectory of older adults at risk for dementia. Of note, current

treatments favor a reactive approach to slow disease progression only when symptoms are severe enough to inhibit daily living. While intervention at a later stage of cognitive decline may provide select benefits, this dissertation posits that intervening at an earlier stage of decline may be more effective.

In favor of a proactive approach, this dissertation highlights the efficacy of early intervention for the mediation of cognitive decline in older adults. Previous B Sharp Arts Engagement results have indicated cognitive benefits to those with abnormal age-related cognitive decline who attended a community-arts based program. Our aim is to replicate this same trend while also bring in an added element of exploring which types of cognitive domains were most improved by program attendance. Two separate papers will investigate these trends, over either an acute timeframe or an extended period of time spanning almost a year. Additionally, though aging studies tend to favor a longitudinal approach, this dissertation will also investigate relationships between cognitive and genetic variables of interest at a single timepoint with the support of the ADNI database. Within this large sample size, evaluating commonalities in variables associated with risk for pathological aging may shed light on underlying associations not previously apparent.

Purpose of the Study

This dissertation identifies methods of proactive identification and intervention for dementia related disorders. For groups most at risk for conversion from MCI-AD, a paradigm shift in favor of a proactive treatment approach may be the best way to stave off disease conversion. Regarding identification, the focus is on understanding how traditional neurocognitive screeners may provide us with greater information regarding their relationship to other relevant risk factors for development of dementia. Regarding intervention, the focus

is on elucidating the cognitive domains which are most sensitive to the positive effects of B Sharp, a community arts-based intervention program, over acute and extended time frames. The process of implementing an early approach for AD defense is contingent upon identifying which types of cognitive decline may be best addressed and improved via these non-pharmacological interventions.

Specific Aims

This dissertation centers on how best to identify early-stage risk-for pathological aging and how to use non-pharmacological interventions to slow the trajectory of cognitive decline in those diagnosed with dementia-related disorders. Specifically, using a large-scale dataset we will focus on examining factors commonly tied to the presence of dementia-related diagnoses as a way to identify individuals most as risk for decline. We will also use a smaller applied dataset to evaluate the efficacy of social intervention in those varying in baseline levels of cognitive dysfunction. In order to converge on trends relating to slowed cognitive conversion from MCI to AD, the present dissertation will adopt a holistic approach in the utilization of numerous neuropsychological, neurobiological, environmental, and genetic measures. In applying such an approach, we have a greater ability to more clearly observe trends in pertinent risk factors and efficacy of rehabilitative efforts for older adults at highest risk for conversion.

Specific Aim 1. Establish the relationship between *acute* effects (evening effects of concert) on cognitive changes in visuospatial and auditory-verbal domains and domain-specific subtests in older adults attending a community-arts music-based social program.

Specific Aim 2. Establish the relationship between *extended*-duration effects (9–10-month concert season) on cognitive changes in visuospatial and auditory-verbal domains in older adults attending a community-arts music-based social programs.

Specific Aim 3. Identify common neuropsychological, neurobiological, and genetic variables present in the health profiles of individuals who vary in different levels of cognitive dysfunction in late adulthood.

Organization of the Study

The goal of paper one is to evaluate cognitive domains, specifically visuospatial and auditory-verbal, and domain-specific subtests which may be most susceptible to the benefits of community arts-based intervention on an *acute* timespan. Paper two also aims to evaluate cognitive domains, specifically visuospatial and auditory-verbal, which may be most susceptible to the benefits of community arts-based intervention, over an *extended* timespan. Lastly, paper three shifts the focus from one of early intervention to one of early identification of AD conversion within a wide range of variables applicable to the field of abnormal aging. The utilization of practices aimed to identify common variables present in varied presentations of cognitive decline in late adulthood, in tandem with an earlier application of intervention strategies, may act as a viable proactive non-pharmaceutical approach to alleviating the burden of dementia-related disorders.

Chapter 2

B SHARP ARTS ENGAGEMENT: AN INVESTIGATION INTO ACUTE DOMAIN-SPECIFIC COGNITIVE CHANGES IN A COMMUNITY ARTS PROGRAM FOR PEOPLE WITH DEMENTIA-RELATED DISORDERS

Overview

Current trends show a significant increase in dementia prevalence rates, reflecting a growing need for innovation in areas related to the proactive identification, prevention, and intervention of Alzheimer's disease and related dementias (ADRD). Recently, nonpharmacological interventions have received increased recognition among researchers as a viable option for ADRD prevention and disease modification. One of these interventions, a music-based community engagement program known as B Sharp Arts Engagement®, aims to investigate the acute cognitive effects of short-duration auditory stimulation in both visual and verbal domains-and subtest-specific cognitive changes in older adult populations with ADRD diagnoses. Spanning from 2017-2020, acute cognitive performance changes in verbal and visual domain-specific subtests were evaluated in persons with ADRD who attended symphony performances. Acute cognitive functioning was assessed before and after individual symphony performances ranging from 1.5 to 3 hours in duration. Acute changes of interest include subtest-specific, auditory-verbal (N=67), and visuospatial (N=49) cognitive domains. In a comparison of pre- and post-symphony performance scores (2017-2020), results indicate several statistically significant differences between specific auditory and visuospatial domains and acute domain-specific subtest changes in cognition resulting from auditory stimulation in the B Sharp Arts Engagement program. Specifically, visuospatial domains and visuospatial-specific subtests showed greater acute cognitive benefits after attending an individual symphony performance. These differences support the study hypothesis of acute subtest-

specific differences in RBANS subtest scores immediately before and after symphony attendance within the B Sharp Arts Engagement program. Future research may benefit from increasing sample size and incorporating medication use and diagnostic severity in investigating this relationship.

Introduction

Recent trends in the field of aging and dementia indicate unprecedented increases in dementia prevalence over the past several decades. Within the United States, current research depicts an alarming trajectory in increased rates of Alzheimer's disease and related dementias (ADRD) when comparing the 7 million active ADRD diagnoses recorded in 2012 to the 12 million active diagnoses anticipated by 2040 (Zhu et al., 2021). Such accelerations in ADRD prevalence present a critical need for innovations related to areas of identification, prevention, and intervention in ADRD. While significant efforts have been directed towards advancing pharmacological pursuits to alleviate the progression and onset of ADRD, the application of these endeavors have yielded little to no success. At present, no pharmacological interventions have shown success in delaying ADRD onset or modifying disease progression (Serafino, 2018). Due to the limited efficacy of these pursuits, nonpharmacological interventions have received increased recognition among researchers as a viable alternative in ADRD prevention and modification.

Within the field of nonpharmacological intervention alternatives, community engagement and cognitive enrichment programs appear to be particularly promising as a viable method to ameliorate the effects of accelerated cognitive decline in individuals with ADRD. As research efforts have begun shifting focus towards engagement intervention strategies, outcome efficacy is predominately evaluated within the framework of extended duration cognitive effects. While

these efforts are critical to furthering our understanding of the cognitive correlates impacted in ADRD over time, in exclusively assessing extended duration program changes it can become difficult to disentangle overarching trends in cognition from the effects of an individual's unique and dynamic disease progression trajectory. Specifically, it is important to pinpoint how community engagement and cognitive enrichment programs impact cognition in acute duration representations without the impacts of confounding disease progression influences. Though typically assessed in an extended duration timeframe (>6 months), shorter duration (<10 weeks) engagement interventions have also been shown to improve cognition in ADRD populations. Recently, a groundbreaking study conducted by researchers in Finland investigated the cognitive effects of short-term (consisting of a 1.5-hour session each week for 10 weeks) music engagement intervention in persons with dementia, and found significant cognitive improvements in areas of orientation, episodic memory, attention, executive function, and general cognition in individuals who completed the 10-week program (Särkämö et al., 2014). This reflects an increased need for the consideration of acute community interventions as an effective strategy to slow the progression of cognitive decline associated with dementia.

One such intervention, a music-based community engagement program known as B Sharp Arts Engagement®, may be useful in identifying acute changes in cognitive decline modification associated with enrichment interventions in individuals diagnosed with ADRD. Initially designed to assess the extended effects of cognitive stimulation in those with ADRD, the B Sharp Arts Engagement program also incorporates assessment of acute changes in cognition as a mechanism for understanding the effects of community engagement interventions on cognition directly following each isolated enrichment event. The B Sharp Arts Engagement program also aims to identify the impact of auditory stimulation in slowing

domain-specific (auditory-verbal and visuospatial) and subtest-specific cognitive decline in older adult populations through acute pre- and post-assessment changes in cognition by administering subtests taken from the Repeatable Battery for Assessment of Neuropsychological States (RBANS) (Randolph et al., 1998).

While past results have indicated the benefits of this program in significantly slowing cognitive decline and even improving cognition in older adult symphony attendees with ADRD over an extended timeframe (Davalos et al., 2019), further investigation is required to identify acute differences in domain and subtest specific cognitive changes before and after an individual symphony performance, lasting between 1.5 and 3 hours in duration. The investigation of both domain and subtest specific changes in cognition provide further insight into the mechanisms involved in acute functional changes in cognition. Represented by cognitive domain, areas most heavily impacted in an ADRD diagnosis may not show significant or observable changes in an acute timeframe. However, specific subtests within distinct domains may capture acute functional differences not readily observable with comparisons exclusive to overall season-long cognitive changes. An investigation into specific types of cognition impacted by acute cognitive enrichment may provide an increased understanding into immediate benefits in cognition within a pinpointed timeframe in an individual's unique ADRD progression. This study seeks to elucidate the underlying cognitive areas which stand to benefit most from the B Sharp Arts Engagement program in an acute capacity (1.5-3-hour duration). These insights will allow for the effective implementation of tailored interventions for individuals with low scores in particular areas of cognition.

Methods

Stemming from an arts-focused enrichment program for older adults based out of

Phoenix, AZ (Banner Alzheimer's Institute), the B Sharp Arts Engagement program partnered with the MasterWorks Symphony in Fort Collins, CO for the purpose of providing music-based enrichment and evaluating subsequent cognitive change in older adults with dementia living within Fort Collins and surrounding areas of Larimer County, CO. Participants with dementia diagnoses were recruited with assistance from researchers at Colorado State University and local dementia-focused community organizations. In compliance with Colorado State University's International Review Board and the Helsinki Declaration of 1975, 138 participants consented to enrollment in the B Sharp Arts Engagement program and associated data collection.

Participants with dementia-related diseases were assessed for domain-specific cognitive changes before and after individual MasterWorks symphony performances to identify acute cognitive benefits of cognitive stimulation from symphony attendance. Acute cognitive functioning was assessed before and after individual symphony performances ranging from 1.5 to 3 hours in duration. Administered by trained undergraduate and graduate students from Colorado State University, participants were asked to take part in a series of cognitive subtests throughout the duration of the concert season. Subtests selected from the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) were administered before and after each concert. The RBANS allows for the sensitive detection of holistic and domain-specific cognitive changes in older adults and has been widely used in diagnostic capacities. While 138 participants were recruited for the study over a 3-year period, participant constraints related to health and other factors allowed for acute subtest data collection of 116 pre and post domain-specific subtest comparisons before and after an individual symphony performance. Performances on verbal (N=67) and visuospatial (N=49) subtest scores were analyzed for pre-

and post-event comparisons of change.

Results

In a statistical comparison of domain-specific improvements related to the B Sharp Arts Engagement program over the course of 3 years (2017-2020), trends in acute cognition change were evaluated in RBANS verbal and visuospatial domain subtest scores before and after each MasterWorks symphony performance. The RBANS, a widely utilized tool for the assessment of cognitive decline in older adults, was selected for its high test-retest reliability. Parallel RBANS subtest forms were used before and after each performance to account for test-retest reliability effects. Differences in domain subtest scores were analyzed for a total of 116 subtest comparison points. Differences in preassessment and post assessment RBANS subtest scores were calculated for all who participated in the cognitive assessments. Though a control group was not implemented for the B Sharp Arts Engagement program directed toward those with age-related cognitive decline, past research has indicated an average yearly decline of 3.5% in RBANS total scores in cognitively healthy older adults (Patton, 2004).

Of the 116 individual pre and post assessment change scores analyzed, several analyses reflected statistically significant differences in subtest and domain comparisons before and after attending a symphony performance. When evaluating pre and post visuospatial (coding subtest) scaled score ($N = 49$, $p = 0.0215$) in comparison to pre and post auditory-verbal (list learning, fluency, story memory, and digit span subtests) scaled scores ($N = 67$, $p = 0.28$), greater acute increases in subtest performance were observed in visuospatial domains than in auditory-verbal domains (see Figure 2.1). When assessing pre and post verbal attention and fluid language skills (verbal fluency and digit span subtest scaled scores) ($N = 38$, $p = 0.767$) in comparison to pre and post coding visuospatial (coding subtest) scaled score ($N = 49$, $p = 0.0215$), greater acute

increases in subtest performance were seen in visuospatial attention based-tasks than in verbal attention and fluid language-based tasks (see Figure 2.2). In a comparison of only the pre and post verbal attention and working memory (digit span subtest) scaled score ($N = 17$, $p = 0.288$) in comparison to pre and post visuospatial (coding subtest) scaled score ($N = 49$, $p = 0.0215$), greater acute increases in subtest performance were observed in tasks emphasizing visual attention (coding) when compared to tasks emphasizing verbal working memory (digit span) (see Figure 2.3).

Within the verbal domain, when comparing pre and post verbal immediate recall (story memory and list learning subtests) scaled scores ($N = 29$, $p = 0.045$) to pre and post fluid language skills (verbal fluency subtest) ($N = 21$, $p = 0.4$), greater acute declines in cognitive performance were observed in tasks emphasizing memory recall than in tasks emphasizing fluid language skills (see Figure 2.4). When evaluating pre and post verbal immediate recall subtests emphasizing memory maintenance, story memory ($N = 22$, $p = 0.037$) showed greater acute declines in cognitive performance than list learning ($N = 7$, $p = 1.0$) after attending an individual symphony performance (see Figure 2.5). These findings indicate several statistically significant differences between specific auditory and visuospatial domains and acute domain-specific subtest changes in cognition resulting from auditory stimulation in the B Sharp Arts Engagement program.

Discussion

In lieu of a pharmacological approach with little efficacy, non-pharmacological interventions have received increased interest as a promising approach to the proactive prevention of dementia. This study presents novel insight into the acute cognitive effects of community-engagement interventions with a focus on cognitive stimulation from symphony

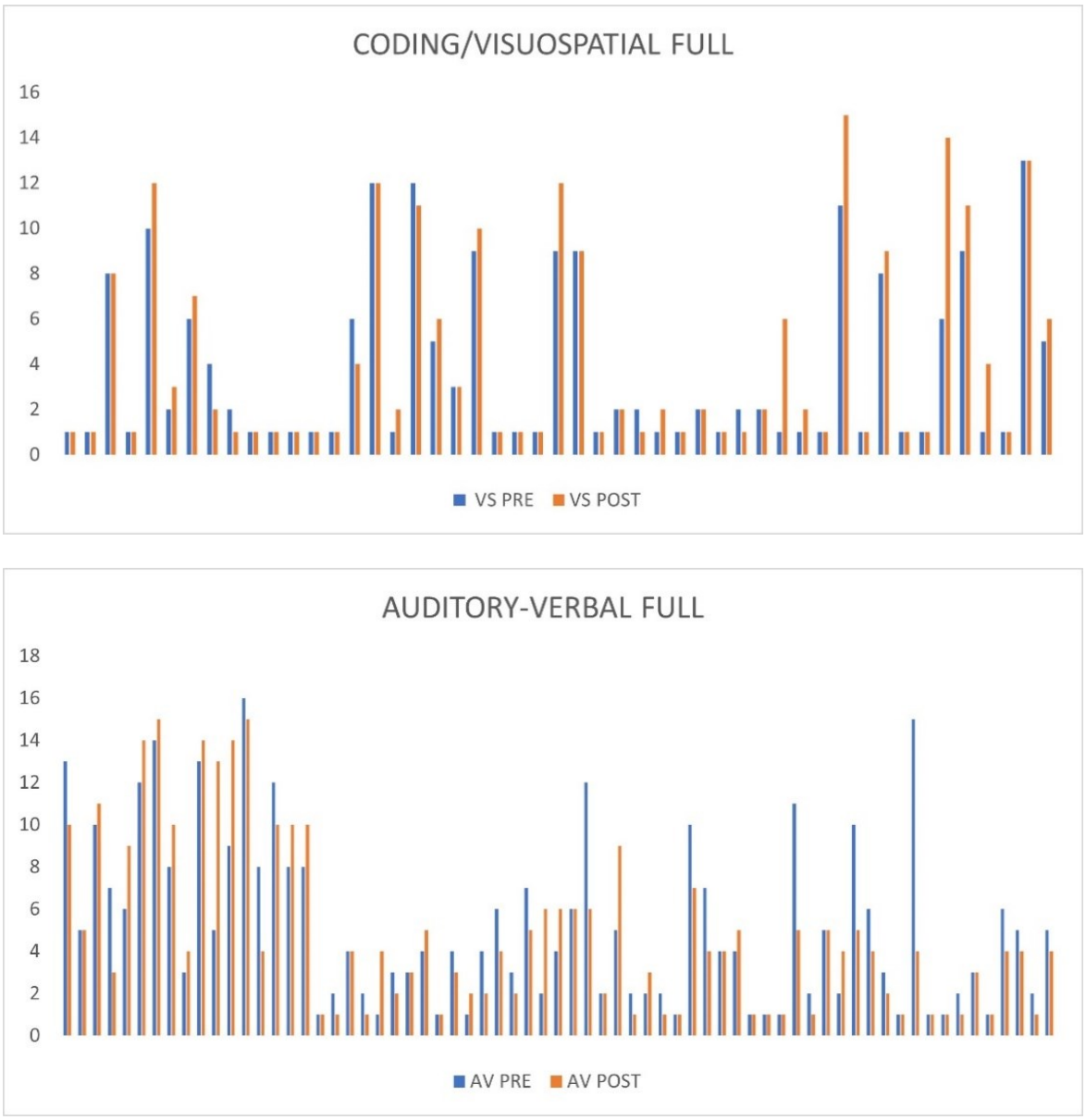
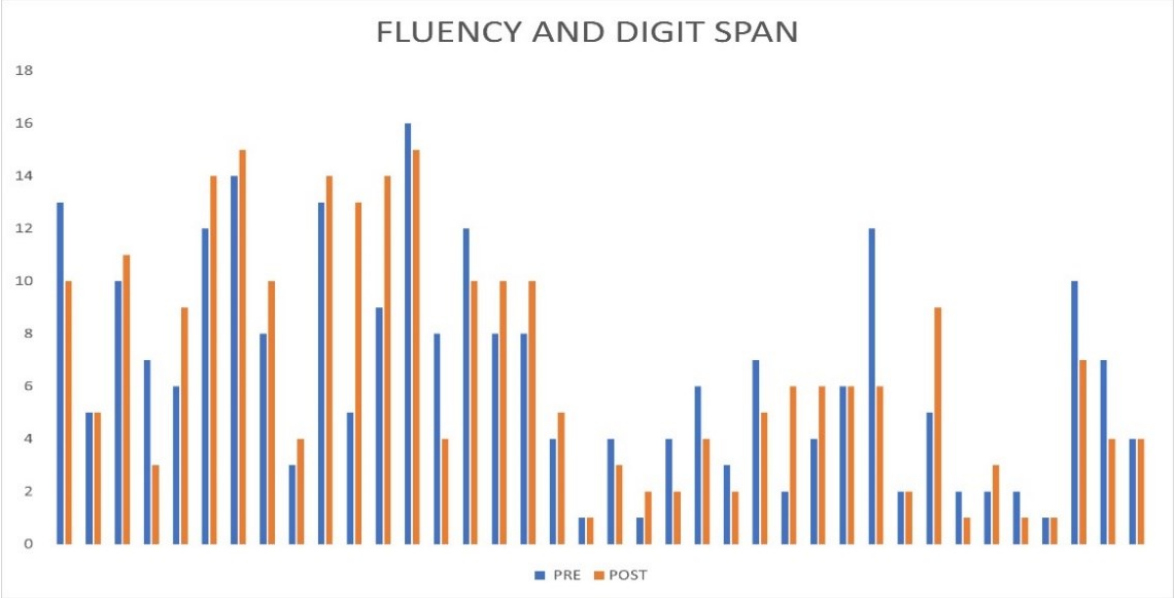


Figure 2.1
A visual comparison between pre and post visuospatial (coding subtest) scaled scores (N = 49, p = 0.0215), and pre and post auditory-verbal (list learning, fluency, story memory, and digit span subtest) scaled scores (N = 67, p = 0.28) to measure differences in the visuospatial domain when compared to the auditory-verbal domain.

performances. Though varied in the trends observed, several significant differences were detected between domains and domain-specific subtests. These differences support the study hypothesis of acute subtest-specific differences in RBANS domain and domain-specific subtest scores immediately before and after symphony attendance within the B Sharp Arts Engagement



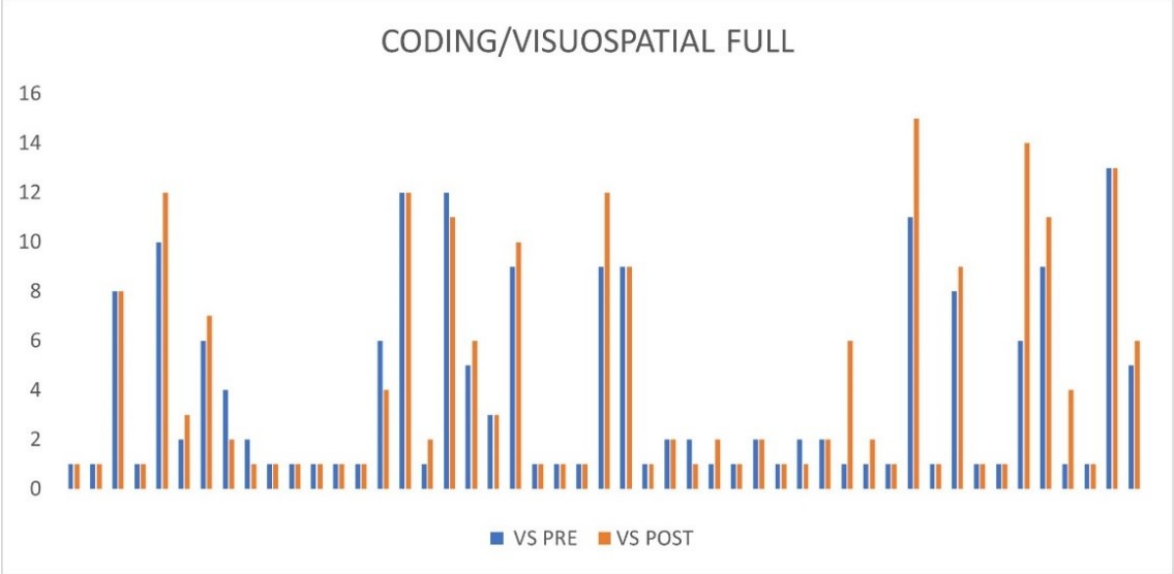
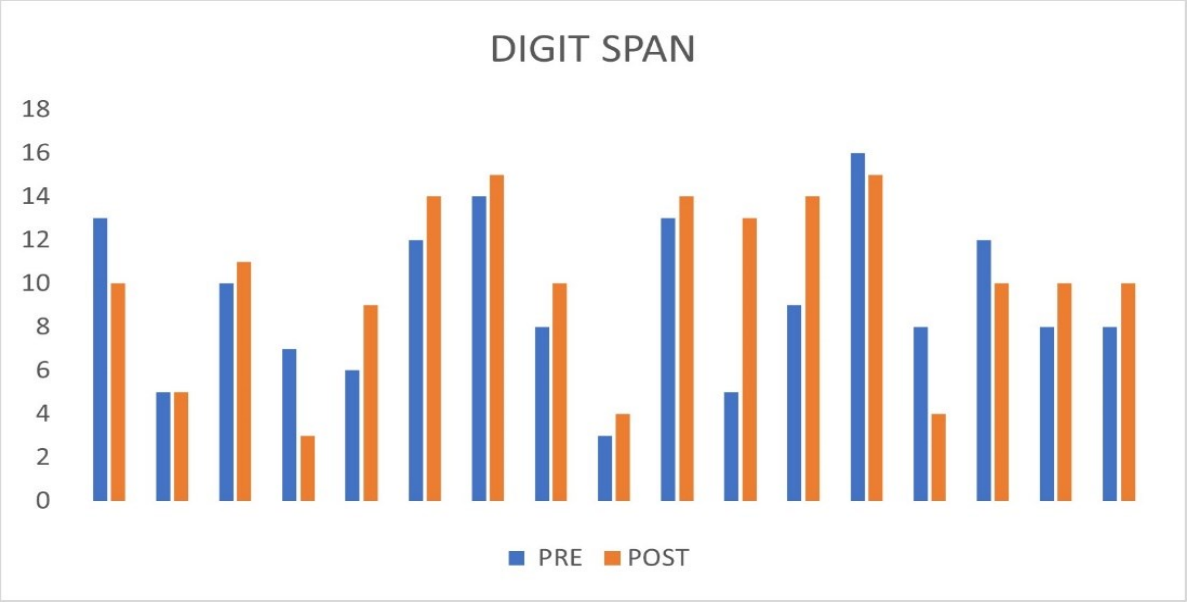


Figure 2.2
A visual comparison between pre and post verbal fluency and digit span subtest scaled scores (N =38, p = 0.767), and pre and post coding subtest scaled scores (N = 49, p = 0.0215) to determine differences in tasks emphasizing visual versus verbal attention and working memory.

program. The findings of this study give rise to common themes regarding the cognitive areas which stand to benefit most from participation in music-based enrichment interventions. The most significant acute cognitive benefits were observed in visuospatial domains, which for the



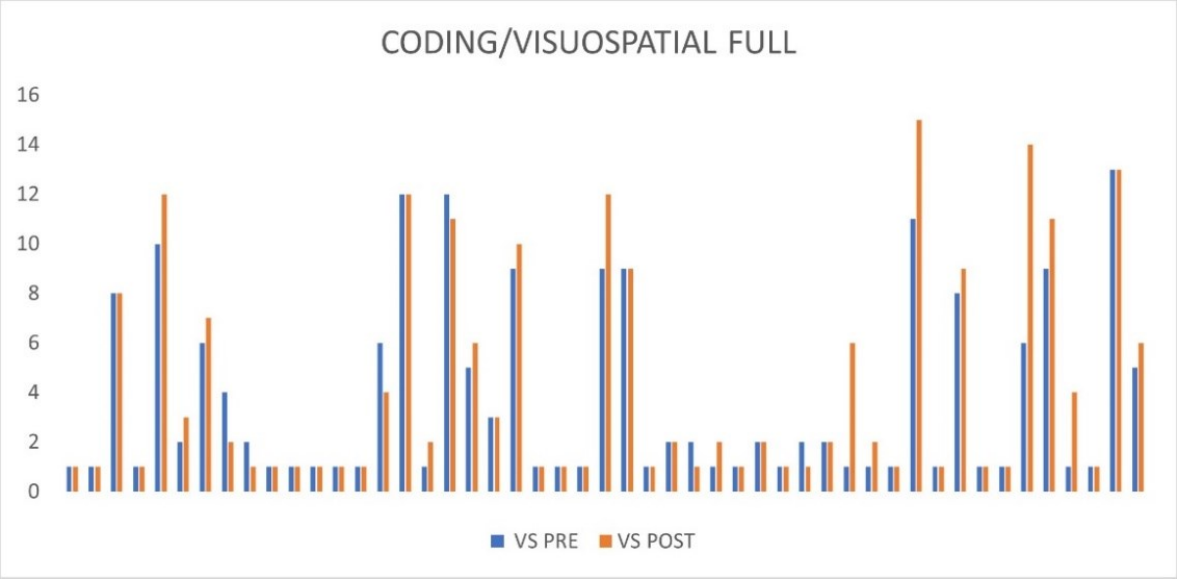


Figure 2.3
A visualization comparison between pre and post digit span subtest scaled scores (N = 17, p = 0.288), and pre and post coding scaled scores (N = 49, p = 0.0215) to measure differences in a task emphasizing verbal attention and working memory (digit span) when compared to a task emphasizing visual attention and working memory (coding).

purposes of this study include only coding subtests. Several logistic and theory-driven variables could impact the observed trends in both domain and subtest-specific changes. Within the visuospatial domain benefits observed, coding is the singular subtest included in the study

Figure 2.4
A visualization comparison between pre and post verbal immediate recall (story memory and list learning subtests) scaled scores (N = 29, p = 0.045), and pre and post verbal fluency scaled scores (N = 21, p = 0.4) to measure differences in tasks emphasizing memory (story memory and list learning) when compared to a task emphasizing fluid language skills (fluency).

which reflects visuospatial domain performance. Therefore, it is important for future studies to compare acute changes in cognitive performance among several visuospatial subtests to gain a better understanding of the mechanisms involved in observed cognitive gains. The coding subtest representing visuospatial cognitive processes appears more sensitive to the acute

Figure 2.5
A visualization comparison of auditory-verbal memory recall between pre and post story memory subtest scaled scores (N = 22, p = 0.037), and pre and post list learning subtest scaled scores (N = 7, p = 1.0) to measure acute performance differences in tasks emphasizing memory maintenance.

benefits of music-based nonpharmacological enrichment intervention. This is perhaps due to the consistent presence of a tangible stimulus, required to successfully complete the coding

subtest. Within subtests assessed, only coding incorporates a physical stimulus to complete the required task. The presence of a physical stimulus, with which one can interact throughout the task, may provide the scaffolding and increased state of cognitive arousal necessary for improved performance over a short duration without needing to heavily rely on memory. Additionally, the coding subtest incorporates a significant number of trials over the course of the task. It is possible the frequent repetitions of identical symbols presented to the participant may impact speed and accuracy, leading to greater increases within an acute timeframe.

Regarding auditory-verbal domains, the contributors of subsequent subtest improvements within auditory-verbal reliant processes are perhaps less apparent. By and large, auditory-verbal domains showed greater levels of decline in subtest performance than visuospatial domain subtests. It may be that, overall, tasks assessed following the arts engagement program show decline, possibly due to a number of reasons. Perhaps this overall pattern of decline is due to the emotional context of the participant's mood following the end of the symphony performance. Many participants reported sadness and hopelessness at the prospect of going home to "normal" life with less enrichment activities directly following such an engaging symphony performance. Many participants also experienced fatigue after the symphony, often due to the late time of day when many participants would typically be asleep. Both fatigue and depressed mood could act as drivers of decline in performance. These effects may become more apparent as decreased performance on subtests requiring greater emphasis on memory or an increase in demand of cognitive arousal required when no stimulus is provided. Further research is needed to adequately determine the efficacy of short-duration music-based enrichment interventions on acute cognitive benefits in individuals with ADRD. These efforts may allow researchers and practitioners to better understand the cognitive substrates associated

with abnormal cognitive decline.

While the exact mechanisms contributing to age-related cognitive decline are not currently understood, this study is able to shed light on important acute domain- and subtest-specific effects of arts-based community-engagement interventions on improving cognition. Still, several limitations of the current study should be noted. First, the B Sharp Arts Engagement program did not include a control group from 2017-2019. Though a control cohort was introduced in the 2019-2020 season, the small sample size was insufficient to adequately relay reliable comparisons between control and dementia groups. Furthermore, this initial study did not consider the effects of individual differences related to severity of cognitive decline. Finally, individual differences in previous and concurrent treatments in the form of medications taken were not factored into domain-specific cognitive outcomes. While often minimally effective in modifying dementia disease progression, there is potential for medication to factor into subsequent cognitive trends.

Future scientific efforts may benefit from adjusting the current experimental design to include a larger sample size to confirm the current study's conclusions. Additionally, future work should include a control group to see the relationship between domain specific benefits in cognition between older adults with normal and abnormal cognitive decline. Subsequent studies should also seek to identify differences in cognitive domains between medicated and non-medicated persons with dementia. Finally, future attention should be given to distinguish between both dementia type and level of severity. While tenuous, these results inform a larger body of research which aims to identify underlying trends in cognition in persons with cognitive decline who attend music-based community interventions.

Funding

This research was funded by the Catalyst for Innovative Partnerships grant program through the Office of the Vice President for Research at Colorado State University and by the Columbine Health Systems Center for Healthy Aging (Pilot Funding for Innovative Research in Aging). Additional funding was provided by Banner Health, Community Foundation of Northern Colorado, Fort Collins Symphony, Home State/Guaranty Bank, International Neuroscience Network Foundation, Kaiser Permanente, Rotary Club of Loveland, Sage Benefit Advisors, and individual community donors. The content is solely the responsibility of the authors and does not necessarily represent the official views of the Office of the Vice President for Research or the Columbine Health Systems Center for Healthy Aging.

Institutional Review Board Statement

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of Colorado State University.

Acknowledgments

Recruitment of participants and support throughout the B Sharp Arts Engagement program would not have been possible without collaboration with Banner Health Stepping Stones Adult Day Program, Larimer County Office on Aging, Alzheimer's Association of Northern Colorado, Fort Collins Symphony, and Dementia Together of Northern Colorado. In addition, the volunteer graduate student research assistants, undergraduate research assistants, and administrative support were critical in supporting the research team. We also thank the anonymous reviewers for their feedback on this manuscript.

REFERENCES

Adbowale, V., Farmer, P., Rose-Quirie, A., Jenkins, P., Greatley, A., Bailey, S. (2014) The pursuit of happiness: A new ambition for our mental health. *CentreForum* 1–61.

Alzheimer's Association. (2020). *Types of Dementia.* Retrieved from https://www.alz.org/alzheimers-dementia/what-is-dementia/types-of-dementia.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders, 5*.

Banner Alzheimer's Institute. Life Enrichment Programs. Banner Alzheimer's Institute Website. http://banneralz.org/education-events/life-enrichment-programs.aspx.

Barkhof, F., van Buchem, M.A. (2016). Neuroimaging in dementia. In: Hodler J, Kubik-Huch RA, von Schulthess GK, eds. *Diseases of the Brain, Head and Neck, Spine*, 79–85.

Chatterjee, H.J., Camic, P.M., Lockyer, B., Thomson, L.J. (2018). Non-clinical community interventions: a systematized review of social prescribing schemes. *Arts & Health 10*:97–123.

Clare, L. & Woods, R.T. (2004). Cognitive training and cognitive rehabilitation for people with early-stage Alzheimer's disease: a review. *Neuropsychological Rehabilitation, 14,* 385-401.

Davalos, D. B., Luxton, I., Thaut, M., & Cross, J. E. (2019). B Sharp—The cognitive effects of a pilot community music program for people with dementia-related disorders. *Alzheimer's and Dementia: Translational Research and Clinical Interventions*, *5*, 592–596. https://doi.org/10.1016/j.trci.2019.08.004

Duff, K., Humphreys-Clark, J.D., O'Bryant, S.E., Mold, J.W., Schiffer, R.B. Sutker, P.B. (2008). Utility of the RBANS in detecting cognitive impairment associated with

Alzheimer's disease: sensitivity, specificity, and positive and negative predictive powers. *Arch Clin Neuropsychol, 23:*603–12.

Farias, S. T., Mungas, D., Reed, B. R., Harvey, D. & DeCarli, C. (2009). Progression of mild cognitive impairment to dementia in clinic- vs community-based cohorts. *Archives of Neurology, 66*, 1151–1157.

Gross, A.L., Rebok, G.W., Unverzagt, F.W., Willis, S.L., Brandt J. (2011). Cognitive predictors of everyday functioning in older adults: Results from the ACTIVE cognitive intervention trial. *J Gerontol B Psychol Sci Soc Sci 66*:557–66.

Hugo, J. & Ganguli, M. (2014). Dementia and Cognitive Impairment: Epidemiology, Diagnosis, and Treatment. *Clinics in Geriatric Medicine, 30*(3), 421-442.

Patton, D.E., Duff, K., Schoenberg, M.R., Mold, J., Scott, J.G., Adams, R.L. (2005). Base rates of longitudinal RBANS discrepancies at one-and two-year intervals in community-dwelling older adults. *Clin Neuropsychol 19*:27–44.

Randolph, C., Tierney, M.C., Mohr, E., Chase, T.N. (1998). The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): preliminary clinical validity. *J Clin Exp Neuropsychol 20*:310–9.

Rinehardt, E., Duff, K., Schoenberg, M., Mattingly, M., Bharucha, K., Scott, J. (2010). Cognitive change on the repeatable battery of neuropsychological status (RBANS) in Parkinson's disease with and without bilateral subthalamic nucleus deep brain stimulation surgery. *Clin Neuropsychol 24*:1339–54.

Särkämö, T., Tervaniemi, M., Laitinen, S., Numminen, A., Kurki, M., Johnson, J.K., & Rantanen, P. (2014). Cognitive, emotional, and social benefits of regular musical activities in early dementia: A randomized controlled study. *The Gerontologist, 54,*

634–650. doi:10.1093/geront/gnt100

Serafino, P. (2018). Another Alzheimer's Drug Fails as Lilly, Astra Halt Tests. Bloomberg Website. Updated June 12, 2018. https://www.bloomberg.com/news/articles/2018-06-12/lilly-astrazeneca-end-trials-as-alzheimerdrug-shows-no-promise.

Woods, B., Aguirre, E., Spector, A. E., & Orrell, M. (2012). Cognitive stimulation to improve cognitive functioning in people with dementia. *Cochrane Database of Systematic Reviews, 2*.

Zhang, Y., Cai, J., An, L., Hui, F., Ren, T., Ma, H., et al. (2017). Does music therapy enhance behavioral and cognitive function in elderly dementia patients? A systematic review and meta-analysis. *Ageing Res Rev 35*:1.

Zhu, Y., Chen, Y., Crimmins, E. M., & Zissimopoulos, J. M. (2021). Sex, Race, and Age Differences in Prevalence of Dementia in Medicare Claims and Survey Data. *The Journals of Gerontology. Series B, Psychological Sciences and Social Sciences, 76*(3), 596–606. https://doi.org/10.1093/geronb/gbaa083

Zissimopoulos, J., Crimmins, E., Clair, P.S. (2015). The value of delaying Alzheimer's disease onset. *Forum Health Econ Policy 18*:25–39.

Chapter 3

B SHARP ARTS ENGAGEMENT: AN INVESTIGATION INTO EXTENDED DOMAIN-SPECIFIC COGNITIVE CHANGES IN A COMMUNITY ARTS PROGRAM FOR PEOPLE WITH DEMENTIA-RELATED DISORDERS

Overview

In recent years, the prevalence of dementia has risen at an alarming rate, prompting accelerated research efforts to stave off cognitive decline in older adults. In stride with these goals, non-pharmacological interventions have gained recognition as a viable method to slow the trajectory of pathological cognitive decline in individuals with dementia. One such intervention, a music-based community engagement program known as B Sharp Arts Engagement®, seeks to investigate the efficacy of auditory-based musical stimulation in slowing domain-specific cognitive decline in these populations. Spanning approximately eight to ten months, auditory and visuospatial domain changes in cognition between preseason and postseason neuropsychological testing were evaluated in thirty-five participants with Alzheimer's disease or related dementias (ADRD) enrolled in the B Sharp Arts Engagement program. No significant differences were observed between changes of auditory and visuospatial RBANS scores from preseason to postseason assessment in all B Sharp Arts Engagement seasons (2015-2019). Results do not support the hypothesized expectation of domain-specific differences in RBANS scores after attending a music-centered community intervention program for improved cognition in individuals with ADRD. No significant differences between seasonal domain scores were observed in any of the four collection years (2015-2016, $p = 0.14$; 2016-2017, $p = 0.57$; 2017-2018, $p = 0.22$; 2018-2019, $p = 0.6$). These findings indicate an overall lack of statistically significant differences between auditory and visuospatial changes in cognition over a concert season. Future research may benefit from

increasing sample size and incorporating medication use and diagnostic severity in investigating this relationship.

Introduction

The prevalence of dementia has risen at an alarming rate in recent years, prompting accelerated research efforts to stave off cognitive decline in older adults. Increasing in both prevalence and incidence each year, rates of Alzheimer's disease or related dementias (ADRD) are expected to double every twenty years according to the World Alzheimer's Report 2020 (Fleming et al., 2020). Such an acceleration warrants attention from researchers and health leaders to reduce this staggering trajectory. Previously, pharmacological interventions have attempted to stave off cognitive decline in older adults with ADRD. However, no such intervention presently exists that can significantly modify the course of ADRD. In addition to limited efficacy, the negative side effects of pharmacological approaches in delaying the onset of ADRD have prompted a shift in focus towards other forms of intervention for older adult populations.

Community-based social prescribing interventions have gained recognition as a viable method to alleviate the accelerated progression of cognitive decline in older adults (Faw et al., 2021). One recent study, reflecting a larger body of research conducted on community-based social prescribing interventions, provides evidence for a decreased trajectory of progression from mild cognitive impairment (MCI) into a diagnosis of ADRD when these interventions were applied (Hughes et al., 2013). Indeed, this field of inquiry may prove to be valuable as a proactive method of "treatment" for those with mild forms of ADRD.

One explanation for the efficacy of social prescribing programs emphasizes the importance of interpersonal interaction for cognitive enrichment benefits (Adbowale et al,

2014). Added improvements in cognition can be observed when combining the benefits of social prescribing with intellectual cognitive stimulation, such as in activities which provide auditory and visuospatial stimulation in addition to social interaction (Foster et al. 2016). Benefits from these types of intervention are typically identified through neuropsychological assessments of cognitive decline over time. Evaluations of cognitive decline are able to detect changes in memory and executive functioning ability, consistently regarded as primary clinical indicators of cognitive decline. The preservation of protective factors against ADRD onset, including the maintenance of normal cognition, may be a viable approach to slow trajectories of progression into ADRD.

One such intervention, a community-based music engagement program known as B Sharp Arts Engagement®, proves to be promising in effectively slowing the trajectory of cognitive decline in individuals diagnosed with ADRD. B Sharp Arts Engagement began in 2015 with the intent to assess the effects of cognitive stimulation in those with ADRD. Cognitive impairment was assessed through the Repeatable Battery for Assessment of Neuropsychological States (RBANS; Randolph et al., 1998) over the course of 8–10-month symphony seasons. The B Sharp Arts Engagement program was shown to significantly benefit cognitive functioning from preassessment to postassessment in older adult symphony attendees with mild to severe levels of ADRD (Davalos et al., 2019).

While gross cognitive improvement was observed, further investigation is needed to identify differences in domain specific cognitive changes (Faw et al., 2021). This study seeks to shed light on differences in efficacy of the B Sharp Arts Engagement program between two cognitive domains (auditory and visuospatial) as defined by the RBANS. Providing insight into the areas of cognition which stand to benefit most from the B Sharp Arts Engagement program

may aid in our current understanding of abnormal cognitive decline and allow for the effective implementation of tailored interventions for individuals with low scores in particular neuropsychological assessment domains.

Methods

Derived from an arts-focused enrichment program for older adults based out of Phoenix, AZ (Banner Alzheimer's Institute), the B Sharp Arts Engagement program, founded in 2015, partnered with the MasterWorks Symphony in Fort Collins, Colorado with the intent of providing music-based enrichment and evaluating cognitive change in older adults with ADRD living within Fort Collins and surrounding areas of Larimer County, Colorado. It is important to note for the purposes of this study, music-based enrichment does not equate to music therapy. B Sharp Arts Engagement is an enrichment and intervention-focused program and is not considered a form of music therapy. Participants with ADRD diagnoses were recruited with assistance from researchers at Colorado State University and local ADRD -focused community organizations. Data was collected as part of a larger study, and all project elements received Institutional Review Board approval for participants providing written informed consent. In compliance with Colorado State University's International Review Board and the Helsinki Declaration of 1975, 138 participants consented to enrollment in the B Sharp Arts Engagement program and associated data collection.

Participants with ADRD were assessed for domain-specific cognitive changes throughout their season-long attendance of MasterWorks symphony performances (typically spanning 8 to 10 months in duration). Administered by trained undergraduate and graduate students from Colorado State University, participants were asked to take part in a series of cognitive assessments throughout the duration of the concert season. The Repeatable Battery for the

Assessment of Neuropsychological Status (RBANS) was administered before and after each concert season. The RBANS, with 4 parallel forms consisting of 12 subtests each, allows for the sensitive detection of holistic and domain-specific cognitive changes in older adults and can be utilized in intervention and clinical trial capacities. While 138 participants were recruited for the study, participant constraints such as poor health, lack of participation, and other factors permitted for the data collection of 87 participants at one testing date time point. Over the course of the program, 35 participants had full RBANS assessment data at two separate time points, representing preseason and postseason assessments, respectively. RBANS domain scores were analyzed for comparisons of change.

Results

In a statistical comparison of domain-specific improvements related to the B Sharp Arts Engagement program over the course of several concert seasons, differences in cognitive change were assessed in RBANS auditory and visuospatial domain scores before and after each season of B Sharp Arts Engagement (2015-2016, 2016-2017, 2017-2018, 2018-2019). The RBANS, a widely utilized tool for the assessment of cognitive decline in older adults, was selected for its high test-retest reliability. Parallel RBANS forms were used before and after each concert season to account for test-retest effects. Differences in both auditory and visuospatial domain scores were analyzed for a total of 35 participants (2015-2016, N = 6; 2016-2017, N = 8; 2017-2018, N = 13; 2018-2019, N = 8).

Differences in preassessment and postassessment RBANS domain scores were calculated for all participants who received both assessments. Positive rate of change scores indicated an increase in a participant's postassessment score when compared to their preassessment score. Though a control group was not implemented for the B Sharp Arts Engagement program

directed toward those with age-related cognitive decline, past research has indicated an average 3.5% decline in RBANS total scores over a 12-month period in cognitively healthy older adult populations (Patton, 2004). Of the 35 participants with pre and post assessments, RBANS domain scores changed at varied rates over the course of each concert season (2015-2016, auditory +6.0%, visuospatial -5.5%, see Figure 3.1; 2016-2017, auditory +11.38%, visuospatial +4.25%, see Figure 3.2; 2017-2018, auditory +5.23%, visuospatial -1.46% , see Figure 3.3; 2018-2019, auditory -0.25%, visuospatial -1.13%, see Figure 3.4).

Further regression analyses (two-sample t-test) were conducted for detection of statistical significance between RBANS domain changes from pre- to post-season. No statistically significant differences between seasonal domain scores were observed in any of the four collection years (2015-2016, $p = 0.14$; 2016-2017, $p = 0.57$; 2017-2018, $p = 0.22$; 2018-2019, $p = 0.6$). These findings indicate an overall lack of statistically significant differences between auditory and visuospatial changes in cognition over a concert season. These trends stand in contrast to acute domain effects in which performance on coding, a visuospatial domain subtest, was statistically significant in suggesting increased benefits received when compared performance on subtests emphasizing auditory-verbal domains.

Discussion

While current research is trending towards non-pharmacological interventions for the proactive prevention of ADRD, few studies have investigated domain-specific changes in cognition resulting from passive participation in music-based community intervention programs. By adding a domain distinction, the present study seeks to expand upon findings indicating the B Sharp Arts Engagement program as having a positive impact on reducing rates of cognitive decline in persons with ADRD (Davalos et al. 2019).

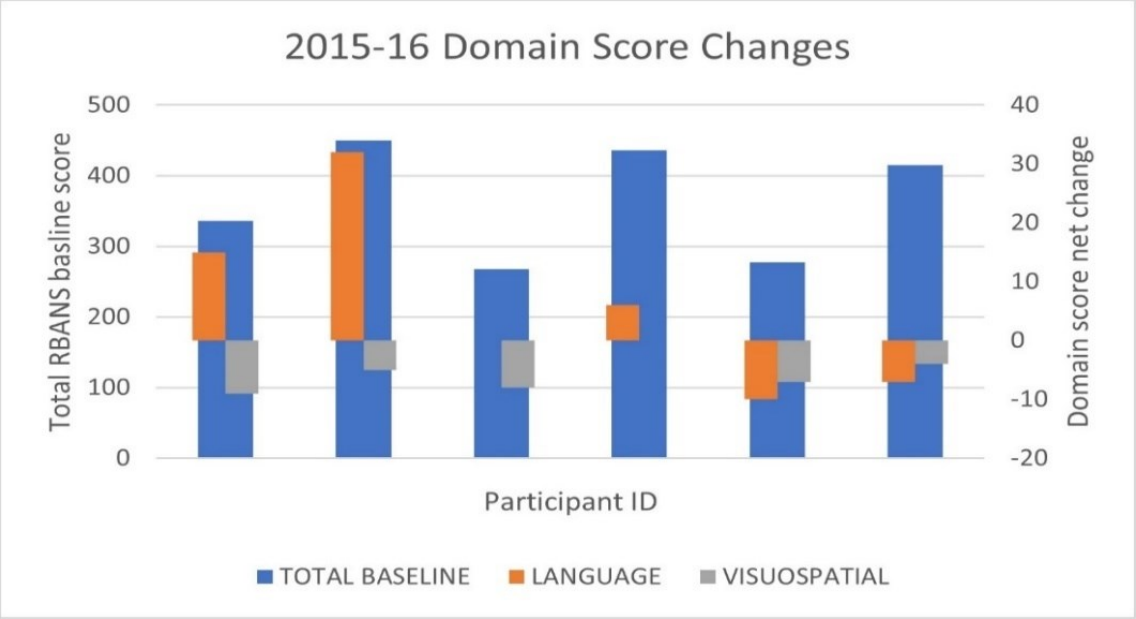


Figure 3.1
Change in 2015-2016 RBANS domain and total index scores per participant from pre- to post-season assessment (N = 6, p = 0.14).

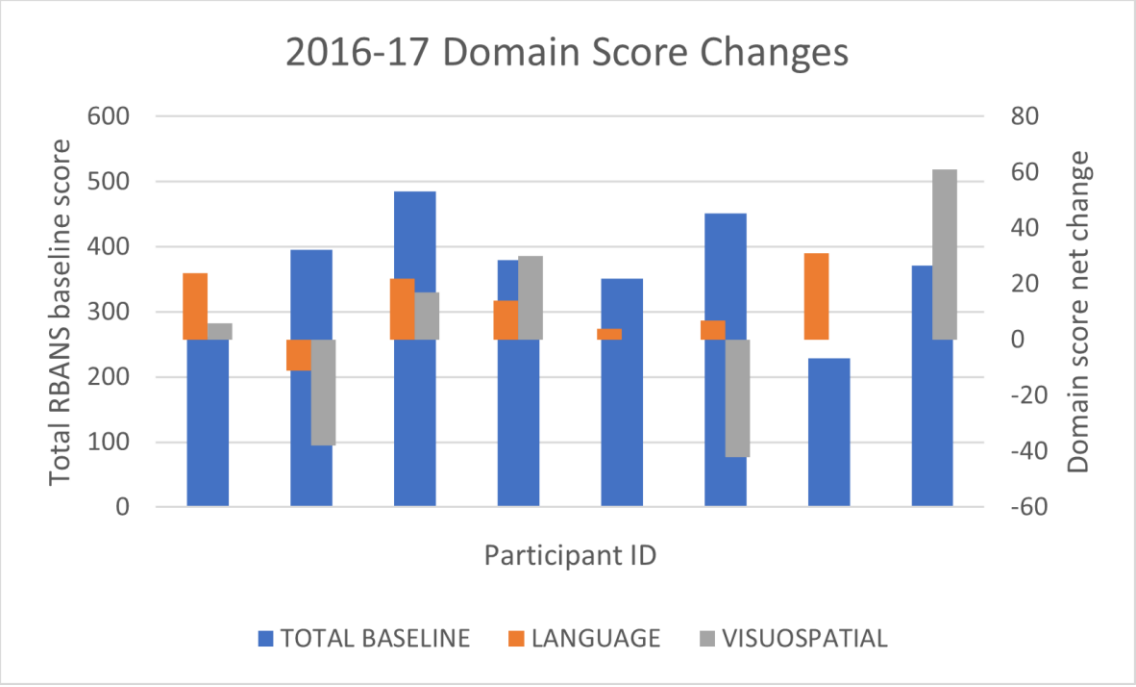


Figure 3.2
Change in 2016-2017 RBANS domain and total index scores per participant from pre- to post-season assessment (N = 8, p = 0.57).

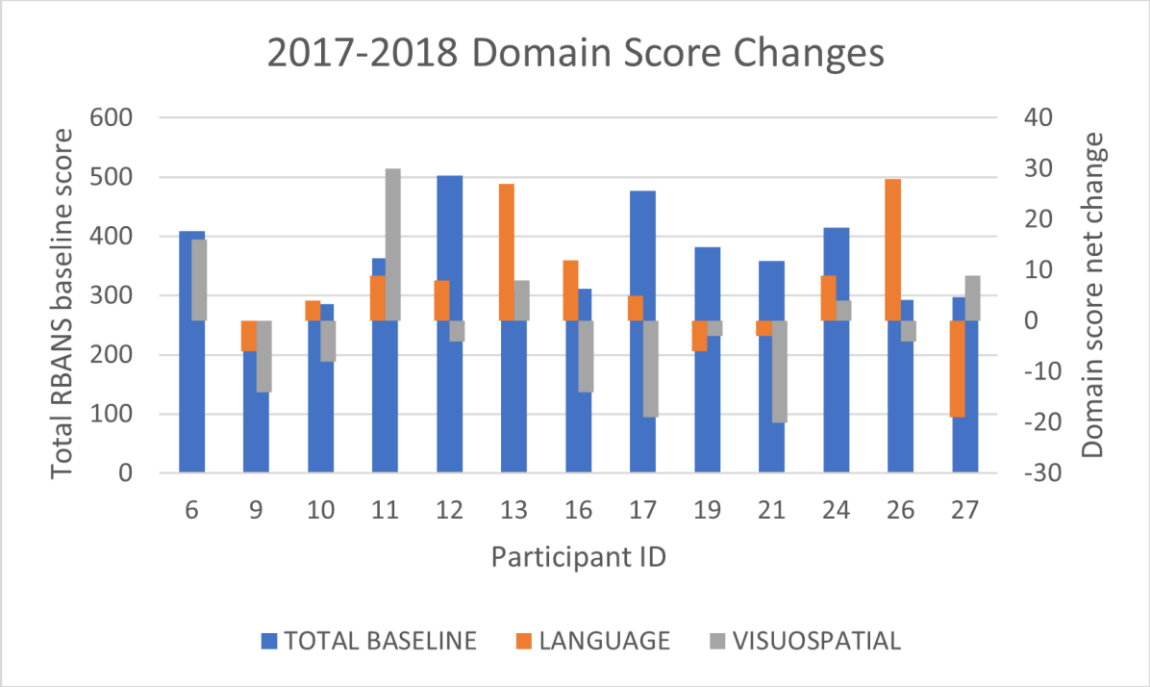


Figure 3.3
Change in 2017-2018 RBANS domain and total index scores per participant from pre- to post-season assessment (N = 13, p = 0.22).

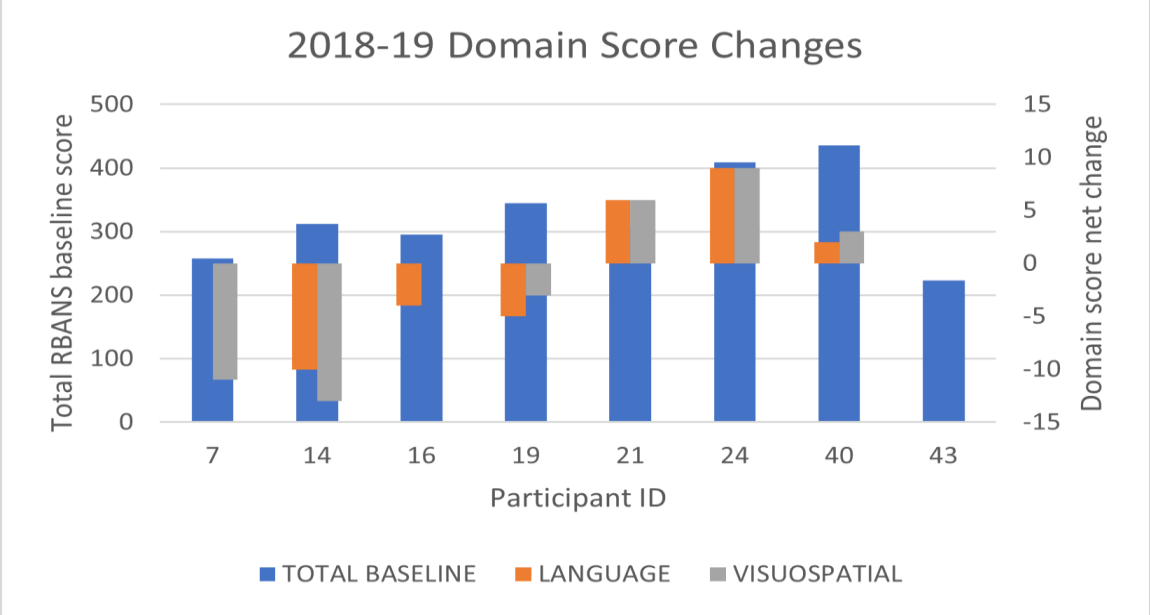


Figure 3.4
Change in 2018-2019 RBANS domain and total index scores per participant from pre- to post-season assessment (N = 8, p = 0.6).

Results for the current study do not support the hypothesized expectation of domain-specific differences in RBANS scores after attending a music-centered community intervention program for improved cognition in individuals with ADRD. No statistically significant differences between pre- and post-season domain scores were observed in any of the four collection years (2015-2016, $p = 0.14$; 2016-2017, $p = 0.57$; 2017-2018, $p = 0.22$; 2018-2019, $p = 0.6$). While these findings indicate an overall lack of statistically significant differences between auditory and visuospatial changes in cognition over concert seasons, it should be noted auditory-based cognition improved to a greater extent than visual-based cognition in three seasons, with the 2015-2016 season approaching significance. And in the 2018-2019 season, when both auditory and visual cognition showed a slight decrease over the concert season, the decrease was smaller in the auditory domain than visual domain.

Currently, there is an inadequate understanding as to the exact mechanisms of improved cognition in older adult populations. This is in part due to the complexity of cognition, which can rarely be isolated from peripheral variables. While this study was able to shed light on an important facet of the domain-specific changes associated with non-pharmacological interventions, several limitations should be noted. No control group was implemented from 2015-2019 in the B Sharp Arts Engagement program. While a control population was included in the 2019-2020 season, the sample size was not large enough to adequately power a meaningful comparison and pre- and post-testing was not sufficiently executed due to the COVID-19 pandemic. Future studies may benefit from increasing sample size in the investigation of this relationship. Due to the lack of a control group, it is unclear how domain differences in persons with ADRD compare to persons without ADRD. Additionally, the present study did not consider differences in the type or level of severity in ADRD diagnosis.

Finally, the use of medication for ADRD-symptom management was not considered in this initial investigation. However minimal in modifying the course of ADRD progression, the beneficial effects of pharmacological treatment may have contributed to resulting cognitive trends.

Future research may benefit from minimizing these limitations by adjusting the experimental design implemented in this study. Subsequent studies should seek to identify differences in cognitive domains between medicated and non-medicated persons with ADRD. Further considerations should be made to distinguish ADRD type and level of severity. Finally, the implementation of both a control group and a larger sample size may aid in increasing the validity of conclusions drawn. While not statistically significant, these results inform an overall body of research which aims to identify underlying trends in cognition present in persons with ADRD who attend music-based community interventions.

Funding

This research was funded by the Catalyst for Innovative Partnerships grant program through the Office of the Vice President for Research at Colorado State University and by the Columbine Health Systems Center for Healthy Aging (Pilot Funding for Innovative Research in Aging). Additional funding was provided by Banner Health, Community Foundation of Northern Colorado, Fort Collins Symphony, Home State/Guaranty Bank, International Neuroscience Network Foundation, Kaiser Permanente, Rotary Club of Loveland, Sage Benefit Advisors, and individual community donors. The content is solely the responsibility of the authors and does not necessarily represent the official views of the Office of the Vice President for Research or the Columbine Health Systems Center for Healthy Aging.

Institutional Review Board Statement

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of Colorado State University.

Acknowledgments

Recruitment of participants and support throughout the B Sharp Arts Engagement program would not have been possible without collaboration with Banner Health Steppingstone Adult Day Program, Larimer County Office on Aging, Alzheimer's Association of Northern Colorado, Fort Collins Symphony, and Dementia Together of Northern Colorado. In addition, the volunteer graduate student research assistants, undergraduate research assistants, and administrative support were critical in supporting the research team. We also thank the anonymous reviewers for their feedback on this manuscript.

REFERENCES

Adbowale, V., Farmer, P., Rose-Quirie, A., Jenkins, P., Greatley, A., Bailey, S. (2014). The pursuit of happiness: A new ambition for our mental health. *CentreForum* 1–61.

Alzheimer's Association. (2020). *Types of Dementia.* Retrieved from https://www.alz.org/alzheimers-dementia/what-is-dementia/types-of-dementia

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders, 5*. https://doi.org/10.1176/appi.books.9780890425596

Banner Alzheimer's Institute. Life Enrichment Programs. Banner Alzheimer's Institute Website. http://banneralz.org/education-events/life-enrichment-programs.aspx.

Barkhof, F., van Buchem, M.A. (2016). Neuroimaging in dementia. In: Hodler J, Kubik-Huch RA, von Schulthess GK, eds. *Diseases of the Brain, Head and Neck, Spine*, 79–85. https://doi.org/10.1007/978-3-319-30081-8_10

Chatterjee, H.J., Camic, P.M., Lockyer, B., Thomson, L.J. (2018). Non-clinical community interventions: a systematised review of social prescribing schemes. *Arts & Health 10*:97–123. https://doi.org/10.1080/17533015.2017.1334002

Clare, L. & Woods, R.T. (2004). Cognitive training and cognitive rehabilitation for people with early-stage Alzheimer's disease: a review. *Neuropsychological Rehabilitation, 14,* 385-401.https://doi.org/10.1080/09602010443000074

Davalos, D. B., Luxton, I., Thaut, M., & Cross, J. E. (2019). B Sharp—The cognitive effects of a pilot community music program for people with dementia-related disorders. *Alzheimer's and Dementia: Translational Research and Clinical Interventions*, *5*, 592–596. https://doi.org/10.1016/j.trci.2019.08.004

Duff, K., Humphreys-Clark, J.D., O'Bryant, S.E., Mold, J.W., Schiffer, R.B. Sutker, P.B.

(2008). Utility of the RBANS in detecting cognitive impairment associated with Alzheimer's disease: sensitivity, specificity, and positive and negative predictive powers. *Arch Clin Neuropsychol, 23:*603. https://doi.org/10.1016/j.acn.2008.06.004

Farias, S. T., Mungas, D., Reed, B. R., Harvey, D. & DeCarli, C. (2009). Progression of mild cognitive impairment to dementia in clinic- vs community-based cohorts. *Archives of Neurology, 66*, 1151–1157. https://doi.org/10.1001/archneurol.2009.106

Faw, M. H., Luxton, I., Cross, J. E., & Davalos, D. B. (2021). Surviving and Thriving: Qualitative Results from a Multi-Year, Multidimensional Intervention to Promote Well-Being among Caregivers of Adults with Dementia. *Int. J. Environ. Res. Public Health, 18,* 4755. https://doi.org/10.3390/ijerph18094755

Fleming, R., Zeisel, J., & Arch, K. B. B. (2020). World Alzheimer Report 2020 Design, Dignity, Dementia: Dementia-related design and the built environment. *Alzheimer's Disease International, 2*.

Foster, B., Pearson, S., & Berends, A. (2016). 10 Domains of Music Care: A Framework for Delivering Music in Canadian Healthcare Settings (Part 3 of 3). *Music and Medicine*, 8(4), 199-206. https://doi.org/10.47513/mmd.v8i4.415

Gross, A.L., Rebok, G.W., Unverzagt, F.W., Willis, S.L., Brandt J. (2011). Cognitive predictors of everyday functioning in older adults: Results from the ACTIVE cognitive intervention trial. *J Gerontol B Psychol Sci Soc Sci 66*:557–66. https://doi.org/10.1093/geronb/gbr033

Hughes, T.F., Flatt, J.D., Fu, B., Chang, C.C., Ganguli, M. (2013). Engagement in social activities and progression from mild to severe cognitive impairment: the MYHAT study. *Int Psychogeriatrics 25*:587–95. https://doi.org/10.1017/S1041610212002086

Hugo, J. & Ganguli, M. (2014). Dementia and Cognitive Impairment: Epidemiology, Diagnosis, and Treatment. *Clinics in Geriatric Medicine, 30*(3), 421-442. https://doi.org/10.1016/j.cger.2014.04.001

Patton, D.E., Duff, K., Schoenberg, M.R., Mold, J., Scott, J.G., Adams, R.L. (2005). Base rates of longitudinal RBANS discrepancies at one-and twoyear intervals in community-dwelling older adults. *Clin Neuropsychol 19*:27–44. https://doi.org/10.1080/13854040490888477

Prince, M., Wimo, A., Guerchet, M., Ali, G.C., Wu, Y.T., Prina, M. (2015). World Alzheimer Report 2015. The Global Impact of Dementia. *Alzheimer's Disease International..*

Randolph, C., Tierney, M.C., Mohr, E., Chase, T.N. (1998). The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): preliminary clinical validity. *J Clin Exp Neuropsychol 20*:310–9. https://doi.org/10.1076/jcen.20.3.310.823

Rinehardt, E., Duff, K., Schoenberg, M., Mattingly, M., Bharucha, K., Scott, J. (2010). Cognitive change on the repeatable battery of neuropsychological status (RBANS) in Parkinson's disease with and without bilateral subthalamic nucleus deep brain stimulation surgery. *Clin Neuropsychol 24*:1339–54. https://doi.org/10.1080/13854046.2010.521770

Serafino, P. (2018). Another Alzheimer's Drug Fails as Lilly, Astra Halt Tests. Bloomberg Website. https://www.bloomberg.com/news/articles/2018-06-12/lilly-astrazeneca-end-trials-as-alzheimerdrug-shows-no-promise.

Woods, B., Aguirre, E., Spector, A. E., & Orrell, M. (2012). Cognitive stimulation to improve cognitive functioning in people with dementia. *Cochrane Database of Systematic Reviews, 2*. https://doi.org/10.1002/14651858.CD005562.pub2

Zhang, Y., Cai, J., An, L., Hui, F., Ren, T., Ma, H., et al. (2017). Does music therapy enhance behavioral and cognitive function in elderly dementia patients? A systematic review and meta-analysis. *Ageing Res Rev 35*:1. https://doi.org/10.1016/j.arr.2016.12.003

Zissimopoulos, J., Crimmins, E., Clair, P.S. (2015). The value of delaying Alzheimer's disease onset. *Forum Health Econ Policy 18*:25–39. https://doi.org/10.1515/fhep-2014-0013

Chapter 4

A NON-LINEAR APPROACH TO ESTABLISHING PATTERNS IN BIOLOGICAL, ENVIRONMENTAL, AND COGNITIVE RISK-FACTOR INTERACTIONS IN HIGH-RISK OLDER ADULTS WITHOUT DEMENTIA

Overview

While incidences of dementia have accelerated in recent decades, the relationship between pre-dementia cognition and trends in underlying mechanisms remains unclear. Elucidating trends in biological, environmental, and psychological underpinnings of dementia-related disorders may provide novel evidence relevant for early intervention. The aim of this study is to establish a relationship between psychological, environmental, and biological risk-factor variables on two widely implemented cognitive decline and dementia assessment screener scores, MOCA and ADAS. Statistical analysis is conducted on a data set obtained from the ADNI-DOD database, which consists of high-risk veterans who did not have baseline dementia diagnoses. Utilizing a Classification and Regression Tree (CART) analysis approach, we observe trends in assessment screener scores and risk-factor presentation interactions. Our analysis further indicates that while the detection of risk-factor patterns between the MOCA and ADAS may be subtle, both assessments show potential utility in detecting novel and overlapping risk-factor characteristics common in older adults with normal and mildly declining cognition. Identifying the interaction and presentation of these factors as either contributors to or buffers against progression into cognitive decline could be invaluable in recognizing profiles of healthy aging without requiring invasive and time-consuming procedures.

Introduction

Incidences of dementia have risen to become a significant burden throughout the world. Rapid increase in daily rates of dementia diagnoses has further emphasized a need for

interventions which might modify the accelerated progression of cognitive decline related to dementia. Currently, clinical therapies have not shown great promise in staving off the progression of cognitive decline in older adults. The lack of efficacy of therapies may be due to the complexity in individual etiological variability of the disease or due to difficulties with early identification of dementia-related disease, when individuals might be most receptive to therapies (Gamberger et al., 2017). For this reason, there is a pressing need for early identification of risk factors related to the onset of dementia (Andrews et al., 2021). While the importance of such research is evident, relationships between pre-dementia cognition and trends in underlying mechanisms remains unclear. Elucidating trends in the biological and psychological underpinnings of dementia-related disorders may provide novel evidence relevant for early intervention.

The most common form of dementia, Alzheimer's disease (AD), serves as a central area of interest for the study of dementia. Within the context of neurobiology, AD is associated with neurodegeneration and increases in both intraneuronal neurofibrillary tangles of phosphorylated tau protein and extracellular Aβ plaque deposition (Hampel et al., 2004; Toledo et al., 2013). Along with neurodegenerative processes, factors related to age, brain injury, familial history, and expression of the apolipoprotein E (APOE) ε4 allele variant have become prevalent in identifying risk for AD (Samtani et al., 2013; Weiner et al., 2017). A common predictive risk factor of AD, mild cognitive impairment (MCI), can serve as an intermediate step between normal cognitive decline associated with age and abnormal cognitive decline seen in dementia. Characterized by comparatively normal functioning in activities of daily living with an absence of dementia, MCI proves to be a promising area of study for earlier identification and intervention of relevant risk factors. Rather than the commonly implemented

reactive approach, typically resulting in suboptimal benefits of intervention, a proactive approach towards early intervention may allow for increased efficacy in staving off significant cognitive decline.

Cognitive decline related to dementia is typically identified through neuropsychological assessment. While numerous assessments focus on identifying cognitive decline in older adults, this study will focus on two widely implemented cognitive assessments. The Montreal Cognitive Assessment (MOCA) and the Alzheimer's Disease Assessment Scale (ADAS) are commonly considered "gold standard' measures for the detection of dementia-related disorders (Schrag & Schott, 2012). Both screeners are known for their ease in administration and interpretation, quick duration, and sensitivity in recognizing declines in cognition (Podhorna et al., 2016). While cognitive measures of decline in older adults, such as the ADAS and MOCA, are well-established, the relationship between genetic, biological, and psychologically rooted risk factors lacks sufficient investigation. Identifying differences in these relationships between healthy and MCI populations may provide insight into underlying mechanisms present in early cognitive decline among older adults (Landau et al., 2010). The identification of such trends may allow for increased efficacy in proactive intervention and a decreased need for invasive biological sample collection (blood and cerebrospinal fluid) in favor of non-invasive cognitive screeners (Amoroso et al., 2019). Understanding the relationship between current cognitive screeners and biological risk factors that are typically not employed until much later in the course of dementia, if ever, may promote a more timely and accurate detection of subtle symptomatic differences in dementia-related decline. Early detection would potentially allow for preventative, customized interventions best suited for each individual patient (Veitch et al., 2019).

To investigate this line of inquiry, this study utilizes data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database to elucidate underlying mechanisms of cognitive decline as they relate to common neuropsychological screeners for the assessment of dementia. The ADNI database includes a comprehensive set of variables related to the identification of risk factors for AD, including cerebrospinal fluid (CSF), positron emission tomography (PET) scan, and cognitive measures. One aspect of ADNI, referred to as the Department of Defense Alzheimer's Disease Neuroimaging Initiative (ADNI-DOD), focuses on factors of healthy cognition and mild cognitive decline in 400 Vietnam War veterans. ADNI-DOD aims to identify the impact of traumatic brain injury (TBI), posttraumatic stress disorder (PTSD), mood disorders, amyloid burden, structural changes, and functional cognitive changes on cognitive decline in a veteran population. Often sustained as a result of combat, both TBI and PTSD are commonly seen in war veteran populations and are suggested to act as a catalyst for early-onset AD due to their impact on worsening cognitive functioning and neurodegenerative disease (Mohamed et al., 2018, 2019; Weiner et al., 2017). While both TBI and PTSD are related to increased risk of developing AD, more work needs to be done regarding the relationship between these risk factors and the presence of Aβ and other relevant biomarkers.

This dataset provides an invaluable look into numerous variables related to healthy and mildly impaired cognition in a population with a significantly increased susceptibility for dementia. Based on neurocognitive assessment scores indicating either healthy or impaired cognition, we can identify trends present in high-risk populations who are aging successfully rather than abnormally. While highly important, it should be noted that trends in populations possessing elevated risk based on an increased presence of TBI and PTSD may not necessarily be generalizable to a larger population of older adults. That being said, this research allows us

to assess individuals who are high on risk factors for dementia, yet do not meet criteria for dementia. Therefore, analyzing this population may contribute to a growing body of work surrounding distinct trends in characteristics related to healthy and abnormal cognitive decline based on differing levels of risk.

The aim of this study is to establish a relationship between psychological, genetic, and biomarker variables on two widely implemented cognitive decline and dementia assessment screener scores (MOCA, ADAS). Such relationships may indicate greater sensitivity in one assessment over another in recognizing underlying mechanisms of cognitive decline and dementia in older adults, which may in turn be useful in clinical application (Llano et al., 2011). Our a priori hypothesis is that participants with a greater number of risk factors, such as existing psychopathology, traumatic brain injury, the APOE ε4 allele, and certain elevated protein levels will score lower on cognitive assessments geared towards the identification of dementia. Rather than establishing a trajectory of dementia progression, the goal of this study is to gauge the level of sensitivity in which two commonly administered neuropsychological assessments detect risk factors widely accepted to be contributors to dementia. In an applied setting, administering an assessment with greater sensitivity to the presence of genetic variants, protein accumulation, and psychopathologies may arise as an effective alternative to more invasive collection methods.

Methods

ADNI Database Overview

The data utilized for the preparation of this inquiry were acquired through the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. Within ADNI, the United States Department of Defense Alzheimer's Disease Neuroimaging Initiative (ADNI-DOD)

dataset provided insight into the effects of combat-related risk factors on future dementia progression. The initiative, started in 2003 and, sponsored by the United States Department of Defense, was implemented for the widespread evaluation of relevant predictors for AD prevention in a cohort of older adult Vietnam War veterans with and without mild cognitive impairment (MCI). ADNI-DOD serves as a retrospective, multimodal, nonrandomized study comprised of Vietnam War veterans with a primary purpose of identifying potential risk factors often occurring in combat (i.e., TBI, PTSD) in the development of Alzheimer's Disease.

Datasets Analyzed

Our sample consisted of 97 subjects from the ADNI-DOD dataset with little to no age-related cognitive impairment. All subjects had MOCA, ADAS, GDS, TBI, APOE, and CSF biomarker data collected at study baseline.

Study Participants

Participants consisted of military veterans ranging from 60-80 years in age with normal to mildly impaired cognition with or without post-traumatic stress disorder (PTSD). Additionally, some of the included individuals had mild to moderate non-penetrating traumatic brain injuries (TBI) relating either to military service or other trauma. Participants were excluded for potential confounding variables, such as psychotic illness, substance abuse, or discomfort with the required MRI testing and lumbar puncture. After excluding participants without data for all variables of interest, 97 individuals from this dataset are included in the following analyses.

Variables of Interest

Measures include a range of neuropsychological and lumbar puncture-based CSF methods to assess variables of interest. Consistent with the study aim of identifying

relationships between risk factor variables present at a single time point for timely diagnostic and early intervention purposes, only data collected at baseline is considered for analysis (Abdullah et al., 2020).

Neuropsychological Measures

For the present study, neuropsychological measures of interest include the Alzheimer's Disease Assessment Scale (ADAS) and the Montreal Cognitive Assessment (MOCA), both of which are widely used for their increased sensitivity in the detection of cognitive changes in older adults. Additionally, the Geriatric Depression Scale (GDS) and the Clinician-Administered PTSD Scale (CAPS) within DSM-IV were also included as psychological measures of interest related to pathological aging.

CSF Measures

Cerebrospinal fluid (CSF) was obtained at baseline using lumbar puncture. Subsequent analyses were performed in accordance with established ADNI methods. Using an xMAP multiplex immunoassay platform, assays from CSF collection indicated levels of p-Tau, Tau, Aβ, Aβ 38, Aβ 40, Aβ 42. A predictive biomarker signature of pathological AD was used in tandem with an APOE ε4 allele risk model.

Statistical Analysis

In lieu of a linear analysis approach, a non-linear analysis approach was implemented for all variables of interest. A non-linear approach was chosen for the elucidation of relationships between variables of interest at baseline due to its specificity in identifying complex and interconnected variable contributions. A decision tree analysis was identified as the most appropriate non-linear method of analysis for this study, as it is a powerful machine learning algorithm that can be used for classification and non-linear regression tasks (Tong et al., 2017).

Decision trees are useful when evaluating complex relationships between predictor and response variables. A tree diagram analysis allows for a more in-depth interpretation of any existing correlations between a wide breadth of physiological and psychological factors present and degree of cognitive decline related to two commonly utilized assessments (MOCA and ADAS) for the evaluation of cognitive decline in older adults. The default stopping criterion is cp=0.01 where cp represents complexity parameters. All analyses were performed using R software version 4.0.2.

Results

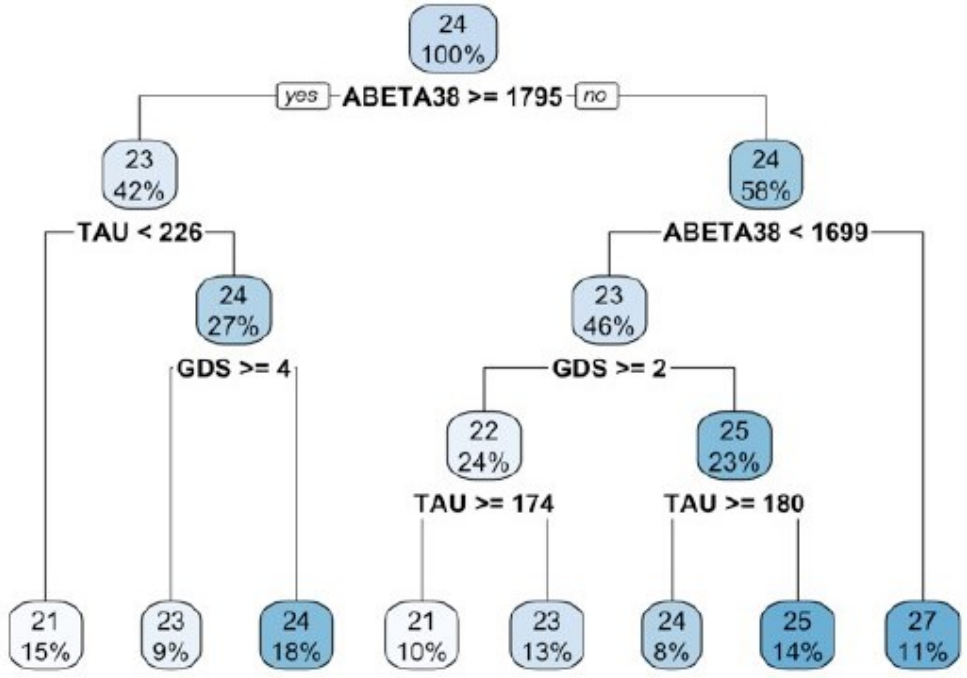
We hypothesized that two commonly used screeners for the detection of pathological aging would show similarities in detecting select factors for identifying risk for dementia as well as detect subtle differences in sensitivity to other specific risk-factors. Understanding the nuances in detection of each screener could contribute to the creation of tailored individual prediction models of substrates underlying cognitive decline assessment scores. Specifically, we expected to see a relationship between poor relative cognitive assessment scores and APOE compositions, elevated protein, and the presence of underlying psychopathologies.

Trends in Neuropsychological Cognitive Assessment Performance

Implementing a Classification and Regression Tree (CART) Analysis Among Baseline Clinical and Biomarker Variables Reflected in MOCA Scores

Using a non-linear decision tree analysis approach, we can identify a correlation between psychological and biomarker variables and degree of cognitive decline related to MOCA scores. Variables of high importance to MOCA score were Aβ 38, Tau, GDS, Aβ 40, p-Tau, PTSD, Aβ, and Aβ 42. Based on the MOCA score reported, several specific biomarker trends can be identified, accounting for approximately 98% of subjects. Using the partition model

seen in Figure 3.1, MOCA scores can be predicted based on a series of binary splits. The first split (Aβ 38 >=1795) divides the decision space into two regions. The first second-level split (Tau < 226) then divides the (Aβ 38 >= 1795) region into two distinct sub-regions, while the second second-level split (Aβ 38 < 1699), divides the (Aβ 38 =< 1795) region into two further sub-regions. These divisions will continue until they reach a point of relative insignificance in association. Using this model, it is possible to identify a specific MOCA score as having one or two likely paths for predicting underlying psychological and biomarker-based trends (see Figure 4.1).



For the first node, partition the data set at ABETA38 would give the smallest SSE.
Split at PTSD=1.5, $SSE = \sum_{PTSD_i=1}(MOCA_i - 24)^2 + \sum_{PTSD_i=2}(MOCA_i - 23)^2 = 815.$
Split at ABETA38 = 1795, $SSE = \sum_{AEBTA38_i<1795}(MOCA_i - 24)^2 + \sum_{ABETA38_i\geq 1795}(MOC_i - 23)^2 = 805.$
Split at TAU = 175, $SSE = \sum_{TAU_i<175}(MOCA_i - 24)^2 + \sum_{TAU_i\geq 175}(MOC_i - 23)^2 = 817.$

Figure 4.1
CART analysis graph for trends in variables related to MOCA scores. Binary nodes are shown with their respective condition, the percentage of sample size accounted for, and the average MOCA score calculated for the given condition. Each right-sided branch indicates an

affirmation of the given condition at each node, while each left-sided branch indicates a lack of affirmation for the given condition at each node. CART = Classification and Regression Tree, MOCA = Montreal Cognitive Assessment.

In an applied setting, an individual's particular score on the MOCA may lend itself to one type of profile which encompasses real-world trends in a composite genetic, biological, environmental, and psychological profile in relation to the cognitive correlates assessed (e.g., MOCA). For example, if an individual receives a score of 24 on the MOCA, results indicate two distinct profiles with differing parameters which are statistically most likely to occur in the majority of individuals with this specific score (see Figure 4.1). Results indicated that 26% of the sample population received a score of 24. Within this subpopulation, two pathways were identified in profiles presented. The first pathway, describing a majority of the subpopulation (18% of total sample, 69.23% of specific subpopulation), offers the most likely presentation for individuals with a MOCA score of 24 and includes the following parameters: GDS <= 4, Tau > 226, Aβ 38 >= 1795. The alternative pathway, describing the second most common profile seen in a MOCA score of 24 (8% of total sample, 30.77% of subpopulation), includes a new set of parameters: Tau >= 180, GDS <= 2, Aβ 38 < 1699, Aβ 38 <= 1795.

Presentation pathways will change when an individual receives a different score on the MOCA. For example, a MOCA score of 25 (14% of total sample) would display the following conditions: Tau <= 180, GDS <= 2, Aβ 38 < 1699, Aβ 38 <= 1795 (see Figure 4.1). These profiles are founded on maximum likelihood estimates of underlying risk-factor presentations for one MOCA score when compared to another. Each score of the MOCA reflects a shift in pathology presentation, which may provide valuable insight into distinct presentation profiles of contributors to both healthy aging and abnormal dementia-related decline.

Correlation Network Diagram Among Baseline Clinical and Biomarker Variables

Reflected in ADAS Scores

Using a non-linear decision tree analysis approach, several trends in variables of importance were indicated. Variables of high importance to ADAS score were PTSD, GDS, Aβ 40, p-Tau, and Tau. ADAS scores can be predicted based on a series of binary splits within the partition model. The first split (PTSD < 2) divides the decision space into two regions. The first second-level split (Tau < 278) then divides the (PTSD < 2) region into two distinct sub-regions, while the second second-level split (Aβ 40 < 6254), divides the (PTSD < 2) region into two further sub-regions. These divisions will likewise continue until they reach a point of relative insignificance in association. Using this model, it is possible to identify a specific ADAS score as having one or two likely paths for predicting underlying psychological and biomarker-based trends (see Figure 4.2).

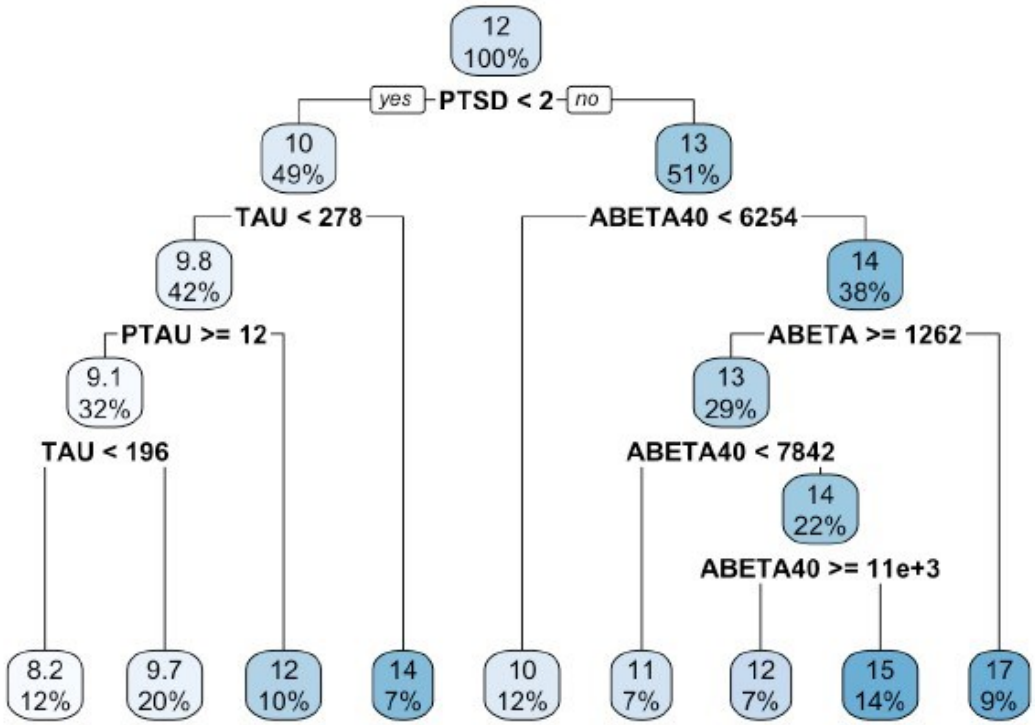


Figure 4.2
CART analysis graph for trends in variables related to ADAS scores. Binary nodes are shown

with their respective condition, percentage of sample size accounted for, and the average ADAS score calculated for the given condition. Each right-sided branch indicates an affirmation of the given condition at each node, while each left-sided branch indicates a lack of affirmation for the given condition at each node. CART = Classification and Regression Tree, ADAS = Alzheimer's Disease Assessment Scale.

Just as with the previously discussed MOCA screener, one's ADAS score may reflect a specific type of multifaceted report which encompasses real-world trends in composite genetic, biological, environmental, and psychological profiles in relation to cognitive correlates assessed within the ADAS. For example, if an individual receives a score of 12 on the ADAS, results will indicate two distinct profiles with differing parameters which are statistically most likely to occur in the majority of individuals with this specific score (see Figure 4.2). Results indicated that 17% of the sample population received a score of 12 on the ADAS. Within this subpopulation, two pathways were identified as likely profiles presentations. The first pathway, describing a majority of the subpopulation (10% of total sample, 59% of specific subpopulation), offers the most likely presentation for individuals with an ADAS score of 12 and includes the following parameters: P-tau <= 12, Tau < 278, PTSD < 2.

The alternative pathway, describing the second most common profile seen in an ADAS score of 12 (7% of total sample, 41% of subpopulation), identifies a new set of parameters: Aβ 40 >= 11e+3, Aβ 40 > 7842, Aβ >= 1262, Aβ 40 > 6254, PTSD > 2. These pathways will change when an individual receives a different score on the ADAS. For example, an individual with an ADAS score of 15 (14% of total sample) would display the following conditions: Aβ 40 <= 11e+3, Aβ 40 > 7842, Aβ >= 1262, Aβ 40 > 6254, PTSD >2 (see Figure 4.2). These profiles are founded on maximum likelihood estimates of underlying risk-factor presentations for one ADAS score when compared to another. Each score of the ADAS reflects a shift in the presentation of underlying mechanisms, thus providing valuable information for distinct

presentations of contributors to both healthy and abnormal dementia-related decline.

Discussion

Recent research suggests AD and dementia-related disorders are likely not a product of acute onset, but rather include a series of processes that begin decades prior to disease onset. In consideration of these findings, an emphasis has been placed on a proactive approach to staving off cognitive decline related to dementia. The current approach tends to favor early intervention as the best course of action in ameliorating the effects of dementia, in lieu of relying on symptom management after disease onset. One step to implement early intervention regiments is to accurately identify relationships between risk-factor presentation profiles in vulnerable populations which do not yet have dementia. While recent advances in biomarker identification have aided in this investigation, procedures related to biomarker collection are often used as a last resort due to their invasive and often painful collection process. Therefore, identifying patterns of underlying mechanisms within the collection of non-invasive neuropsychological measures of cognition may assist efforts in early identification and intervention.

We used a non-linear analysis approach to investigate trends in risk-factor presentation in a high-risk veteran population related to cognition scores on two commonly administered neuropsychological assessments for dementia diagnosis (MOCA and ADAS). These assessments were analyzed for their respective sensitivities in detecting common patterns in underlying mechanisms associated with dementia. The major findings of these analyses are summarized here. Differences in MOCA scores reflected several important pathways of interactions between variables of interest. In order of highest to lowest detected contribution, specific presentations of Aβ 38, tau, GDS, Aβ 40, p-tau, PTSD, Aβ, and Aβ 42 were determined

to be key interacting variables associated with variations in MOCA scores (see Figure 4.1).

In reference to interactions between in ADAS scores and underlying mechanisms, analyses revealed variable interactions in several distinct pathways. In order of highest to lowest detected contribution, specific presentations of PTSD, GDS, Aβ 40, p-tau, and tau were identified as key interacting variables associated with variations in ADAS scores (see Figure 4.2). It should be noted that several of these interactions were only associated with cognitive outcomes when within a certain threshold. For example, in the relationship between tau and ADAS scores, a strong association was detected for tau levels between 195 and 278 while tau levels exceeding 278 showed little, if any, association on ADAS scores. This emphasizes the need to consider relative protein accumulation thresholds as variables of importance rather than a simplified approach of equal weighting.

These findings suggest differences regarding sensitivity of specific neuropsychological screeners in detecting patterns of presentation in underlying mechanisms associated with cognitive decline in older adults. In application, there is potential for clinicians to bypass invasive biomarker collection in their aim for early risk-factor identification. Future clinicians may have access to probable patterns in underlying biomarkers associated with easily collected neuropsychological cognitive assessment outcomes, in conjunction with accessible psychopathology and environmental information. Based on a patient's individual medical background and the clinician's particular biomarker presentations of interest, these findings may aid in tailored approaches to which neuropsychological assessment to administer for early identification of cognitive decline.

There are several strengths inherent in this study. First, this report presents a novel look into non-linear relationships between several diagnostic fields of interest within the area of

risk-factor identification in Alzheimer's Disease and related dementias. Further strengths include the utilization of the ADNI database. This large-scale multi-site database is one of the most comprehensive datasets in the world for housing longitudinal data of demographic, behavioral, neurological, biological, psychological, and environmental measures in older adult populations. The comprehensive nature of its measures and large sample size makes the ADNI dataset an invaluable resource for investigating the underlying mechanisms associated with an increased risk of abnormal aging. The ADNI-DOD division of this database includes data on both normal and mildly abnormal cognitive decline (MCI) in aging populations, thus allowing for increased sensitivity between comparison groups most likely to benefit from risk-factor informed interventions for the prevention of accelerated cognitive decline.

In addition to strengths, this study also presents several limitations. Regarding the applicability of the presented findings, it is important to note that this sample, though a comprehensive representation of the individuals included, does not necessarily represent older adult populations as a whole. ADNI subjects were recruited from numerous nationwide academic research centers, which may result in a skewed representation of individuals who have familiarity and proximity to these centers. In assessing a veteran population, one must consider the stark contrast in prior daily environment settings between veterans and non-veterans, as well as the varied consequences associated with these differences. This is observed in the increased endorsement of TBI and PTSD diagnoses both during and after service among veterans. Such variables may act as a catalyst for accelerated cognitive decline, in turn making the studied population more vulnerable to Alzheimer's Disease and other dementia-type disorders than non-veteran populations. Finally, rather than a snapshot baseline view of risk factors and associated neurocognitive assessment scores, future studies may seek to further

investigate changes in these variables longitudinally to better capture relevant trends in trajectory of cognitive decline over time.

Conclusion

Within the field of aging research, it is widely understood that the mechanisms underlying cognitive decline are complex. For this reason, research is shifting focus toward the interaction of risk factors spanning several disciplines. Using a non-linear analysis approach for baseline data, we sought to investigate the link between risk factor presentation profiles in older adults who display healthy and mildly impaired cognition. This report includes trends in the presentation of numerous dementia risk factors within the context of performance in two commonly used neuropsychological assessments. Our aim was to determine whether one assessment showed greater sensitivity than another in detecting trends in psychological, environmental, and biological characteristics. Analyses indicate that while the detection of risk-factor patterns between the MOCA and ADAS may be subtle, both assessments show potential utility in detecting novel and overlapping risk-factor characteristics common in older adults with normal and mildly declining cognition. Identifying the interaction and presentation of these factors as either contributors to or buffers against progression into cognitive decline is invaluable for the use of identifying profiles of healthy aging without requiring invasive and time-consuming procedures. This expanded snapshot view can help elucidate baseline characteristics of risk factors present in those with mild levels of cognitive decline when compared to those without, allowing for the exploration of relevant trends in cognitive measures and biomarkers for AD.

Funding

No funding was provided for this research.

Acknowledgments

Recruitment of participants and support throughout this research study would not have been possible without collaboration with volunteer faculty and graduate students from Colorado State University, which include Dr. Deana Davalos, Dr. Haonan Wang, and Mengting Lin.

REFERENCES

Abdullah, L., Crawford, F., Tsolaki, M., Börjesson-Hanson, A., Olde Rikkert, M., Pasquier, F., Wallin, A., Kennelly, S., Ait-Ghezala, G., Paris, D., Hendrix, S., Blennow, K., Lawlor, B., & Mullan, M. (2020). The Influence of Baseline Alzheimer's Disease Severity on Cognitive Decline and CSF Biomarkers in the NILVAD Trial. *Frontiers in Neurology, 11,* 1–13. https://doi.org/10.3389/fneur.2020.00149

Amoroso, N., Rocca, M. La, Bruno, S., Maggipinto, T., Monaco, A., Bellotti, R., & Tangaro, S. (2019). Multiplex networks for early diagnosis of Alzheimer's disease. *Frontiers in Aging Neuroscience, 10*, 1–15. https://doi.org/10.3389/fnagi.2018.00365

Andrews, M., Ross, R., Malhotra, A., Ancoli-Israel, S., Brewer, J. B., & Banks, S. J. (2021). Sleep and Tau Pathology in Vietnam War Veterans with Preclinical and Prodromal Alzheimer's Disease. *Journal of Alzheimer's Disease Reports, 5*(1), 41–48. https://doi.org/10.3233/ADR-200245

Gamberger, D., Lavrač, N., Srivatsa, S., Tanzi, R. E., & Doraiswamy, P. M. (2017). Identification of clusters of rapid and slow decliners among subjects at risk for *Alzheimer's disease. Scientific Reports, 7*(1), 1–12. https://doi.org/10.1038/s41598-017-06624-y

Hampel, H., Teipel, S. J., Fuchsberger, T., Andreasen, N., Wiltfang, J., Otto, M., Shen, Y., Dodel, R., Du, Y., Farlow, M., Möller, H. J., Blennow, K., & Buerger, K. (2004). Value of CSF β-amyloid1-42 and tau as predictors of Alzheimer's disease in patients with mild cognitive impairment. *Molecular Psychiatry, 9*(7), 705–710. https://doi.org/10.1038/sj.mp.4001473

Landau, S. M., Harvey, D., Madison, C. M., Reiman, E. M., Foster, N. L., Aisen, P. S.,

Petersen, R. C., Shaw, L. M., Trojanowski, J. Q., Jack, C. R., Weiner, M. W., & Jagust, W. J. (2010). Comparing predictors of conversion and decline in mild cognitive impairment. *Neurology, 75*(3), 230 – 238. https://doi.org/10.1212/WNL.0b013e3181e8e8b8

Llano, D. A., Laforet, G., & Devanarayan, V. (2011). Derivation of a New ADAS-cog Composite Using Tree-based Multivariate Analysis: Prediction of Conversion from Mild Cognitive Impairment to Alzheimer Disease. *Alzheimer Disease & Associated Disorders, 25*(1).

Mohamed, A. Z., Cumming, P., Götz, J., & Nasrallah, F. (2019). Tauopathy in veterans with long-term posttraumatic stress disorder and traumatic brain injury. *European Journal of Nuclear Medicine and Molecular Imaging, 46*(5), 1139–1151. https://doi.org/10.1007/s00259-018-4241-7

Mohamed, A. Z., Cumming, P., Srour, H., Gunasena, T., Uchida, A., Haller, C. N., & Nasrallah, F. (2018). Amyloid pathology fingerprint differentiates post-traumatic stress disorder and traumatic brain injury. *NeuroImage: Clinical, 19,* 716–726. https://doi.org/10.1016/j.nicl.2018.05.016

Podhorna, J., Krahnke, T., Shear, M., & E Harrison, J. (2016). Alzheimer's Disease Assessment Scale-Cognitive subscale variants in mild cognitive impairment and mild Alzheimer's disease: Change over time and the effect of enrichment strategies. *Alzheimer's Research and Therapy, 8*(1). https://doi.org/10.1186/s13195-016-0170-5

Samtani, M. N., Raghavan, N., Shi, Y., Novak, G., Farnum, M., Lobanov, V., Schultz, T., Yang, E., Dibernardo, A., & Narayan, V. A. (2013). Disease progression model in subjects with mild cognitive impairment from the Alzheimer's disease neuroimaging

initiative: CSF biomarkers predict population subtypes. *British Journal of Clinical Pharmacology, 75(*1), 146–161. https://doi.org/10.1111/j.1365-2125.2012.04308.x

Schrag, A., & Schott, J. M. (2012). What is the clinically relevant change on the ADAS-Cog? *Journal of Neurology, Neurosurgery and Psychiatry, 83*(2), 171–173. https://doi.org/10.1136/jnnp-2011-300881

Toledo, J. B., Xie, S. X., Trojanowski, J. Q., & Shaw, L. M. (2013). Longitudinal change in CSF Tau and Aβ biomarkers for up to 48 months in ADNI. *Acta Neuropathologica, 126*(5), 659–670. https://doi.org/10.1007/s00401-013-1151-4

Tong, T., Gray, K., Gao, Q., Chen, L., & Rueckert, D. (2017). Multi-modal classification of Alzheimer's disease using nonlinear graph fusion. *Pattern Recognition, 63*, 171–181. https://doi.org/10.1016/j.patcog.2016.10.009

Veitch, D. P., Weiner, M. W., Aisen, P. S., Beckett, L. A., Cairns, N. J., Green, R. C., Harvey, D., Jack, C. R., Jagust, W., Morris, J. C., Petersen, R. C., Saykin, A. J., Shaw, L. M., Toga, A. W., & Trojanowski, J. Q. (2019). Understanding disease progression and improving Alzheimer's disease clinical trials: Recent highlights from the Alzheimer's Disease Neuroimaging Initiative. In *Alzheimer's and Dementia* (Vol. 15, Issue 1, pp. 106–152). https://doi.org/10.1016/j.jalz.2018.08.005

Weiner, M., Harvey, D., Hayes, J., Landau, S., Aisen, P., Petersen, R., Tosun, D., Veitch, D., Jack, C., Decarli, C., Saykin, A., Grafman, J., & Neylan, T. (2017). Effects of traumatic brain injury and posttraumatic stress disorder on development of Alzheimer's disease in Vietnam Veterans using the Alzheimer's Disease Neuroimaging Initiative: Preliminary report. *Alzheimer's and Dementia: Translational Research and Clinical Interventions, 3*(2), 177–188. https://doi.org/10.1016/j.trci.2017.02.005

Chapter 5

CONCLUSION

This manuscript brings to attention critical issues surrounding abnormal cognitive decline in older adult populations by addressing gaps present in the current body of work related to dementia related disorders, as well as future research efforts needed to further investigate drivers of cognitive decline in ADRD. Considered together, the varied topics discussed in this dissertation converge to shed light on the efficacy of proactive targeted identification and intervention practices tailored to an individual's unique circumstances surrounding age-related cognitive decline. The etiology of abnormal aging observed in ADRD is an inherently intricate and multifaceted topic. Rather than identifying a single facet of abnormal age-related decline, we sought to investigate the relationship between varied profiles in environment, lifestyle, cognition, physiology, and psychopathology. In applying such an approach, we can more clearly elucidate pertinent risk factor presentations and efficacy of rehabilitative efforts for older adults at highest risk for conversion. The three studies addressed allow for the multidisciplinary investigation of mechanisms of healthy and abnormal cognitive decline, in addition to identifying effective interventions for disease modification in those with present ADRD.

Specifically, several trends were observed regarding identification and intervention strategies for older adult populations with normal and abnormal age-related cognitive decline include the following: First, within the context of the B Sharp Arts Engagement program, a comparison of acute cognitive performance scores after auditory stimulation (symphony performance) indicated several statistically significant differences between specific auditory and visuospatial domains and acute domain-specific subtest changes in cognition. Specifically, visuospatial domains and visuospatial domain-specific subtests showed greater acute cognitive

benefits after before and after attending an individual symphony performance. These indicate the presence of immediate benefits received in specific cognitive areas following acute nonpharmacological enrichment interventions. When investigating extended duration effects of the B Sharp Arts Engagement program on cognitive performance, no significant differences were observed in performance between auditory and visuospatial domains over the course of 8-10 months. In reference to the identification of patterns in risk-factor presentation in a healthy high ADRD-risk population, we saw promising results related to the relationship between cognition performance scores on two commonly administered neuropsychological assessments and trends in risk-factors related to environment, physiology, and psychopathology.

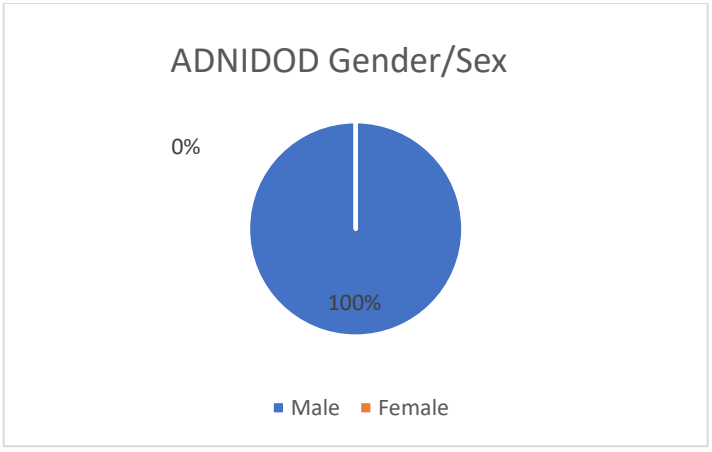
Limitations

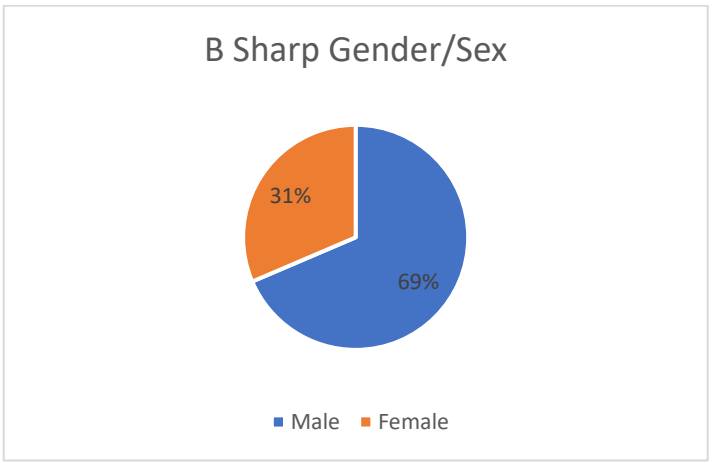
While the research presented in this manuscript had notable strengths and presented a novel approach to the understanding of both healthy age-related cognitive decline and ADRD, several limitations should be addressed. Within the B Sharp Arts Engagement program, no control group was included until 2019. The lack of comparison between populations with ADRD and healthy aging populations may inhibit the relative strength of effects after participation in this nonpharmacological intervention. In addition, individual differences related to severity of cognitive decline, medications taken, and side effects associated with concomitant medication interactions were not initially considered in the research study piloted in 2015.

A lack of racial, ethnic, sex and gender diversity should also be noted as a limitation when evaluating the generalizability of the three manuscripts detailed in this document. According to the US Census, as of 2019 the United States is comprised of over 328 million individuals. Considering such a large and diverse group, no single database utilized in this dissertation can

account for the varied environmental, genetic, psychological, and physiological variations present among individuals in the United States. While accounting for all possible variations in US compositions is unrealistic, it is vitally important to call attention to relevant differences in sample representation so as not to relay erroneous conclusions regarding the substrates of pathological aging or related intervention efficacy. Specifically, differences were observed in a general US population when compared to the samples included in this dissertation.

Regarding demographics, in comparison to the general US population as recorded by the US Census (49.2% male, 50.8% female), the analyzed ADNIDOD sample was entirely comprised of male participants (100.0% male, 0.0% female), and the B Sharp Arts engagement dataset consisted mostly of male participants (68.6% male, 31.4% female) (See Figure 5.1).





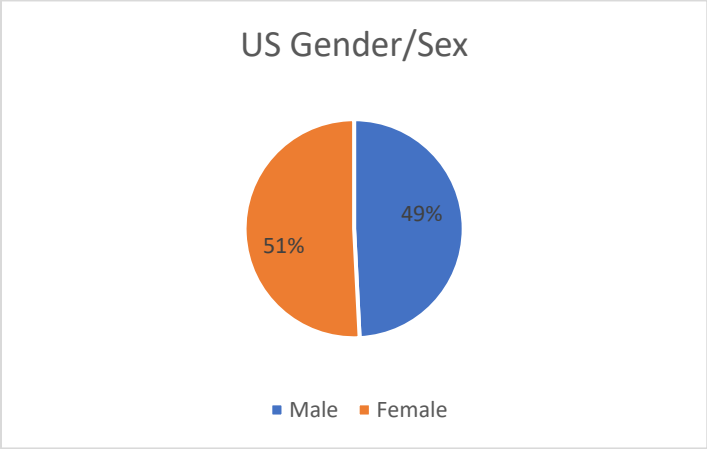


Figure 5.1
Gender/sex demographic comparison across populations.

Additionally, within both the ADNIDOD and intervention samples, most participants identified as non-Hispanic and white, reflecting a lack of ethnic (See Figure 5.2) and racial (See Figure 5.3) diversity among populations analyzed when compared to a broader US population. Regarding age representation, the ADNIDOD dataset had a greater proportion of "younger" older adults (93.8% being below the age of 74), whereas the B Sharp intervention had a greater proportion of "older" older adults (71.4% at or above the age of 80) (See Figure 5.4). Due to the differing proportions in age demographics assessed, risk factor and intervention trends should consider the implications of early versus late older adulthood in the outcomes observed.

Within the risk-factor identification research presented, it is important to acknowledge that the healthy population assessed within the ADNIDOD database may not be representative of a general older adult population. Our data was drawn from a population of Vietnam War veterans whose previous past life experiences may stand in stark contrast from the life experiences of a civilian. We must also consider the consequences associated with these differences. As reported by the US Department of Veteran Affairs and the Center for Disease

Control, traumatic brain injuries are endorsed at an increased rate in veteran populations (as high as 50%) when compared to a general US population (5.2%). The ADNIDOD dataset utilized reflects similar rates of veteran traumatic brain injury prevalence (46%) (See Figure 5.5).

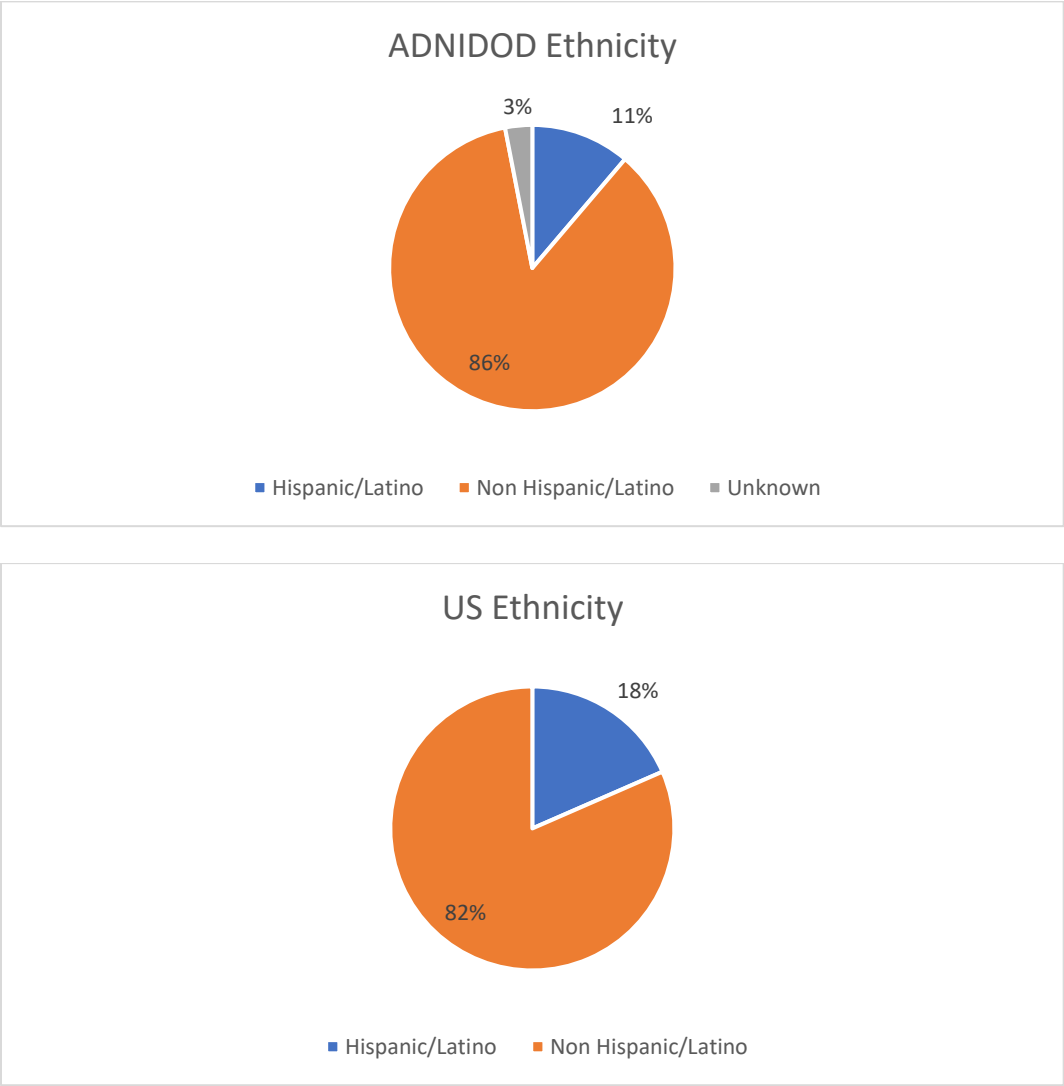
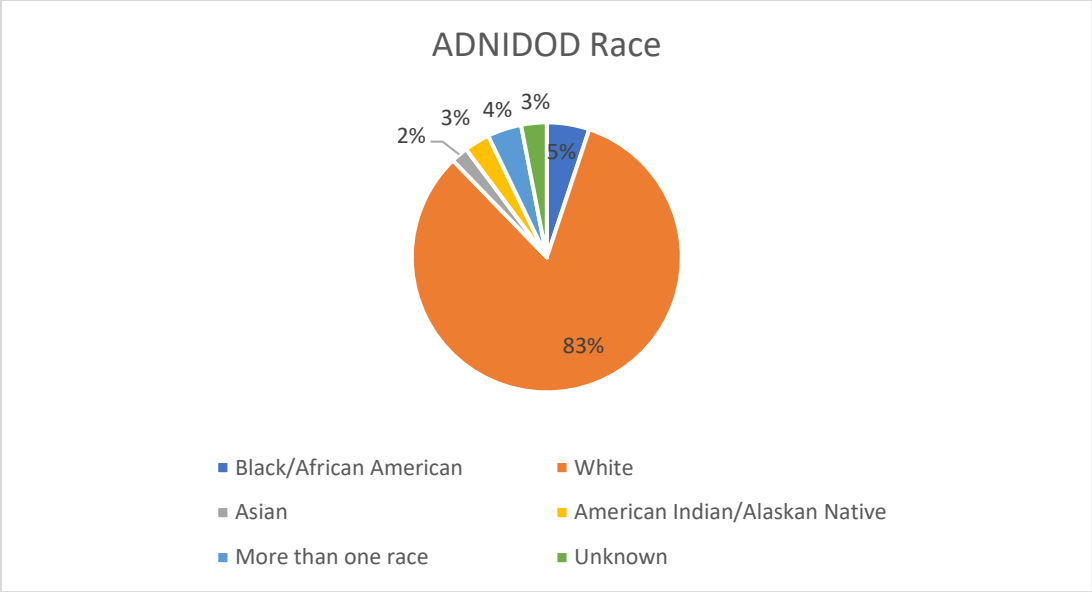


Figure 5.2
Ethnicity demographic comparison across populations.

Likewise, lifetime PTSD is endorsed at an increased rate in veteran populations (28.9%) when compared to a general US population (3.5%). The ADNIDOD dataset utilized reflects even higher rates of PTD prevalence (50%) than the average US veteran sample (See Figure



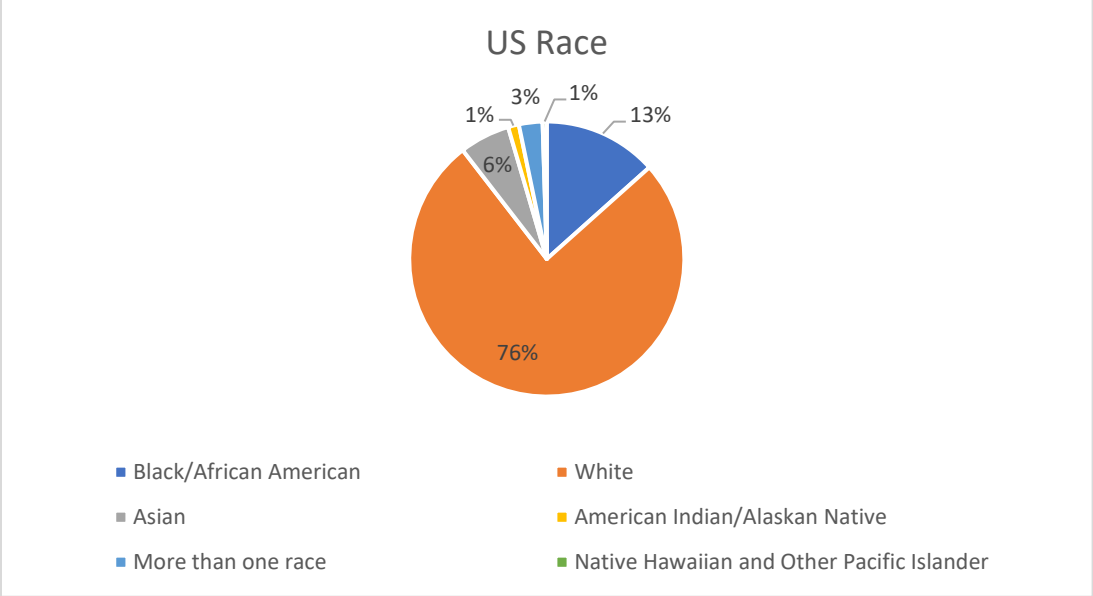


Figure 5.3
Race demographic comparison across populations.

5.6). Factors related to increased prevalence of multiple traumatic brain injuries, and increased severity of psychopathologies such as PTSD may not be generalizable to a larger population, all of which place veteran populations at a significantly elevated risk of future ADRD diagnoses.

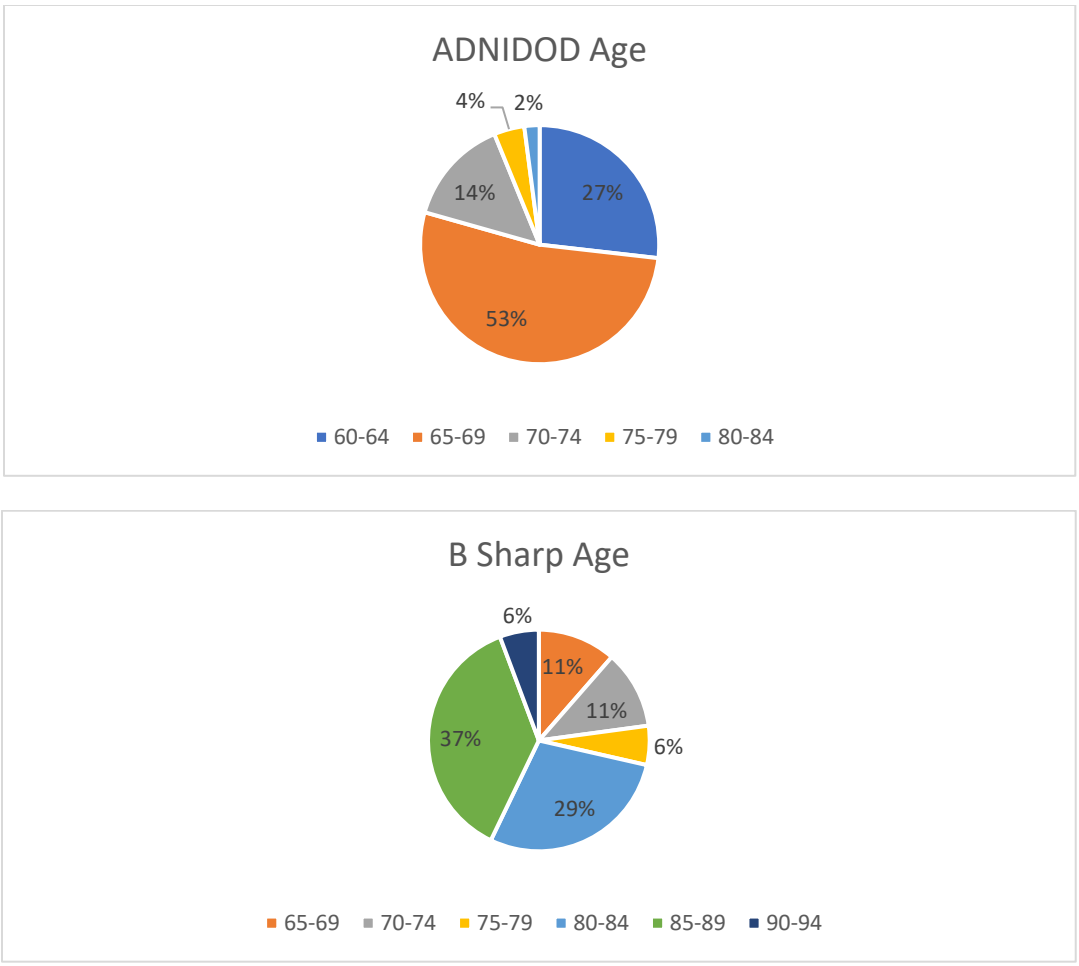


Figure 5.4
Age demographic comparison across populations.

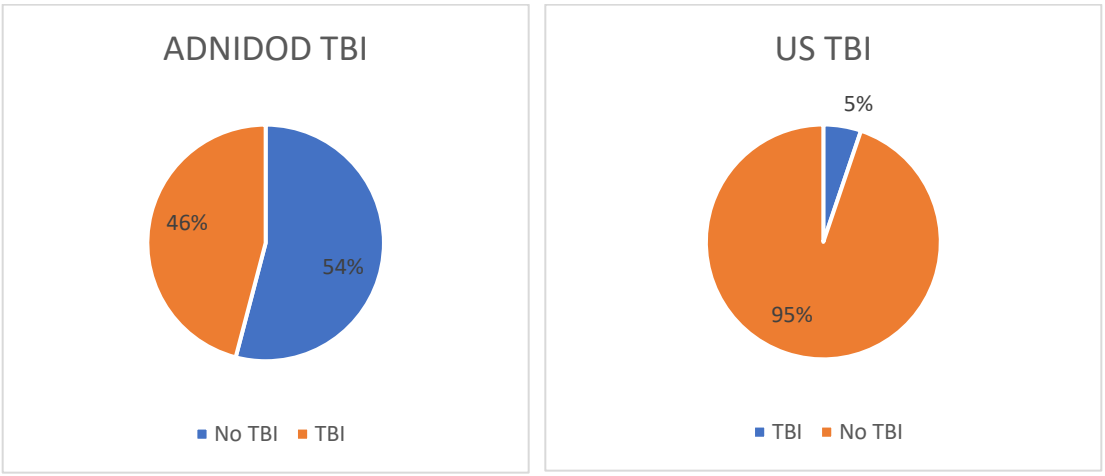


Figure 5.5
TBI prevalence comparison across populations.

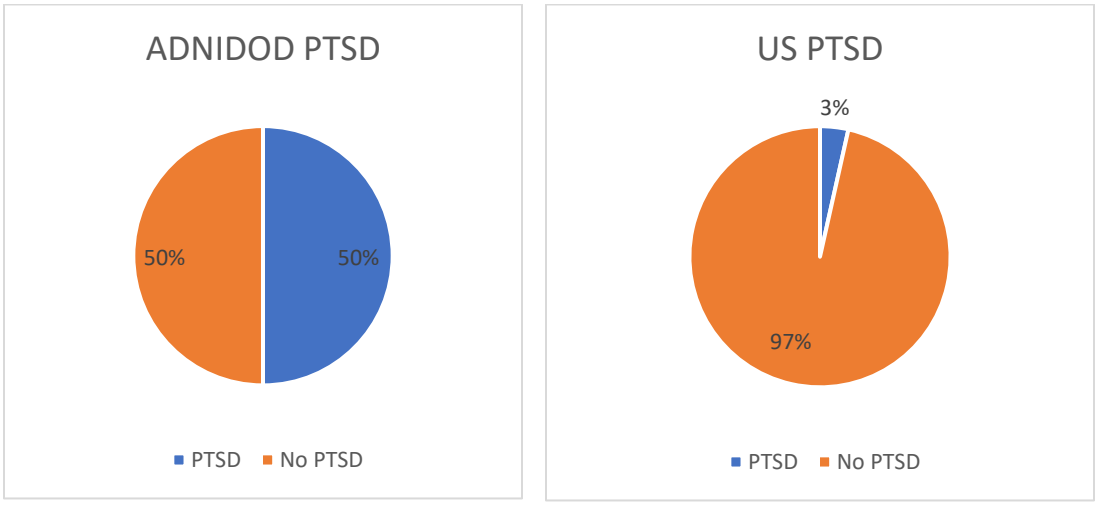


Figure 5.6
PTSD prevalence comparison across populations.

Future Directions

Future research efforts may benefit from building upon and adjusting the research designs utilized in this research compilation. In reference to chapter one, it may be of interest to compare acute changes in cognitive performance among several visuospatial subtests to gain a better understanding of the mechanisms involved in observed cognitive gains. In reference to chapter two, one change to consider may be to compare extended-duration progressions of dementia over time to performance on specific subtests at varied time points. Both studies detailed in chapter should consider differences in cognitive domains between medicated and non-medicated persons with dementia, in addition to comparing performance change effects in different types of dementia with differing levels of severity. In reference to chapter three, future studies may wish to compare changes in risk-factor presentations longitudinally to better capture relevant patterns in trajectory of cognitive decline over time. All three manuscripts would benefit from the inclusion of a larger, more heterogenous sample reflecting current demographic trends, as well as a control group.

Significance

At present, ADRD modification typically favor a reactive "treatment" approach to decrease functional age-related decline only when symptoms inhibit daily living. While some benefits may be observed as a result of later stage intervening efforts, this dissertation posits that the benefits of implementing a proactive "prevention and intervention" approach may have greater efficacy in preventing ADRD onset or ameliorating the effects of ADRD which can significantly impact a patient's quality of life. In application, evaluating commonalities in variables for those with varying stages of cognitive decline may shed light on underlying associations not previously apparent which may prove to be critical in establishing treatments with greatest efficacy in areas of ADRD modification. Additionally, elucidating the cognitive domains which are most sensitive to the positive effects of nonpharmacological alternatives may provide opportunities for intervention options tailored to the specific needs on an individual with ADRD.

Furthermore, tailored clinical measures for staving off cognitive decline can be more proactively implemented when comparing a patient's individual cognitive performance on a simple noninvasive cognitive screener assessment to well-validated likelihoods of underlying risk-factor presentations without requiring invasive collection methods. Indeed, the ability to quickly identify interaction and presentation of these factors as either contributors to or buffers against progression into cognitive decline is invaluable for the use of identifying profiles of healthy aging Together, these results inform a larger body of research of underlying the mechanisms involved in ADRD in addition to establishing viable intervention strategies to alleviate the effects of ADRD progression.

REFERENCES

Adbowale, V., Farmer, P., Rose-Quirie, A., Jenkins, P., Greatley, A., Bailey, S. (2014). The pursuit of happiness: A new ambition for our mental health. *CentreForum 1–61*.

Abdullah, L., Crawford, F., Tsolaki, M., Börjesson-Hanson, A., Olde Rikkert, M., Pasquier, F., Wallin, A., Kennelly, S., Ait-Ghezala, G., Paris, D., Hendrix, S., Blennow, K., Lawlor, B., & Mullan, M. (2020). The Influence of Baseline Alzheimer's Disease Severity on Cognitive Decline and CSF Biomarkers in the NILVAD Trial. *Frontiers in Neurology, 11,* 1–13. https://doi.org/10.3389/fneur.2020.00149

Alzheimer's Association. (2020). Types of Dementia. Retrieved from https://www.alz.org/alzheimers-dementia/what-is-dementia/types-of-dementia

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders, 5.* https://doi.org/10.1176/appi.books.9780890425596

Amoroso, N., Rocca, M. La, Bruno, S., Maggipinto, T., Monaco, A., Bellotti, R., & Tangaro, S. (2019). Multiplex networks for early diagnosis of Alzheimer's disease. *Frontiers in Aging Neuroscience, 10,* 1–15. https://doi.org/10.3389/fnagi.2018.00365

Andrews, M., Ross, R., Malhotra, A., Ancoli-Israel, S., Brewer, J. B., & Banks, S. J. (2021). Sleep and Tau Pathology in Vietnam War Veterans with Preclinical and Prodromal Alzheimer's Disease. *Journal of Alzheimer's Disease Reports, 5*(1), 41–48. https://doi.org/10.3233/ADR-200245

Banner Alzheimer's Institute. Life Enrichment Programs. Banner Alzheimer's Institute Website. http://banneralz.org/education-events/life-enrichment-programs.aspx.

Barkhof, F., van Buchem, M.A. (2016). Neuroimaging in dementia. In: Hodler J, Kubik-Huch RA, von Schulthess GK, eds. *Diseases of the Brain, Head and Neck, Spine, 79–85*.

https://doi.org/10.1007/978-3-319-30081-8_10

Bird, T.D. (1998). Alzheimer Disease Overview. *Gene Reviews, 4*, 12-16.

Burnside, I.M. (1979). Alzheimer's Disease: An Overview. *Journal of Gerontological Nursing. 5(*4):14-20.

Chatterjee, H.J., Camic, P.M., Lockyer, B., Thomson, L.J. (2018). Non-clinical community interventions: a systematised review of social prescribing schemes. *Arts & Health 10*:97–123. https://doi.org/10.1080/17533015.2017.1334002

Clare, L. & Woods, R.T. (2004). Cognitive training and cognitive rehabilitation for people with early-stage Alzheimer's disease: a review. *Neuropsychological Rehabilitation, 14,* 385-401. https://doi.org/10.1080/09602010443000074

Davalos, D. B., Luxton, I., Thaut, M., & Cross, J. E. (2019). B Sharp—The cognitive effects of a pilot community music program for people with dementia-related disorders. Alzheimer's and Dementia: *Translational Research and Clinical Interventions, 5*, 592–596. https://doi.org/10.1016/j.trci.2019.08.004

Duff, K., Humphreys-Clark, J.D., O'Bryant, S.E., Mold, J.W., Schiffer, R.B. Sutker, P.B. (2008). Utility of the RBANS in detecting cognitive impairment associated with Alzheimer's disease: sensitivity, specificity, and positive and negative predictive powers. *Arch Clin Neuropsychol, 23*:603–12. https://doi.org/10.1016/j.acn.2008.06.004

Farias, S. T., Mungas, D., Reed, B. R., Harvey, D. & DeCarli, C. (2009). Progression of mild cognitive impairment to dementia in clinic- vs community-based cohorts. *Archives of Neurology, 66,* 1151–1157. https://doi.org/10.1001/archneurol.2009.106

Faw, M. H., Luxton, I., Cross, J. E., & Davalos, D. B. (2021). Surviving and Thriving: Qualitative Results from a Multi-Year, Multidimensional Intervention to Promote Well-

Being among Caregivers of Adults with Dementia. *Int. J. Environ. Res. Public Health, 18,* 4755. https://doi.org/10.3390/ijerph18094755

Felician, O., & Sandson, T.A., (1999). The Neurobiology and Pharmacotherapy of Alzheimer's Disease. *The Journal of Neuropsychiatry, 10,* 1176.

Fleming, R., Zeisel, J., & Arch, K. B. B. (2020). World Alzheimer Report 2020 Design, Dignity, Dementia: Dementia-related design and the built environment. *Alzheimer's Disease International, 2*.

Foster, B., Pearson, S., & Berends, A. (2016). 10 Domains of Music Care: A Framework for Delivering Music in Canadian Healthcare Settings (Part 3 of 3). *Music and Medicine, 8*(4), 199-206. https://doi.org/10.47513/mmd.v8i4.415

Gamberger, D., Lavrač, N., Srivatsa, S., Tanzi, R. E., & Doraiswamy, P. M. (2017). Identification of clusters of rapid and slow decliners among subjects at risk for Alzheimer's disease. *Scientific Reports, 7(*1), 1–12. https://doi.org/10.1038/s41598-017-06624-y

Gross, A.L., Rebok, G.W., Unverzagt, F.W., Willis, S.L., Brandt J. (2011). Cognitive predictors of everyday functioning in older adults: Results from the ACTIVE cognitive intervention trial. *J Gerontol B Psychol Sci Soc Sci 66*:557–66. https://doi.org/10.1093/geronb/gbr033

Hampel, H., Teipel, S. J., Fuchsberger, T., Andreasen, N., Wiltfang, J., Otto, M., Shen, Y., Dodel, R., Du, Y., Farlow, M., Möller, H. J., Blennow, K., & Buerger, K. (2004). Value of CSF β-amyloid1-42 and tau as predictors of Alzheimer's disease in patients with mild cognitive impairment. *Molecular Psychiatry, 9*(7), 705–710. https://doi.org/10.1038/sj.mp.4001473

Hughes, T.F., Flatt, J.D., Fu, B., Chang, C.C., Ganguli, M. (2013). Engagement in social activities and progression from mild to severe cognitive impairment: the MYHAT study. *Int Psychogeriatrics 25*:587–95.https://doi.org/10.1017/S1041610212002086

Hugo, J. & Ganguli, M. (2014). Dementia and Cognitive Impairment: Epidemiology, Diagnosis, and Treatment. *Clinics in Geriatric Medicine, 30*(3), 421-442. https://doi.org/10.1016/j.cger.2014.04.001

Jiang, J., Dong, Y., Huang, W., & Bao, M. (2017). General anesthesia exposure and risk of dementia: a meta-analysis of epidemiological studies (Vol. 8). Retrieved from www.impactjournals.com/oncotarget.

Kim, C. T., Myung, W., Lewis, M., Lee, H., Kim, S. E., Lee, K., … Kim, D. K. (2018). Exposure to General Anesthesia and Risk of Dementia: A Nationwide Population-Based Cohort Study. *Journal of Alzheimer's Disease, 63*(1), 395–405. https://doi.org/10.3233/JAD-170951

Landau, S. M., Harvey, D., Madison, C. M., Reiman, E. M., Foster, N. L., Aisen, P. S., Petersen, R. C., Shaw, L. M., Trojanowski, J. Q., Jack, C. R., Weiner, M. W., & Jagust, W. J. (2010). Comparing predictors of conversion and decline in mild cognitive impairment. *Neurology, 75*(3), 230 LP – 238. https://doi.org/10.1212/WNL.0b013e3181e8e8b8

Li, K., Chan, W., Doody, R. S., Quinn, J., & Luo, S. (2017). Prediction of Conversion to Alzheimer's Disease with Longitudinal Measures and Time-To-Event Data. Journal of Alzheimer's Disease, 58(2), 361–371. https://doi.org/10.3233/JAD-161201Petersen, R., & Negash, S. (2008). Mild Cognitive Impairment: An Overview. *CNS Spectrums, 13*(1), 45-53.

Llano, D. A., Laforet, G., & Devanarayan, V. (2011). Derivation of a New ADAS-cog

Composite Using Tree-based Multivariate Analysis: Prediction of Conversion from Mild Cognitive Impairment to Alzheimer Disease. *Alzheimer Disease & Associated Disorders, 25*(1).

Mohamed, A. Z., Cumming, P., Götz, J., & Nasrallah, F. (2019). Tauopathy in veterans with long-term posttraumatic stress disorder and traumatic brain injury. *European Journal of Nuclear Medicine and Molecular Imaging, 46*(5), 1139–1151. https://doi.org/10.1007/s00259-018-4241-7

Mohamed, A. Z., Cumming, P., Srour, H., Gunasena, T., Uchida, A., Haller, C. N., & Nasrallah, F. (2018). Amyloid pathology fingerprint differentiates post-traumatic stress disorder and traumatic brain injury. *NeuroImage: Clinical, 19,* 716–726. https://doi.org/10.1016/j.nicl.2018.05.016

Patton, D.E., Duff, K., Schoenberg, M.R., Mold, J., Scott, J.G., Adams, R.L. (2005). Base rates of longitudinal RBANS discrepancies at one-and two-year intervals in community-dwelling older adults. *Clin Neuropsychol 19:*27–44. https://doi.org/10.1080/13854040490888477

Podhorna, J., Krahnke, T., Shear, M., & E Harrison, J. (2016). Alzheimer's Disease Assessment Scale-Cognitive subscale variants in mild cognitive impairment and mild Alzheimer's disease: Change over time and the effect of enrichment strategies. *Alzheimer's Research and Therapy, 8(*1). https://doi.org/10.1186/s13195-016-0170-5

Prince, M., Wimo, A., Guerchet, M., Ali, G.C., Wu, Y.T., Prina, M. (2015). World Alzheimer Report 2015. The Global Impact of Dementia. Alzheimer's Disease International (ADI).

Randolph, C., Tierney, M.C., Mohr, E., Chase, T.N. (1998). The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): preliminary clinical validity. *J*

Clin Exp Neuropsychol 20:310–9. https://doi.org/10.1076/jcen.20.3.310.823

Rinehardt, E., Duff, K., Schoenberg, M., Mattingly, M., Bharucha, K., Scott, J. (2010). Cognitive change on the repeatable battery of neuropsychological status (RBANS) in Parkinson's disease with and without bilateral subthalamic nucleus deep brain stimulation surgery. *Clin Neuropsychol 24:*1339–54. https://doi.org/10.1080/13854046.2010.521770

Samtani, M. N., Raghavan, N., Shi, Y., Novak, G., Farnum, M., Lobanov, V., Schultz, T., Yang, E., Dibernardo, A., & Narayan, V. A. (2013). Disease progression model in subjects with mild cognitive impairment from the Alzheimer's disease neuroimaging initiative: CSF biomarkers predict population subtypes. *British Journal of Clinical Pharmacology, 75(*1), 146–161. https://doi.org/10.1111/j.1365-2125.2012.04308.x

Särkämö, T., Tervaniemi, M., Laitinen, S., Numminen, A., Kurki, M., Johnson, J.K., & Rantanen, P. (2014). Cognitive, emotional, and social benefits of regular musical activities in early dementia: A randomized controlled study. *The Gerontologist, 54*, 634–650. doi:10.1093/geront/gnt100

Schneck, M. K., Reisberg, B., & Ferris, S. H. (1982). An overview of current concepts of Alzheimer's disease. *The American Journal of Psychiatry, 139*(2), 165-173.

Schrag, A., & Schott, J. M. (2012). What is the clinically relevant change on the ADAS-Cog? *Journal of Neurology, Neurosurgery and Psychiatry, 83*(2), 171–173. https://doi.org/10.1136/jnnp-2011-300881

Serafino, P. (2018). Another Alzheimer's Drug Fails as Lilly, Astra Halt Tests. Bloomberg Website. https://www.bloomberg.com/news/articles/2018-06-12/lilly-astrazeneca-end-trials-as-alzheimerdrug-shows-no-promise.

Thies, W., Bleiler, L., (2011). Alzheimer's disease facts and figures. *Alzheimer's & Dementia, 7*, 208–244.

Toledo, J. B., Xie, S. X., Trojanowski, J. Q., & Shaw, L. M. (2013). Longitudinal change in CSF Tau and Aβ biomarkers for up to 48 months in ADNI. *Acta Neuropathologica, 126*(5), 659–670. https://doi.org/10.1007/s00401-013-1151-4

Tong, T., Gray, K., Gao, Q., Chen, L., & Rueckert, D. (2017). Multi-modal classification of Alzheimer's disease using nonlinear graph fusion. *Pattern Recognition, 63*, 171–181. https://doi.org/10.1016/j.patcog.2016.10.009

Veitch, D. P., Weiner, M. W., Aisen, P. S., Beckett, L. A., Cairns, N. J., Green, R. C., Harvey, D., Jack, C. R., Jagust, W., Morris, J. C., Petersen, R. C., Saykin, A. J., Shaw, L. M., Toga, A. W., & Trojanowski, J. Q. (2019). Understanding disease progression and improving Alzheimer's disease clinical trials: Recent highlights from the Alzheimer's Disease Neuroimaging Initiative. In *Alzheimer's and Dementia* (Vol. 15, Issue 1, pp. 106–152). https://doi.org/10.1016/j.jalz.2018.08.005

Velkers, C., Whitehead, M., Reimer, C., Eckenhoff, R., Berger, M., Rochon, P. Seitz, D. (2018). Risk of developing dementia among older adults undergoing elective surgical procedures with general anesthesia when compared to regional anesthesia. *Alzheimer's & Dementia, 14*(7), P1353. https://doi.org/10.1016/j.jalz.2018.06.

Weiner, M., Harvey, D., Hayes, J., Landau, S., Aisen, P., Petersen, R., Tosun, D., Veitch, D., Jack, C., Decarli, C., Saykin, A., Grafman, J., & Neylan, T. (2017). Effects of traumatic brain injury and posttraumatic stress disorder on development of Alzheimer's disease in Vietnam Veterans using the Alzheimer's Disease Neuroimaging Initiative: Preliminary report. Alzheimer's and Dementia: *Translational Research and Clinical Interventions,*

*3(*2), 177–188. https://doi.org/10.1016/j.trci.2017.02.005

Woods, B., Aguirre, E., Spector, A. E., & Orrell, M. (2012). Cognitive stimulation to improve cognitive functioning in people with dementia. Cochrane *Database of Systematic Reviews, 2.* https://doi.org/10.1002/14651858.CD005562.pub2

Zhang, Y., Cai, J., An, L., Hui, F., Ren, T., Ma, H., et al. (2017). Does music therapy enhance behavioral and cognitive function in elderly dementia patients? A systematic review and meta-analysis. *Ageing Res Rev 35:*1. https://doi.org/10.1016/j.arr.2016.12.003

Zhu, Y., Chen, Y., Crimmins, E. M., & Zissimopoulos, J. M. (2021). Sex, Race, and Age Differences in Prevalence of Dementia in Medicare Claims and Survey Data. *The Journals of Gerontology. Series B, Psychological Sciences and Social Sciences, 76*(3), 596–606. https://doi.org/10.1093/geronb/gbaa083

Zissimopoulos, J., Crimmins, E., Clair, P.S. (2015). The value of delaying Alzheimer's disease onset*. Forum Health Econ Policy 18*:25–39. https://doi.org/10.1515/fhep-2014-0013